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The contribution of chest CT-scan at diagnosis in children with unilateral Wilms' tumour. Results of the SIOP 2001 study

Anne M.J.B. Smets [a,*], *Harm van Tinteren* [b], *Christophe Bergeron* [c], *Beatriz De Camargo* [d], *Norbert Graf* [e], *Kathy Pritchard-Jones* [f], *Jan de Kraker* [g]

[a] *Department of Radiology, Academic Medical Center, Amsterdam, The Netherlands*
[b] *Biometrics Department, Netherlands Cancer Institute, Amsterdam, The Netherlands*
[c] *Institut d'Hémato-oncologie Pédiatrique, Centre Léon Bérard, Lyon, France*
[d] *Pediatric Hematology and Oncology Program, Research Center, Instituto Nacional de Câncer, Rio de Janeiro, Brazil*
[e] *Department of Paediatric Oncology, Universität des Saarlandes, Homburg, Germany*
[f] *Molecular Haematology and Cancer Biology Unit, University College London Institute of Child Health, London, UK*
[g] *Department of Paediatric Oncology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands*

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ABSTRACT

Background: The SIOP 2001 nephroblastoma study hypothesised that patients with 'CT-only' pulmonary nodules would have the same outcome as patients with localised disease of same stage and histology.

Patients: Unilateral Wilms' tumour (WT) patients, who had chest CT scans at diagnosis showing any sized pulmonary nodules undetected on chest X-ray, between November 2001 and November 2009, were selected from the SIOP 2001 database.

Results: Among 2532 WT patients, 103 unilateral nephroblastoma patients with CT-only lung lesions were found. Thirty-seven patients received preoperative treatment according to the localised-disease protocol, and 66 according to the metastatic-disease protocol. The 3-year event-free survival (EFS) was 70% (95% CI: 55–89%) and 77% (95% CI: 66–89%), respectively. Corresponding 3-year overall survival (OS) was 89% (95% CI: 77–100%) and 85% (95% CI: 75–96%), respectively (p-value not significant). EFS and OS of all 2071 patients with true localised disease were 87% (95% CI: 86–89%) and 96% (95% CI: 94–97%), respectively. Patients with metastatic disease ($n = 358$) had 3-year EFS and OS estimates of 68% (95% CI: 63–74%) and 77% (95% CI: 72–82%), respectively.

Conclusions: EFS and OS of patients with CT-only lung lesions were inferior to that of true localised-disease patients and superior to that of patients with metastatic disease. However, no significant difference was found in EFS and OS between CT-only patients treated for localised or metastatic disease. The clinician's preference to treat patients with CT-only pulmonary nodules as metastatic disease is not evidence-based. Chest CT at diagnosis does not improve outcome but presents paediatric oncologists with a difficult dilemma.

* *Corresponding author:* Address: Department of Radiology, Academic Medical Center (AMC), University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands. Tel.: +31 20 5669111.
E-mail address: a.m.smets@amc.uva.nl (A.M.J.B. Smets).
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1. Introduction

Physicians are often tempted to use newer and more sophisticated procedures in the diagnostic workup of patients. However, before introducing and accepting a new procedure, its effects on treatment and outcome as well as its potential for increased risk, such as late effects of ionising radiation must be considered. In paediatric oncology, the benefit of chest computed tomography (CT) is often discussed.[1] In Wilms' tumour (WT) particularly, there is an on-going debate on the necessity of the routine use of chest CT scans at diagnosis to detect small pulmonary metastases.[2,3] The risk of a lesion being malignant is known to increase with the size of the nodule.[4] Based on inherent limitations, chest radiograph (CXR) reliably shows only nodules 10 mm or more in diameter. CT represents the most sensitive imaging method for very small nodules.[5,6] Based on the different sensitivity cut-offs of the 2 methods, chest CT is known to be less specific than CXR in distinguishing between pulmonary metastasis and benign pulmonary nodules.[7] This is important, because small benign pulmonary lesions are frequently seen in young patients.[8,9]

No prospective study has evaluated the outcome of patients with WT using the criterion of CT-only lesions. The SIOP 2001 study recommended treating patients with nodules visible on CT, but not on CXR, the same way as patients with localised disease. If the outcome did not differ from that of patients diagnosed with localised disease, this would suggest that patients with small pulmonary metastases do not have an adverse prognosis. Chest CT would then be unnecessary in the workup and these patients could benefit from less radiation exposure, less treatment and late effects, and the overall costs of the workup would be lower.

2. Patients and methods

2.1. Study protocol

SIOP-2001 is an international, multi-centre, registration study and randomised clinical trial of different treatment regimens for children with nephroblastoma aged between 6 months and 18 years. The study started in November 2001, and is still open for inclusion. The randomised part of the study closed on January 1, 2010. All patients are required to have a CXR (antero-posterior and lateral views) as part of their diagnostic workup. Chest CT scan to investigate suspicious or equivocal lesions on CXR was optional. Patients with CT-only lung lesions were to receive the same preoperative treatment as patients with localised disease. One national group (UK) performed a single view CXR and included a further requirement that the largest lesion seen on chest CT should be no more than 10 mm in maximum diameter in order to be ignored for initial staging purposes.

For localised disease, preoperative chemotherapy consisted of actinomycin-D 45 μg/kg intravenously on days 1 and 14, and vincristine 1.5 mg/m^2 intravenously administered weekly for 4 weeks. Before nephrectomy, both CXR and CT (if performed at diagnosis) were repeated. If both investigations showed no lesions suspicious for lung metastases, postoperative chemotherapy was continued according to the recommended regimen for the localised tumour stage and histological risk group. This was also true for patients with persisting pulmonary lesions, surgically removed, and proved to contain no vital tumour cells. In case of inoperable or otherwise remaining pulmonary metastases, the postoperative treatment was according to stage IV protocol. Pulmonary radiotherapy was given to all patients with primary tumours with high risk histology. For patients with 'true' metastatic disease (stage IV), i.e. lung metastasis visible on CXR or metastatic spread elsewhere, preoperative chemotherapy was more intensive, with the addition of two doses of doxorubicin 50 mg/m^2 for a total duration of six weeks. Postoperatively, the treatment depended on the disappearance or persistence of metastases and the local tumour stage.

2.2. Data collection

Data from all patients with CT-only lung lesions were collected and reviewed with respect to the number of pulmonary lesions, the size of the largest pulmonary lesion, tumour histology, tumour stage, pre- and postoperative therapy, presence or absence of pulmonary metastases after preoperative chemotherapy, histology of metastases, and outcome. For obvious organisational reasons, data analysis was not based on a central review of the original radiological images nor on the radiological reports available for analysis, but on the study files. In case of equivocal or incomplete data, the individual centres were contacted for additional information. Since chest CT was not a mandatory test in this study, the exact number of patients who had a chest CT at diagnosis is unknown.

2.3. Statistical methods

Comparison of categorical variables between treatment approaches for localised and metastatic disease was made using Fisher's exact test or trend tests for ordered classes. Survival curves were established using the Kaplan–Meier technique and differences were tested using the log-rank test.

3. Results

Of 3310 patients registered by November 2009, 592 had suspicious lesions outside the kidney at diagnosis. Lesions in the lungs were reported in only 411 patients. In 139 patients, pulmonary lesions were detected on the CT-scan but not the CXR. Of these 139 patients, 36 were excluded as follows: 12 patients with bilateral disease, 1 patient with extra-renal localisation of the primary tumour, and 8 patients for whom crucial information was lacking. Fifteen patients were non-WT (6 malignant rhabdoid tumours, 3 clear cell sarcoma, 1 neuroblastoma and 5 non-classifiable tumours).

Of the 103 remaining patients with CT-only pulmonary lesions out of a total of 2532 unilateral WT patients, pre-operative therapy for localised disease was given to 37, and preoperative therapy for metastatic disease was given to 66. The characteristics of both groups are given in Table 1. No significant difference in the number of lesions between these two groups was detected ($p = 0.28$), but the group treated for

Table 1 – Patients characteristics in all groups.

Characteristics	CT-only duration of pre-operative chemotherapy			
	True localised (*n* = 2071)	4 Weeks (*n* = 37)	6 Weeks (*n* = 66)	Metastatic (*n* = 358)
Age in months – mean (sd)	43.2 (30.2)	56 (31.6)	54 (26.2)	58 (30.8)
Males	46%	54%	48%	46%
Number of lesions mean (sd)	–	2.8 (2.4)	4.6 (5.5)	12.5 (18.1)
Diameter of largest lesion in mm – mean (sd)	–	5.0 (2.5)	9.7 (6.3)	17.5 (17.1)
Abdominal stage				
I	1073 (52%)	13 (35%)	23 (35%)	93 (26%)
II	478 (23%)	14 (38%)	16 (24%)	71 (19.8%)
III	439 (21%)	9 (24%)	25 (38%)	173 (48.3%)
Missing	81 (4%)	1 (3%)	2 (3%)	21 (6%)
Histology				
Low risk	86 (4.2%)	2 (5.4%)	11 (16.7%)	46 (13%)
Completely necrotic	64 (3.1%)	2 (5.4%)	11 (16.7%)	46 (13%)
Intermediate risk	1647 (79.5%)	26 (70.3%)	48 (72.7%)	245 (68%)
Unspecified	6 (<1%)	0	1 (1.5%)	2 (1%)
Epithelial type	155 (7.5%)	2 (5.4%)	1 (1.5%)	17 (4.7%)
Stromal type	254 (12.3)	2 (5.4%)	3 (4.5%)	22 (6.1%)
Mixed type	560 (27.0%)	9 (24.3%)	8 (12.1%)	38 (10.6%)
Regressive	626 (30.2)	11 (29.7%)	33 (50.0%)	158 (44.1%)
Focal anaplasia	31 (1.5%)	2 (5.4%)	1 (1.5%)	6 (1.7%)
Non-anaplastic + variants	15(<1%)	0	1 (1.5%)	2 (<1%)
High risk	247 (11.9%)	9 (24.3%)	7 (10.6%)	51 (14%)
Blastemal	169 (8.2%)	5 (13.5%)	2 (3.0%)	16 (4.5%)
Diffuse anaplasia	78 (3.8%)	4 (10.8%)	5 (7.6%)	34 (9.5%)
Response of lung lesions after preoperative chemotherapy				
CR		11 (29.7%)	34 (51.5%)	
PR		6 (16.2%)	21 (31.8%)	
SD		1 (2.7%)	5 (7.6%)	
PD		1 (2.7%)	0	
Unknown		18 (48.6%)	6 (9.1%)	
Post-operative treatment				
AV1		6 (16.2%)	3 (4.5%)	
AV2		3 (8.1%)	3 (4.5%)	
AVD		14 (37.8%)	40 (60.6%)	
VCCD		8 (21.6%)	13 (19.7%)	
No postop CT		3 (8.1%)	1 (1.5%)	
Unknown		3 (8.1%)	5 (7.5%)	
Single dose VCR		0	1 (1.5%)	
Surgery for pulmonary lesions		4 (10.8%)	13 (19.7%)	
Recurrences	233 (11.3%)	9 (24.3%)	12 (18.2%)	100 (27.9%)
Lung relapse	81 (3.8%)	6 (16.2%)	8 (12.1%)	54 (15.1%)
Lung and other	31 (1.5%)			15 (4.2%)
Other	89 (4.2%)	3 (8.1%)	1 (1.5%)	14 (3.9%)
Unknown	32 (1.5%)			17 (4.7%)

AV1: 4 doses of vincristine 1.5 mg/m^2 for 4 weeks and 1 dose of actinomycin-D 45 μg/kg in week 2; AV2: 20 doses of vincristine 1.5 mg/m^2 and 9 doses of actinomycin-D 45 μg/kg over 27 weeks; AVD: 8 doses of vincristine 1.5 mg/m^2, 9 doses of actinomycin-D 45 μg/kg and 3 doses of doxorubicin 50 mg/m^2; VCCD: 24 doses of VP16 150 mg/m^2, 24 doses of carboplatin 200 mg/m^2, 12 doses of cyclophosphamide 450 mg/m^2 and 4 doses of doxorubicin 50 mg/m^2; VCR: vincristine.

metastatic disease had larger lesions ($p = 0.0013$). The histological risk distribution was slightly more favourable in the group treated for metastatic disease ($p = 0.02$).

Nine of 37 patients treated for localised disease had a recurrence. Five patients had recurrences in the lungs and three died of lung relapse. All three had high risk histology stage III, with solitary lesions of 10 mm and 3 mm in two patients, respectively, and 3 lesions of unknown diameter in one patient. One patient had received pulmonary radiotherapy.

Among 66 patients treated for metastatic disease after diagnosis, 9 had a recurrence. Eight were lung relapses, and eight patients died. Five patients with intermediate risk histology died of lung relapse; 1 stage I, 1 stage II and 3 stage III. The number of lung lesions/diameter of largest lesion (mm) at diagnosis for these patients were as follows: 25/18 mm, 4/29 mm, 15/unknown, and 2/7 mm. Data were unavailable for 1 patient. The other 3 patients died of secondary malignancy, therapy-related death and local relapse.

Seventeen patients had surgery for remaining pulmonary lesions after preoperative chemotherapy: 7 had completely necrotic lesions only and in 3 patients a benign anatomical substrate (anatomic anomaly, pulmonary lymph node) was found and no signs of tumour. Three patients had intermediate histology and 2 highrisk histology lesions. The nature of the specimen is unknown in 2 patients.

Three-year event-free survival (EFS) was 70% (95% confidence interval [CI]: 55–89%) versus 77% (95% CI: 66–89%) for the groups treated for localised versus metastatic disease, respectively. Overall survival (OS) was 89% (95% CI: 77–100%) versus 85% (95% CI: 75–96%) for the groups treated for localised versus metastatic disease, respectively. There was no statistically significant difference between the groups for OS or EFS (Figs. 1 and 2). EFS and OS of all registered patients with true localised disease ($n = 2071$) following the recommended diagnostic procedures as defined by the SIOP protocol were 87% (95% CI: 86–89%) and 96% (95% CI: 94–96%), respectively. These survival estimates compared favourable to the EFS and OS of all CT-only patients together (respectively EFS 74% (95% CI: 65–84), $p = 0.003$ and OS 86% (95% CI: 78–95), $p = 0.001$). Patients with metastatic disease ($n = 358$) had 3-year EFS and OS estimates of 68.4% (95% CI: 63.4–73.9%) and 76.9% (95% CI: 72.2–82.0%), respectively. These estimates were not significantly different from those of the CT-only group together (respectively $p = 0.17$ and $p = 0.09$).

4. Discussion

The outcome of WT patients is very good. When the tumour is confined to the kidney, 5-year overall survival figures of 90% and more are common.[10] Studying downgrading treatment intensity in a randomised fashion in patients with a good prognosis is challenging.[11] Intensive therapy can then be limited to high risk patients. The same reasoning should also apply to diagnostic procedures.[12]

In the current SIOP nephroblastoma study, a CXR with good quality antero-posterior and lateral view images was the only mandatory imaging investigation for detecting pulmonary metastases. When the presence or the nature of lesions detected on the CXR was in doubt, a chest CT scan was performed. Chest CT has been part of the routine workup at diagnosis for WT in the United States for over 25 years without firm data to support its use. Although the sensitivity of CT to detect small pulmonary lesions is unquestionably higher compared with CXR,[5,6] it must be noted that not all these lesions necessarily represent metastases.[8,9] Both Mc Carville et al. and Silva et al. reported difficulties in differentiating benign from malignant pulmonary lesions on chest CT scans in children with malignancies.[7,13] The approach towards CT-only lung lesions in paediatric tumours, particularly in WT, is a continuing subject of debate.[1,14–17] Retrospective studies addressing this issue are conflicting. Owens et al. reported that chest CT at diagnosis in children with WT provides no additional predictive value except in patients who, after surgery (and without preoperative chemotherapy), appear to be stage I. Only children with biopsy-proven metastatic disease may benefit from more aggressive postoperative treatment than just single-agent therapy (vincristine).[15] This does not apply to the current SIOP-population since all children receive a 2-drug preoperative chemotherapy. The importance of preoperative chemotherapy in metastatic disease was demonstrated in an earlier SIOP study where 27 of 36 patients had a normal CXR after pre-operative chemotherapy.[18]

In the National Wilms Tumour Study (NWTS)-III, intensified treatment for CT-only patients did not improve survival.[19] Meisel et al. studied different treatment regimens in children with favourable histology and CT-only lung lesions. Children treated for stage IV with intensive chemotherapy and whole-lung irradiation appeared to not have a better outcome. This was explained by a higher number of therapy-related deaths in patients with CT-only lesions, raising a major concern about potentially fatal treatment side-effects in patients who may have only benign disease and no malignant lung lesions.[9]

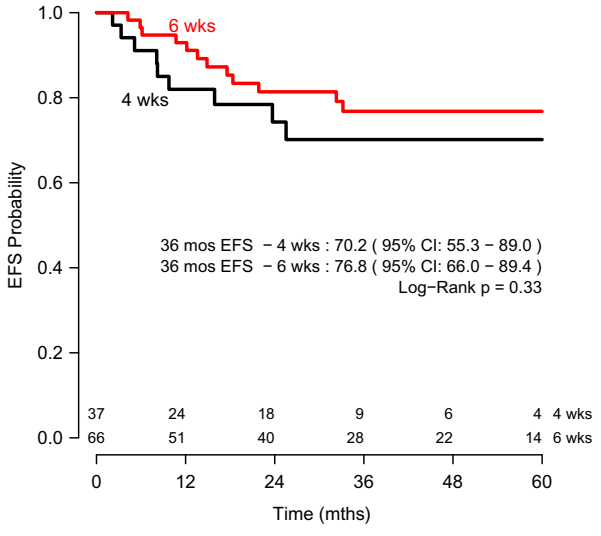

Fig. 1 – Event-free survival (EFS) in patients with 'CT-only' lesions according to treatment.

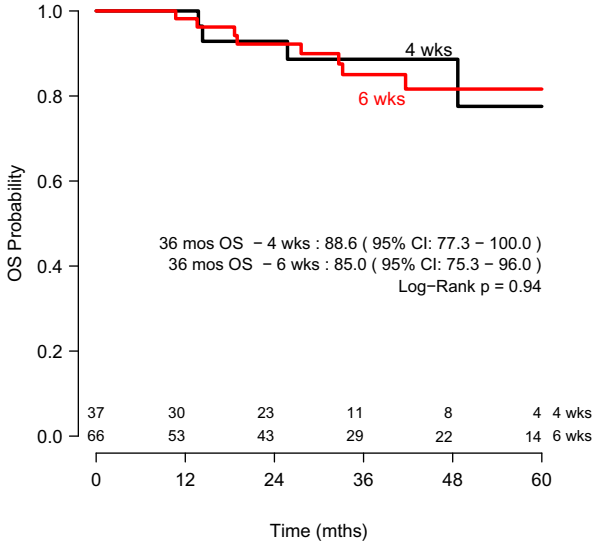

Fig. 2 – Overall survival (OS) in patients with 'CT-only' lesions according to treatment.

Cohen states that children should benefit from imaging tools that are the most sensitive in detecting tumour spread, including chest CT, unless there is proof that this does not affect patient outcome.[20] Cohen's statement ignores the potential health risks of CT, which are too often overlooked.[21–23] CT involves at least 40 times more radiation exposure than CXR when the tube current settings are adjusted for a paediatric patient, and 100 times or more when the settings are not tailored to a child.[24] The awareness of the risks of ionising radiation, expressed in the ALARA guidelines and the Image Gently campaign, requires us to scrutinise and justify the need for a CT scan before introducing it as a mandatory tool in a protocol.[25,26]

CT-only patients represent a very small subgroup. D'Angio reported that less than 2% of 2500 patients in the NWTS-III study had CT-only lung lesions.[27]

Because of the design of the SIOP-2001 study registration form, not all information submitted included whether patients had a chest CT at diagnosis. However, based on clinical experience, we presume that most patients had CT-scans of the thorax as part of their diagnostic work up. If so, CT-only patients would represent 4% of all those eligible for treatment in the SIOP 2001 study. This small proportion of CT-only detected pulmonary lesions also makes it difficult to justify the routine use of this technique for diagnostic purposes and for monitoring chemosensitivity. The protocol recommended that patients with CT-only lesions be treated as patients with localised disease in the preoperative chemotherapy phase, with subsequent treatment determined by the response of the lesions. It appeared, however, that most of the CT-only patients were treated like patients with metastatic disease from the outset, reflecting the clinician's uncertainty in this situation. In 6 patients, this could be explained by the centre's decision to intensify treatment for patients with a lesion larger than 10 mm. In all other patients, the decision to treat the patients with CT-only pulmonary lesions as stage IV patients was based on a fear of undertreating. This reflects the lack of firm evidence in this situation, and also a trend towards defensive medicine. However, the risk of overtreatment, including the harmful long-term effects associated with pulmonary radiation and increased drug toxicity that may appear many years later, should be carefully considered.[28–30] In the National Wilms Tumour studies (NWTS)-1, -2, -3, and -4, the frequency of congestive heart failure 20 years after diagnosis was 4.4% for patients treated with doxorubicin at initial diagnosis.[19,30] In the latest SIOP series, pulmonary radiation was given at a dose of 15 Gy. With this dose, radiation-induced lung injury can be expected. The combination of doxorubicin and radiation therapy is of even greater concern, with doxorubicin being a radiation sensitiser.

In our population, some patients had surgery for remaining pulmonary lesions after preoperative chemotherapy. Arguably, if these lesions had remained undetected at diagnosis, surgery would not have taken place and this could have influenced the outcome. However, only 17 such patients were in the study: in 10 patients no vital tumour could be found in the resected tissue. It remains speculative whether this procedure influenced the outcome. We also looked at a possible relationship between tumour load (size and number of lung lesions) and relapse. All patients with pulmonary relapse in the group treated for localised disease had a maximum lung lesion diameter of 10 mm or less, and a total of 5 or fewer lesions. Of the 4 patients with lung-relapse in the group treated for metastatic disease for whom we have complete data, 1 patient had a lesion with a diameter greater than 10 mm and 1 patient had more than 3 lesions. If we compare the outcome of the patients treated for localised disease with the patients treated for metastatic disease, there was no statistically significant difference between EFS and OS in these 2 groups (Figs. 1 and 2). However, the observation that the outcomes of both groups are inferior to that of patients with localised tumours suggests that further work is required to define the exact role of chest CT in unilateral WT.

Our study has two inevitable limitations. Because of a low incidence of the disease, even in an international cooperative group, the final study group was relatively small. In addition, data were retrieved retrospectively from the patients' files, and were not based on a re-review of the radiological images for obvious organisational reasons.

Although the outcome of all CT-only patients was inferior to those with localised disease, there was no difference in the outcome whether the lung lesions were taken into account for staging and treatment purposes or not. Interestingly, we found an obvious clinician's preference to treat children with CT-only lung lesions as stage IV, although there is currently no clinical evidence to justify this. These results highlight the difficult dilemma that the introduction of a chest CT scan at diagnosis brings about; treating children with CT-only lesions with intensified treatment will save a very small proportion of children from relapse, but may increase the incidence of late toxic effects.

In conclusion, the contribution of chest CT as a staging procedure at diagnosis in unilateral WT patients is limited. Current clinical decision making is based on the fear of undertreating. The results of this study do not support routine chest CT at diagnosis for all patients with unilateral WT. It might, however, play a role after preoperative chemotherapy and nephrectomy in selecting children with (persisting) pulmonary lesions. This finding in combination with high risk histology and/or stage III disease proved to have a bad prognosis. Hence these patients might benefit from intensified therapy.

Conflict of interest statement

None declared.

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