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Progression of localised Wilms' tumour during preoperative chemotherapy is an independent prognostic factor: A report from the SIOP 93–01 nephroblastoma trial and study

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ABSTRACT

The SIOP nephroblastoma clinical trials have previously demonstrated that preoperative chemotherapy is advantageous for patients with nephroblastoma (Wilms' tumour). However, some primary tumours increase in size during preoperative chemotherapy, and to investigate the clinical relevance of this progression we studied the patient cohort with increasing tumours included in the SIOP 93–01 study (June 1993 to June 2000). Patients were considered eligible if they had a confirmed localised Wilms' tumour that had been measured in at least two dimensions at diagnosis and before surgery. Tumour response to preoperative chemotherapy was defined according to criteria set by the World Health Organisation (WHO). Patient characteristics in the different response groups were compared and related to event-free survival and overall survival. Patient records were studied regarding compliance with protocol.

Tumour progression during preoperative chemotherapy was observed in 57 of 1090 patients (5%) with localised Wilms' tumours. In those cases, the tumours were significantly smaller at diagnosis and were more often stage III ($p = 0.05$) and associated with high risk histopathology ($p = 0.03$). After adjustment for stage and risk group, progression was proved to be correlated with poorer event-free and overall survival (hazard ratio 1.9, $p = 0.026$ and 3.2, $p = 0.002$ respectively). In summary, progression of localised Wilms' tumours is rarely seen in patients during preoperative chemotherapy. However, independent of stage distribution and histopathological risk group, those whose tumours do increase in size have poorer event-free and overall survival.

1. Introduction

Use of preoperative chemotherapy has been the standard treatment approach in the International Society of Paediatric Oncology (SIOP) nephroblastoma trial and study since the beginning of the 1970s,[1–4] whereas the North American National Wilms' Tumour Study Group (NWTSG) recommends primary surgical resection of the tumour and kidney.[5–7] There

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are no apparent differences in event-free and overall survival between the patients who are and are not given chemotherapy before nephrectomy.[8,9]

The regimen of 4–6 weeks of preoperative chemotherapy is intended to reduce tumour size in order to facilitate the surgical procedure and lower the risk of peroperative tumour ruptures. Furthermore, preoperative chemotherapy results in a shift towards lower tumour stages after surgery, which leads to less postoperative treatment for the patients. Evidence of the importance of preoperative chemotherapy in this context was gained in studies performed in the 1970s and 1980s.[1,2] Critics of the policy to use this approach argue that it might delay administration of drugs that are effective against renal tumours that do not respond to the standard preoperative chemotherapy.

According to clinical experience, most Wilms' tumours decrease in size during preoperative chemotherapy, and many show changes in consistency and/or structure rather than size, features that are associated with an excellent prognosis. However, in rare cases, tumour progression does occur, and the clinical implication of such behaviour has not yet been clarified. The SIOP 93–01 treatment protocol recommended that abdominal ultrasound should be performed halfway through the preoperative chemotherapy to assess tumour response, and that any unexpected findings should be discussed with the study centre.

The SIOP 93–01 protocol was used to treat almost 3000 Wilms' tumour patients from 1993 to 2000, which has provided a unique set of data to study clinically relevant questions. The results of the SIOP 93–01 trial were recently published.[10] In the present study, we addressed the issue of whether a standardised response evaluation could provide data that would justify intervention or changes in the current SIOP 93–01 managing of Wilms' tumour patients. We investigated the characteristics of progression of primary Wilms' tumours during preoperative therapy by analysing all progressive cases in the SIOP 93–01 trial as comprehensively as possible and comparing the results with the patient groups with other responses during chemotherapy.

2. Patients and methods

2.1. Patients

A total of 2905 children with renal tumours were registered in the international SIOP 93–01 clinical trial from June 1993 to June 2000. Minimum requirements for diagnosis were abdominal ultrasound, chest radiograph, and measurement of catecholamine metabolites in 24 h urine to exclude neuroblastoma. Preoperative chemotherapy was recommended for children older than 6 months and less than 18 years of age who presented with characteristic findings of nephroblastoma. Measurement of the primary tumour was requested at diagnosis and after preoperative chemotherapy.

Eligible for inclusion in the present study were 1090 patients who had localised Wilms' tumours that had been subjected to preoperative chemotherapy and had been measured in at least two dimensions at diagnosis and before surgery. The following clinical information was collected: patient characteristics, surgical details, chemotherapy data, pathological classification from both the local pathologist and the central pathology review panel, and follow-up data. In addition, patient records on the localised progressive tumours were studied in detail with regard to compliance with the protocol concerning pre- and postoperative treatment.

2.2. Treatment schedules

Patients with unilateral localised disease received preoperative chemotherapy consisting of 1.5 mg/m^2 vincristine (max. 2 mg) weekly for four consecutive weeks and 15μg/kg actinomycin-D for three consecutive days, weeks 1 and 3. Postoperative treatment depended on the stage of the local tumour and the histopathological risk group found at surgery (after preoperative chemotherapy). Local stage and risk group were reviewed by a central panel of pathologists. The histological prognostic groups of renal tumours were classified as belonging to low risk, intermediate risk, and high risk according to the revised SIOP classification of renal tumours published in 2002.[11]

2.3. Response evaluation

To evaluate responses to preoperative chemotherapy treatment, we used criteria defined by the World Health Organisation (WHO), which are based on changes in the product of the measurements of the longest perpendicular diameters of the primary tumour. The calculated values are categorised as follows: complete response (CR): total disappearance; partial response (PR): $\geqslant$ 50% decrease; stable disease (SD): not corresponding to PR or PD; progressive disease (PD): $\geqslant$ 25% increase.

Only a few cases exhibited a complete response, and they were therefore grouped together with the partial response cases in a category designated CR/PR.

2.4. Statistical methods

Logistic regression, chi-square tests, and ordered non-parametric tests were used to study associations between the WHO treatment response classification and age, sex, and tumour size at diagnosis, and also stage and histopathological risk group at surgery. The potential effects of treatment response on event-free and overall survival were investigated by means of Cox proportional hazard analysis. The length of event-free and overall survival was defined as the time from the date of diagnosis to the date of any event or death due to any cause, or to the date of last follow-up. Linearity and additivity with respect to log hazard were checked for all predictors.

3. Results

Of the 1090 patients with localised Wilms' tumours, 451 (41%) showed complete or partial response (CR/PR), 582 (53%) had stable disease (SD), and 57 (5%) had tumour progression after end of preoperative chemotherapy (Table 1). The average bidimensional product decreased by 67% in the CR/PR group (95% CI 65–70) and by 22% in the SD group (95% CI 20–24), and increased by 62% in the PD group (95% CI 56–68). At the time of diagnosis, the PD tumours were significantly smaller than

Table 1 – Patient and tumour characteristics in relation to response to preoperative chemotherapy

		CR/PR N = 451 (41%)	SD N = 582 (53%)	PD N = 57 (5%)	All N = 1090
Age (months)	Mean (Std)	46 (27)	43 (30)	42 (28)	44 (29)
	Median	43	37	37	40
	Range	7–206	6–193	7–165	6–206
Sex	Male	196 (43%)	262 (45%)	34 (60%)	492 (45%)
	Female	255 (57%)	320 (55%)	23 (40%)	598 (55%)
Bidimensional size at diagnosis	Mean (Std)	107 (64)	103 (55)	88 (44)	104 (59)
	Median	97	98	82	96
	Range	10–506	11–304	8–208	8–506

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; size in cm^2.

Table 2 – Stage and risk distribution in relation to response to preoperative chemotherapy

		CR/PRN = 451 (41%)	SD N = 582 (53%)	PD N = 57 (5%)	All N = 1090
Stage (all info)	I	224 (50%)	315 (54%)	21 (37%)	560 (51%)
	II	138 (31%)	164 (28%)	20 (35%)	322 (30%)
	III	60 (13%)	71 (12%)	12 (22%)	101 (9%)
	Missing	29 (6%)	32 (5%)	4 (7%)	65 (6%)
Risk	Low	29 (6%)	17 (7%)	4 (7%)	50 (5%)
	Intermediate	374 (83%)	485 (83%)	36 (63%)	895 (82%)
	High	18 (4%)	39 (7%)	14 (25%)	71 (6%)
	Missing/ Indeterminable	30 (7%)	41 (7%)	3 (5%)	74 (7%)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

the CR/PR tumours; values representing the bidimensional products at diagnosis for the three groups were 107 cm^2 (95% CI 100–114), 103 cm^2 (95% CI 97–109), and 88 cm^2 (95% CI 69–107), respectively. We found no relationship between treatment response and age or sex (Table 1).

Stage distribution and histopathological risk classification determined at surgery are shown in Table 2. There was no overall correlation between treatment response and stage. However, when we combined the CR/PR and SD groups, tumours that increased in size had less favourable stage distribution ($p = 0.05$). Response was significantly correlated with the histopathological risk classification ($p = 0.03$). Notably, a CR/PR was seen in only 25% of the high risk tumours compared to 42% and 58% of the intermediate and low risk tumours. Likewise, progression occurred more often in high risk tumours (20%) than in those with lower histopathological risk (4% for intermediate and 8% for low risk tumours). Nevertheless, due to the limited number of cases, no particular histopathological subtype could be identified as dominant in the progressive tumours.

With a median follow-up of 5 years, 128 recurrences and 57 deaths were observed. The results obtained using a Cox proportional hazard model including age, stage, histopathological risk groups, and response to preoperative chemotherapy are shown in Table 3. Besides illustrating the mentioned factors, analysis of the response to preoperative chemotherapy provided additional (independent) prognostic information. Tumours showing CR/PR were associated with slightly better survival than those in the SD group. Furthermore, for patients with tumours in the PD group, the risk of recurrence was almost doubled (HR 1.9, 95% CI 1.1–3.4) and the risk of death was threefold higher (HR 3.2. 95% CI 1.5–6.6) (Table 4). The hazard ratios are illustrated with confidence intervals in Fig. 1.

As mentioned, tumour size increased in 57 patients during preoperative chemotherapy, and the treatment was discontinued and early surgery was performed in three of those cases: two after 3 weeks of treatment due to progression, and one after 1 week of treatment because of intratumoural bleeding. All but two patients received postoperative treatment according to stage and histology defined at surgery (one by mistake, and one for whom epirubicin was omitted as physicians choice).

Complication in the form of peroperative rupture occurred in three of the 57 patients whose tumours increased in size during preoperative treatment.

Table 3 – Analysis of maximum likelihood estimates for event-free survival

Variable	DF	Pr > ChiSq	Hazard ratio	95% hazard ratio confidence limits	
Age (mos.)	1	0.1513	1.004	0.998	1.010
Stage II	1	0.9554	0.988	0.648	1.507
Stage III	1	0.0015	2.045	1.314	3.182
High risk	1	0.0004	2.420	1.490	3.929
CR/PR	1	0.0979	0.723	0.492	1.062
PD	1	0.0263	1.920	1.080	3.415

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4 – Analysis of maximum likelihood estimates for overall survival

Variable	DF	Pr> ChiSq	Hazard ratio	95% hazard ratio confidence limits	
Age (mos.)	1	0.0567	1.008	1.000	1.016
Stage II	1	0.5045	1.262	0.637	2.502
Stage III	1	0.0002	3.527	1.828	6.804
High risk	1	0.0062	2.546	1.304	4.972
CR/PR	1	0.1074	0.593	0.313	1.120
PD	1	0.0020	3.188	1.529	6.646

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

4. Discussion

The advantages of preoperative chemotherapy have long been emphasised in the SIOP nephroblastoma clinical trial and study. For localised disease, the current approach is to give four weekly doses of vincristine and two weekly doses of actinomycin-D concurrently, which has proven to be well tolerated and to reduce the number of peroperative ruptures and other surgical complications.[12,13] The tumour and the affected kidney are surgically resected after preoperative chemotherapy, and the postoperative treatment is determined according to the local stage of the tumour and its histopathological risk classification at surgery. Applying this response-adapted strategy after 4 weeks of chemotherapy has been successful, but change in tumour size has never been taken into account in the stratification of the postoperative treatment.

To our knowledge, no criteria for judging the response to chemotherapy in Wilms' tumour have been developed and validated. Tumour volume regression has been observed in previous SIOP studies, but different definitions of poor and good response were used in those investigations.[4,14] Therefore, with the aim to test a standardised method for analysing treatment response, we used the WHO criteria that are commonly implemented to evaluate treatment response in adult oncology. We investigated almost 1100 patients with localised tumours and found that only about 5% of the primary tumours increased in size after 4 weeks of therapy, which implies that clinicians will rarely be confronted with a progressive tumour before surgery.

We noted that progressive disease was related to histopathological subtypes that are associated with high risk, and, albeit to a much lesser extent, also to the stage of the tumour at surgery. No other factors were identified that could explain variation in treatment response.

A connection between progressive tumour behaviour during preoperative chemotherapy and poorer event-free and overall survival in patients with Wilms' tumour has not yet been described. In light of the heterogeneity of Wilms' tumours and observations of non-response and progression in more differentiated subtypes that are associated with excellent prognosis, it has been difficult to conclude that progression per se can predict treatment outcome. Our results show that the WHO criteria for treatment response can be used as a tool to recognise differences that are predictive, and this was evident even after adjusting for stage and risk classification. Moreover, even though there were fewer deaths than recurrences, the degree of significance was greater for survival than for recurrence. A probable explanation for this

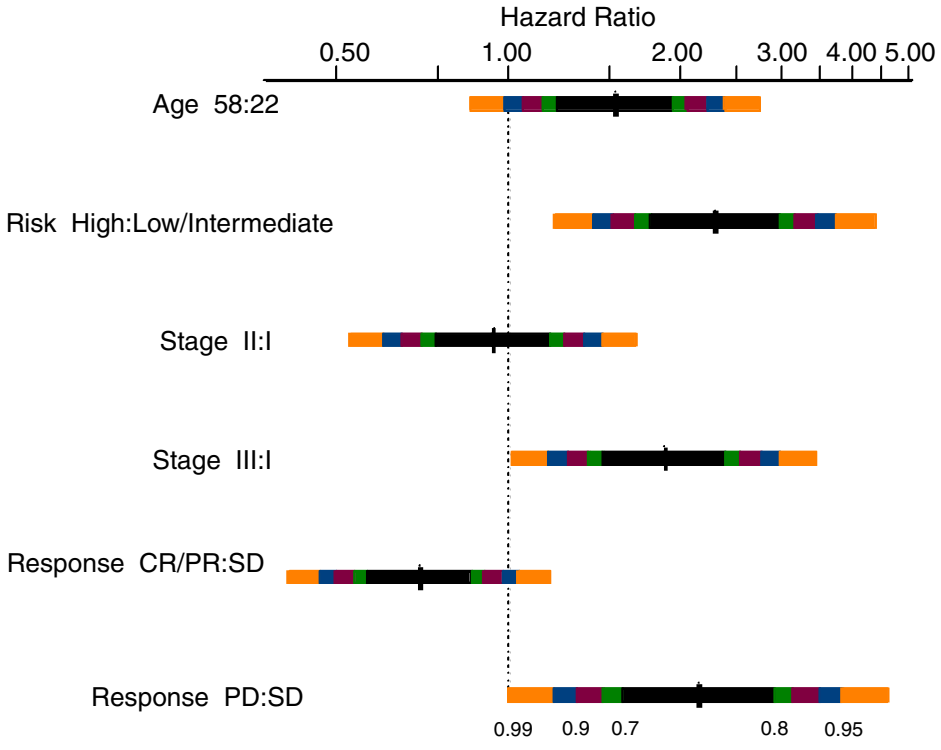

Fig. 1 – Graphical presentation of the results of Cox proportional hazard analysis.

finding is that the tumours that increased in size during preoperative treatment were insensitive to the drugs that were administered, both pre- and postoperatively, and also to the drugs used in the recommended second line treatment.

When treating other highly malignant paediatric solid tumours, the regular approach is to use primary preoperative chemotherapy to reduce tumour size and to evaluate the response to the cytotoxic drugs. This type of response-adapted treatment has been found to improve the outcome in a number of malignant diseases in childhood, including leukaemia, osteosarcoma, and Ewing's sarcoma.[15,16] Clinicians experience that tumour progression during standard treatment is associated with chemotherapy resistance and poor survival in neuroblastoma and rhabdomyosarcoma. Wilms' tumours are known to be sensitive to chemotherapy, which explains why a relatively mild regimen results in an excellent overall survival rate of more than 90% for localised disease and over 70% for metastatic disease. Nevertheless, studies have also shown that there are subtypes of Wilms' tumours that do not change in size in response to treatment despite good prognosis and more differentiated subtypes can also be resistant to chemotherapy even though the prognosis is good.[14,17,18] Furthermore, it has been observed that complete necrosis in the tumour mass remaining after chemotherapy, regardless of its size, is associated with good prognosis.[19] Similarly, intratumoural bleeding results in increased tumour size without compromising treatment outcome.

We limited our dataset to the largest group of patients with localised Wilms' tumour. Progression of the primary tumour occurred in only seven (3%) of the 215 patients with metastatic disease at diagnosis, and those patients were excluded from our study, because they received a different preoperative chemotherapy regimen. A higher percentage of CR/PR was seen in the primary of metastatic cases than in those with localised tumours (72% versus 42%), possibly due to an effect of the comparatively more intensive preoperative treatment lasting 6 weeks and with addition of epirubicin.

Early surgery before completion of preoperative chemotherapy was performed in two cases with progressive tumours. Both those patients had a peroperative rupture: one had a tumour with intermediate histopathological risk and is still alive; the other had a high risk tumour and relapsed and subsequently died of the disease. Lack of treatment response or tumour growth that could not be measured by the WHO criteria was the reason for early surgery in seven other cases. In all, peroperative rupture occurred in three (5.3%) of the 57 patients with tumour progression, which is slightly higher than the rate in the whole group receiving preoperative chemotherapy (2.8%).[12] A possible explanation for this is that their tumours were on average larger at the time of surgery compared to the tumours in the CR/PR and SD groups. One patient with a 'progressive' tumour had early surgery due to intratumoural bleeding, and such bleeding was also the reason for discontinuing preoperative chemotherapy in five other patients whose tumours could not be classified as PD according to the WHO criteria. It is not likely that an increase in tumour volume due to intratumoural bleeding can in itself be seen as a prognostic factor, because there is no evidence that bleeding will occur more frequently in high risk or advanced stage tumours. It seems that progression during chemotherapy did not lead to change or intensification of the recommended postoperative treatment, depending on the stage and risk group.

In conclusion, tumour progression during preoperative chemotherapy identified according to the WHO criteria is a new independent prognostic factor, which, together with other risk factors, defines a small group of high-risk patients. In our opinion, there is no reason to change the currently recommended preoperative regimen for these patients, unless early surgical intervention is deemed necessary due to aggressive growth or large size of tumours, or symptomatic intratumoural bleeding. Further analyses of progressive tumours are being conducted in the ongoing SIOP-2001 study, and the results will be used to suitably adjust the postoperative treatment for this group of patients. Our findings give additional evidence of the advantages of using a response-adapted approach in the treatment of patients with Wilms' tumour.

Conflict of interest statement

None declared.

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REFERENCES

1. Lemerle J, Voute PA, Tournade MF, et al. Preoperative versus postoperative radiotherapy, single versus multiple courses of actinomycin D, in the treatment of Wilms' tumor. Preliminary results of a controlled clinical trial conducted by the International Society of Paediatric Oncology (S.I.O.P.). *Cancer* 1976;**38**:47–654.
2. Lemerle J, Voute PA, Tournade MF, et al. Effectiveness of preoperative chemotherapy in Wilms' tumor: results of an International Society of Paediatric Oncology (SIOP) clinical trial. *J Clin Oncol* 1983;**1**:604–9.
3. Tournade MF, Com-Nougue C, Voute PA, et al. Results of the Sixth International Society of Pediatric Oncology Wilms' Tumor Trial and Study: a risk-adapted therapeutic approach in Wilms' tumor. *J Clin Oncol* 1993;**11**:1014–23.
4. Tournade MF, Com-Nougue C, de Kraker J, et al. Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms' tumor in children older than 6 months: results of the Ninth International Society of Pediatric Oncology Wilms' Tumor Trial and Study. *J Clin Oncol* 2001;**19**:488–500.
5. Green DM, D'Angio GJ, Beckwith JB, et al. Wilms tumor. *CA Cancer J Clin* 1996;**46**:46–63.
6. Neville HL, Ritchey ML. Wilms' tumor. Overview of National Wilms' Tumor Study Group results. *Urol Clin North Am* 2000;**27**:434–42.
7. Green DM. The treatment of stages I-IV favorable histology Wilms' tumor. *J Clin Oncol* 2004;**22**:1366–72.
8. Pritchard-Jones K, Pritchard J. Success of clinical trials in childhood Wilms' tumour around the world. *Lancet* 2004;**364**:1468–70.

9. Wu HY, Snyder III HM, D'Angio GJ. Wilms' tumor management. *Curr Opin Urol* 2005;**15**:273–6.
10. de Kraker J, Graf N, van Tinteren H, 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**: 1229–1235.
11. Vujanic GM, Sandstedt B, Harms D, Kelsey A, Leuschner I, de Kraker J. Revised International Society of Paediatric Oncology (SIOP) working classification of renal tumors of childhood. *Med Pediatr Oncol* 2002;**38**:79–82.
12. Godzinski J, Tournade MF, deKraker J, et al. Rarity of surgical complications after postchemotherapy nephrectomy for nephroblastoma. Experience of the International Society of Paediatric Oncology-Trial and Study "SIOP-9. International Society of Paediatric Oncology Nephroblastoma Trial and Study Committee. *Eur J Pediatr Surg* 1998;**8**:83–6.
13. Godzinski J, Weirich A, Tournade MF, et al. Primary nephrectomy for emergency: a rare event in the International Society of Paediatric Oncology Nephroblastoma Trial and Study no. 9. *Eur J Pediatr Surg* 2001;**11**:36–9.
14. Weirich A, Ludwig R, Graf N, et al. Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity. *Ann Oncol* 2004;**15**:808–20.
15. Bacci G, Longhi A, Versari M, Mercuri M, Briccoli A, Picci P. Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. *Cancer* 2006;**106**:1154–61.
16. Paulussen M, Ahrens S, Dunst J, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's Sarcoma Study CESS 86. *J Clin Oncol* 2001;**19**:1818–29.
17. Anderson J, Slater O, McHugh K, Duffy P, Pritchard J. Response without shrinkage in bilateral Wilms tumor: significance of rhabdomyomatous histology. *J Pediatr Hematol Oncol* 2002;**24**:31–4.
18. Maes P, DeLemarre J, de Kraker J, Ninane J. Fetal rhabdomyomatous nephroblastoma: a tumour of good prognosis but resistant to chemotherapy. *Eur J Cancer* 1999;**35**:1356–60.
19. Boccon-Gibod L, Rey A, Sandstedt B, et al. Complete necrosis induced by preoperative chemotherapy in Wilms tumor as an indicator of low risk: report of the international society of paediatric oncology (SIOP) nephroblastoma trial and study 9. *Med Pediatr Oncol* 2000;**34**:183–90.