

Outcomes of non-anaplastic stage III and ‘inoperable’ Wilms tumour treated in the UKW3 trial.

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Abstract (199 words)

Background and Purpose: To describe the outcome of patients with stage III Wilms tumours (WT) treated in the UKW3 trial.

Material and Methods: Patients with a pathologically confirmed stage III non-anaplastic WT at nephrectomy (Group A) or with an ‘inoperable’ tumour at diagnosis managed by biopsy and pre-operative chemotherapy (ActinomycinD-Vincristine-Doxorubicin) but stage I or II at subsequent nephrectomy (Group B) were included.

Results: The 4-year overall (OS)/event free survival (EFS) for Group A (n=117) patients was 90%(95%CI:83-94)/81%(CI:73-87) and for Group B (n=32) 94%(CI:77-98)/88%(CI:70-95). The 4-year OS/EFS of patients with pathological stage III WT according to whether they received flank/abdominal radiotherapy (95 patients) or not (37 patients, 22 from UKW3 pooled with 17 patients from UKW2) were 91%(CI:83-95)/82%(CI:73-89), and 84%(CI:67-92)/78%(CI:61-89), respectively. The 4-year OS/EFS for patients having one reason to be stage III versus two or three was 92%(CI:84-96)/83%(CI:73-90) and 85%(CI:70-93)/78%(CI:61-88), respectively.

Conclusion: Our findings question the inclusion of biopsy or pre-operative chemotherapy as sole criteria for assigning a tumour stage III. Selected patients with pathological stage III WT can survive without radiotherapy. Whilst cautious interpretation is needed due to the post hoc nature of these analyses, further biological studies may better characterize those who could benefit from reduced therapy.

Introduction (2981 words)

Postoperative treatment of Wilms tumour (WT) is stratified according to histology and tumour stage, with stage III tumours requiring a heavier burden of treatment, including doxorubicin and radiotherapy (RT) [1-5]. Stage III is defined by the spread of the disease beyond the limits of the kidney [6] but also by the use of biopsy. The International Society of Paediatric Oncology – Renal Tumour Study Group (SIOP-RTSG) allows fine-needle aspiration (FNA) and percutaneous cutting needle biopsy (PCNB) without affecting tumour stage while open biopsy makes a tumour stage III, regardless of the pathological findings at subsequent nephrectomy. In the last Children Oncology Group (COG) protocol, tumours that have been biopsied by any means are considered as stage III whatever the ultimate pathological stage at subsequent nephrectomy. In COG studies, patients with stage III do as well as patients with stage I or II whereas in SIOP studies, they fare worse though are proportionately less frequent [7-10].

For all stage III tumours, RT is usually limited to the flank except for abdominal tumour rupture that leads to a whole abdominal irradiation. The long-term side effects of RT include impaired bone and soft tissue growth, reduced fertility in females and increased risk of secondary tumours [11-15]. Hence, improved understanding of the characteristics of stage III WT that are associated with worse event free and overall survival is needed if further refinements to risk-adapted use of doxorubicin and RT are to be considered.

The UK Children's Cancer and Leukaemia Group conducted a national trial, UKW3, to compare the stage distribution for patients who had a unilateral WT deemed amenable to immediate surgery by the local surgeon based on clinical and imaging evaluation and who were randomised to either immediate nephrectomy or preoperative chemotherapy and delayed surgery [16]. If pre-operative chemotherapy was felt to be clinically advisable to reduce the

risks of surgery, the recommended chemotherapy regimen was according to the stage III regimen with pre and postoperative Actinomycin D, Vincristine and Doxorubicin (AVD) for one year regardless of the abdominal tumour stage found at nephrectomy. The timing of nephrectomy was left to the local team's discretion according to tumour response to chemotherapy, and flank RT was only indicated if the tumour specimen was stage III. The UKW3 trial also included routine PCNB at diagnosis for all tumours receiving pre-operative chemotherapy without upstaging the tumour. Hence, the UKW3 trial offers the unique opportunity to describe the outcome of children treated as stage III because their tumours met the criteria for 'inoperability' yet who did not receive flank RT because their tumours were pathological stage I or II at time of nephrectomy. We also describe the clinical parameters and survival of the children with pathological stage III tumours at time of nephrectomy that did not receive flank RT, despite this being the protocol recommendation.

Material and Methods

Patient selection

The patients eligible for the present analysis were all those registered in UKW3 trial (1991-2001) with previously untreated localised unilateral non-anaplastic WT "treatment stage III" [3]. "Treatment stage III" was assigned to patients treated with doxorubicin for 6–12 months and/or who also received flank RT regardless of whether their tumour at the time of nephrectomy was pathological stage III. This category included patients with 'inoperable' tumours at diagnosis treated with addition of doxorubicin. Criteria for 'inoperability' were IVC invasion determined by ultrasound or CT scan, very large tumours predicted to cause difficult access to the renal hilum or suspected high risk of rupture.

The patients excluded from the analysis were 'operable' patients with stages other than stage III at time of primary nephrectomy, metastatic patients, and patients with extra-renal WT as

the tumour cannot be staged in the same way as for an intra-renal tumour. Patients who did not have nephrectomy or who died at or very soon after nephrectomy and therefore never had time to receive RT were also excluded from the analysis (Figure 1).

Prospective data on patient and tumour demographics, treatment and outcome were collected on case report forms (CRF), with parent/guardian written informed consent.

Reasons for a tumour to be stage III at final pathological analysis of the specimen were as follow: tumoral involvement of lymph nodes (LN); clinical tumour rupture or spillage at diagnosis, during the preoperative chemotherapy period or during surgery; extension of the tumour to the surgical margins either micro- or macroscopically. This was stated either on the local pathology CRF or at the centralised pathology review. Presence of completely necrotic tumour in LN or at resection margins was ignored for staging purposes in this trial, unlike in the subsequent SIOPWT2001 trial. Analysed patients were then classified into two groups: those ultimately histological stage III (Group A), whether treated with immediate nephrectomy or pre-operative chemotherapy and whether they were randomised or not, and those treated according to the 'inoperable' tumour protocol who ultimately did not have a histological stage III tumour at delayed nephrectomy (Group B).

Statistical considerations

Event-free (EFS) and overall survival (OS) were estimated using Kaplan-Meier method. EFS was calculated from the date of the initial diagnosis to the date of relapse or death from any cause. OS was calculated from the date of the initial diagnosis to the date of death from any cause. Overall survival after a relapse was defined as the time from a first relapse to death. All patients who did not experience these events were censored at the time of their last follow up. Comparisons were made using the univariable Cox method and summarised using the hazard

ratio (HR) with the corresponding 95% confidence intervals (CI). The calculations were done using Stata version 10.0.

Due to the small number of patients from UKW3 that did not receive radiotherapy, in order to analyse outcomes, they were combined with seventeen similar patients who received no RT treatment from UKW2 trial [7].

Results

Among 842 patients with renal tumours registered onto UKW3 trial, 163 (19.4%) were non-anaplastic WT 'treatment stage III' patients (Figure 1) of whom 117 (71.8%) were pathological stage III (group A) and 32 (19.6%) were group B (22 stage I and 10 stage II). There were 14 exclusions from the analysis due to no nephrectomy (n=4), metastasis documented after initial registration (n=4), and missing pathological stage (n=6). The median follow-up for alive patients for group A and B were 9.22 and 6.57 years respectively.

Group A patients

Seventy-nine patients were staged III after immediate nephrectomy, and 38 were stage III after preoperative chemotherapy, of whom 36 (94.7%) had a biopsy (biopsy was not performed on two patients, one due to high risk of spillage and the other due to coagulopathy at diagnosis). Patients and tumour characteristics are given in Table 1. The median tumour diameter for this group of patients was 12 cm [1-20].

The 4-year EFS/OS were 81.2%(CI:72.9%-87.2%) and 89.7%(CI:82.6%-94.0%) respectively (Supplemental Figures 2A-3A).

16/117 (13.7%) patients died, 12 because of tumour and four of complications or toxicity (one case each of cardiac toxicity, cardiac arrest during operation, acute renal failure and massive

thrombus from IVC to right atrium) (Table 1). The last two recorded deaths were after 9.4 and 9.5 years of follow up respectively, both due to tumour.

Seventy-six patients had immediate nephrectomy (Table 2A). Another three patients were initially considered in the ‘inoperable at diagnosis’ category but the surgeon then proceeded to immediate nephrectomy during the biopsy procedure. Postoperative chemotherapy was given to 78 patients, one receiving VA and 77 AVD (Table 2A). For 70 patients treated with postoperative AVD and RT, 4-year EFS/OS were 88.6%(CI:78.4%-94.1%) and 91.4%(CI:81.8%-96.0%) respectively.

LN metastases were present in 51/117 (44%) patients (Table 3). The 4-year EFS and OS for the patients with and without LN metastases were 76.5%(CI:62.3%-85.9%)/84.3%(CI:71.1%-91.8%) and 85.2%(CI:72.6%-92.3%)/92.6%(CI:81.5%-97.2%) respectively (Supplemental Figures 2B-3B). However, the HRs for OS (2.28 (CI:0.78-6.67, p=0.13)) and EFS (1.84 (CI:0.76-4.45, p=0.17)) for the two groups were not significant.

In 72 patients (62%), tumour was regarded as stage III because of positive resection margins, including five patients with IVC thrombus, and one with renal vein thrombosis. Tumour rupture was documented in 42 patients (36%). Due to small group sizes, no formal comparisons were made of frequencies of reasons to be stage III between the two treatment approaches.

Of the three categories for being stage III, eight patients had tumours with all three reasons, 32 had two and 77 had just one reason. The 4-year OS for patients with one reason was 92.2%(CI:83.5%-96.4%) and for those with two or three reasons was 85.0%(CI:69.6%-93.0%) whilst the 4-year EFS was 83.1%(CI:72.7%-89.8%) and 77.5%(CI:61.2%-87.6%), respectively

(Supplemental Figures 2C-3C). There was no significant difference in OS and EFS for the patients who had just one reason versus two or three reasons.

Preoperative chemotherapy was given to 38 patients among whom 14 were classified as having localised operable and 24 as non-operable tumours. Preoperative drugs included V (n=3), VA (n=15) and AVD (n=20) (Table 2A). The median time to nephrectomy for this group of patients was 62 days [18-175]. Twenty-eight patients received AVD postoperatively (Table 2A). Two patients received additional drugs after surgery, VD-Cyclophosphamide and VA-Carboplatin. For one patient, the post-operative chemotherapy given was not recorded on the CRF. The patient who died after surgery due to postoperative bleeding did not receive postoperative chemotherapy.

Overall, 20/117 (17 %) group A patients relapsed. Their median age was 4.4 years [2.9 months-8.1 years]. Details of the treatments they received as first line therapy are given in table 4. Seventeen patients were given flank RT with a total dose of 16 Gy (n=1), 18 Gy (n=1), 20 Gy (n=13) and 30 Gy (n=2). The relapse sites included chest (n=10), abdomen (n=5), pelvis (n=1), maxillary sinus and skull with bone metastases (n=1) and remaining kidney (n=1). Two patients had relapses in both lung and liver. The longest recorded interval to the first relapse was 4.0 years (chest relapse). Thirteen relapsed patients died, 12 due to tumour. The 4-year survival for the patients after relapse was 50.0% (CI:27.1%-69.1%).

Group B patients

Group B comprised 32 patients deemed ‘inoperable’ at diagnosis who received elective preoperative chemotherapy followed by delayed nephrectomy and who subsequently had only a pathological stage I or II tumour at time of nephrectomy (Table 1). The median time from

diagnosis to nephrectomy was 63.5 days [21-160]. The median tumour diameter for this group of patients was 15 cm [8-18]. Chemotherapy was fully according to the protocol recommendations (AVD pre- and post-operatively) in 21 patients and a further three received doxorubicin only in the post-operative phase. Twenty-seven patients were not given RT, again in accordance with the protocol recommendations (Table 2B). The 4-year EFS/OS were 87.5%(CI:70.0%-95.1%) and 93.7%(CI:76.9%-98.4%) respectively.

In total four patients relapsed and two died, both due to tumour. The site of relapses included abdomen (n=3) and multiple relapses at lung and renal bed (n=1). Three had received AVD and one VA only. None had received RT as part of their initial treatment.

Use of radiotherapy in Group A patients (confirmed stage III pathologically)

Among the 95 Group A patients who received abdominal RT, 89 received flank RT, three patients were given whole abdominal RT and two received RT to LN only (Table 2A). For one patient, the RT field was not further specified. The dose of RT for 83 patients was 20 Gy, including 77 who received flank RT, three who received RT to the whole abdomen area, two who received RT to LN only and for one patient the type of RT was not specified. Another six patients received 30 Gy of flank RT, and each of the other five patients was given 14.4/15/16/18/28 Gy. For one patient, the dose was unknown.

22/117 (19%) Group A patients did not receive RT to the abdomen, in contradiction to the protocol recommendations. The median age at diagnosis for patients in UKW3 trial with pathological confirmed stage III tumour who did not receive RT was younger (2.5 years, [0.23 months-10.5 years]) than those who did (4.01 years, [1.07-11.8]) (p = 0.015). **Sixteen patients from the UKW2 trial that did not have radiotherapy received AVD and one patient received VA.** Twelve patients were treated with immediate nephrectomy and five had delayed

nephrectomy. Two of the UKW3 trial patients died during or shortly after surgery and therefore RT treatment was never given. These patients were not included in the survival calculations. The 4-year EFS/OS for the patients who were treated with RT versus those without RT were 82.1%(CI:72.8%-88.5%)/90.5%(CI:82.5%-94.9%) and 78.4%(CI:61.4%-88.6%)/83.8%(CI:67.4%-92.4%) respectively.

Discussion

This retrospective analysis of patients registered onto UKW3 trial provides important clinical observational experience on survival of patients with non-anaplastic WT ‘treatment stage III’, that is relevant to risk stratification across the entire spectrum of treatment strategies used internationally.

The prevalence of 26% (163/616) stage III as a percentage of all localised non-anaplastic WT was comparable to those found in other national published series (14.4% in German Paediatric Oncology and Haematology Society (GPOH), 19.2% for the Italians and 24.2% in National WT Study (NWTS) 5) [8-9, 16]. The 4-year OS/EFS for patients with pathological stage III tumours at nephrectomy were similar to other contemporaneous published series [8-9, 17].

Indeed, for the 70 patients in Group A, who were treated according to the full protocol recommendations, their 4-year EFS/OS equal those reported in the NWTS 5 (8-year EFS/OS of 82%/91% respectively), the COG AREN0532 (4-year EFS/OS of 88%/97%) and SIOP 93-01 (5-year EFS/OS of 84.3%/91.5% respectively) trials. Our study was not powered to test if there were differences in survival between patients who were treated with preoperative chemotherapy prior to planned delayed nephrectomy versus those who were treated with immediate nephrectomy.

Patients whose tumours had just one reason versus two or three reasons to be stage III had numerically higher OS and EFS in our study but the hazard ratios did not reach statistical

significance. Similarly, the impact of positive LN as a reason to be stage III was associated with numerically worse EFS and OS that again did not reach statistical significance, due to small numbers of patients and events. These data are consistent with published data from larger series that did show a significant impact of positive LN and increased numbers of reasons to be stage III with adverse survival. **Positive LN showed a significant impact on EFS but not on OS in the GPOH paper (EFS 70% versus 86% for those patients with or without positive LN respectively, $p=0.006$) [7] whilst for the NWTSS5 patients, EFS and OS were less favourable for those with LN involvement without reaching statistical significance.** By contrast, multivariate analysis demonstrated that combining both LN involvement and microscopic residual disease was most predictive of adverse EFS (69% when both factors are positive versus 91% when both are negative, $p=0.004$) [9]. However, local relapse did not seem to be associated with the subtype of stage III. The Italian group was the only national group showing a significant negative impact of LN involvement alone on both EFS and OS [17]. They also proposed a new sub classification of stage III patients based on outcome, those having only microscopic residual disease faring better than those with macroscopic residual tumour than those with LN involvement (4-year EFS of 94% versus 86% versus 73% respectively, $p=0.04$) [17].

All these data suggest that it should be possible, perhaps purely on clinical grounds, to distinguish a specific sub-group of stage III tumours potentially requiring a lower burden of treatment. It is clinically intuitive that stage III tumours represent different biological entities, e.g. large fragile tumours that can easily rupture for mechanical reasons versus those that have invaded adjacent structures and are therefore more difficult to remove (surgical expertise as well as biological reason) versus those that have metastasised to regional LN (adverse biology). The last recent published analysis of stage III patients involved in the AREN0532 trial showed a high predictive value of combined LN and allele loss status of 1p and 16q [18].

In clinical practice, some patients are selected on an ad hoc basis not to receive flank or abdominal RT for a pathologically proven stage III tumour. Our data show that omission of RT does not necessarily impact on survival, but this is based on small numbers of patients and events [19]. Clinical trials executed in countries that lack RT facilities have shown that some stage III WT can achieve long-term survival without RT [20-21].

In our study the observed outcome of the patients who were deemed 'inoperable' at diagnosis but who ultimately did not have a stage III tumour after usually fairly prolonged AVD was very good, despite no abdominal RT and larger tumours at diagnosis. It is already known that patients having upfront surgery have significantly lower tumour size than the 'inoperable' patients having delayed nephrectomy [22]. These good outcome data call into question the practice of including biopsy and/or pre-operative chemotherapy as the sole reasons to upstage a tumour to stage III, with the consequences for radiotherapy and overtreatment.

This retrospective study of patients with non-anaplastic 'treatment stage III' WT demonstrated survival rates commensurate with contemporaneous trials and a trend toward a worse outcome for patients with LN involvement or more than one reason to be stage III. However, the small number of events precluded demonstrating any significant difference in survival according to reasons for stage III. In this trial, where biopsy and pre-operative chemotherapy did not upstage tumours to stage III as a sole reason, both EFS and OS were very good, calling into question the need to use these two factors in staging schemes applied in countries where immediate nephrectomy is the usual approach. Selected patients with pathological stage III WT can survive without radiotherapy. Whilst cautious interpretation is needed due to the post hoc nature of these analyses, these mature clinical outcomes linked to detailed treatment data should stimulate further biological studies of stage III tumours to better characterize which could be treated with reduced therapy.

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Figures Legends

Figure 1. Consort statement.

Supplemental Figure 2. OS Kaplan-Meier survival estimates according to various clinical parameters (A) Group A patients, (B) lymph node metastases among Group A patients, (C) reasons to be stage III among Group A patients.

Supplemental Figure 3. EFS Kaplan-Meier survival estimates according to various clinical parameters (A) Group A patients, (B) lymph node metastases among Group A patients, (C) reasons to be stage III among Group A patients.