Published in final edited form as:

Pediatr Blood Cancer. 2019 January ; 66(1): e27430. doi:10.1002/pbc.27430.

Outcome of Wilms Tumor patients with bone metastasis enrolled on National Wilms Tumor Studies 1-5: A report from the Children's Oncology Group.

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Abstract

BACKGROUND: Wilms tumor (WT) is the most common renal tumor in children. We describe the outcomes for patients with WT that metastasized to bone (WTBM) to assist in decision-making for these uncommon patients.

PROCEDURE: We retrospectively reviewed the research records of patients identified with WTBM from the National Wilms Tumor Study (NWTS 1–5) database. We then related overall survival to histology, chemotherapy, radiation therapy to bone, location of metastasis, and when bone metastasis presented.

RESULTS: Thirty-eight of 8609 patients enrolled on NWTS 1–5 (0.44%) developed bone metastasis. Bone metastasis most commonly first occurred at progression or relapse (29/38, 76%). Five of thirty-eight survived (13%) with the 5-year overall survival following presentation of bone metastasis of 14.3% (95% CI: 2.7–25.8%). The primary cause of death was tumor (29/33, 88%). Of those who died, the median survival time was 10.9 months (range 0.49–61.4). Four of nine (44%) patients presenting at diagnosis and 3% (1/29) of patients presenting in progression or relapse survived ($p=0.0075$). Nineteen percent (5/26) of patients with favorable histology and 0% (0/12) with anaplastic histology survived ($p=0.16$). Of the 5 survivors, median follow up was 14 years (range 6.7–23.8). Radiation to metastatic bone sites was used in 3 of 5 survivors. No consistent chemotherapeutic approach appeared to be associated with disease outcome.

CONCLUSION: Bone metastasis is rare in patients with WT, occurring more commonly in progression or relapse than at initial diagnosis. Patients with WTBM have poor prognosis. We could not identify a consistent chemotherapeutic strategy associated with survival.

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Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

This work has been presented at the American Society of Pediatric Hematology/Oncology Annual Meeting (April 26th – April 29th 2017, Montreal Canada) and Dalhousie's Research in Medicine Research Day (April 8th 2017, Halifax Canada)

Keywords

Wilms Tumor; Metastasis; Oncology; Chart Review; Tumors; bone

INTRODUCTION

Wilms tumor (WT or nephroblastoma) is the most common renal tumor in children and the fourth most common childhood malignancy.^{1–4} Approximately 650 children are diagnosed with the malignancy each year in North America and over 80% of these cases (an incidence of 15–17 cases per million) occur before 5 years of age.^{1,4} The 5-year survival of favorable histology Wilms tumor has remained above 90% since the 1980s.⁵ As bone metastases are rare, there is a paucity of guidance in the literature as to optimal strategies and outcomes in these patients.

Few studies have been published on Wilms tumor with bone metastasis (WTBM).^{6,7} Marsden *et al.* used data from the Oxford survey of Childhood Cancer, recorded between 1953 and 1973, to determine that the prevalence of bone metastasis (out of 1368 patients) was 1.3% with no reported survivors.⁶ WTBM was found to present most commonly in the spine. The authors characterized the demographics and survival of WTBM and compared it to clear cell sarcoma of the kidney (CCSK).⁶ Prognostic factors were not investigated as there were no survivors. Ultimately, Marsden *et al.* determined that CCSK metastasizes to bone far more often than WT.⁶ Bond and Martin performed a similar study on 81 patients with WT and combined their data with that from case series from the literature (published between 1966 and 1975, with patients from Europe and America) to total 1267 patients with WT where 45 developed BM (3.5%).⁷ Of the 45 patients, there was only 1 survivor.⁷ Aside from these two older studies, recent publications have been restricted to individual or small number case reports.^{8–11} Watanabe *et al.*, reported successful treatment of WTBM using chemotherapy and radiation therapy according to the DD4A regimen recommended by NWTSG for stage IV WT.¹⁰ Although current strategies for relapsed tumor include either intensified chemotherapy and/or autologous bone marrow transplant,¹² there is no consensus treatment approach specific to WTBM.

Large clinical trial groups such as NWTSG, SIOP and the UKCCSG have all contributed to an enhanced understanding of prognostic factors and treatment in Wilms tumor.^{13–15} Prognostic features include stage, tumor weight, histology at baseline and following pre-operative chemotherapy,¹⁶ and genetic markers such as 1q gain and Loss of Heterozygosity at 1p and 16q.^{17,18} The most common sites of metastasis in stage IV WT patients are the lung followed by the liver.^{13,16,19} Other sites are rare, but bone and brain have been reported, more often at relapse rather than at primary diagnosis.^{13,16,20} A recent review suggests that a combination of radiation therapy and chemotherapy is essential in the management of brain metastases in Wilms tumor.²¹ Due to the low frequency of WT metastasizing to bone, no studies have descriptively related this type of metastasis to other clinical factors or described management. Herein, we describe the outcomes for patients with bone metastases enrolled on National Wilms Tumor Studies 1–5 to assist clinicians in decision-making for these uncommon patients.

METHODS

All patients or their guardians enrolled on NWTs trials provided consent for collection of clinical treatment and outcome data. The IWK Health Centre research ethics board provided approval for this retrospective review of study data.

Study Design

NWTs has maintained a detailed clinical research registry of all renal tumor patients enrolled on 5 successive studies since 1969. Chemotherapy and radiotherapy regimens varied over the course of the five NWTs studies and have been previously published.^{13,16,19,22–24} Clinical details at diagnosis and information on treatment outcome were reported on checklists, narratives and flow sheets submitted by the pediatric oncologist, surgeon and pathologist involved in the actual care of the patient. Long-term follow-up was incorporated into the studies or patients were enrolled on a companion long-term follow-up study.

A review of the research records was conducted on patients coded with a diagnosis of Wilms tumor and bone metastasis in the NWTs database (NWTs 1–5). Only cases of Wilms tumor were included for this study; all other renal tumors, such as rhabdoid tumors, renal cell carcinoma, and clear cell sarcoma of the kidney, were excluded.

Data was abstracted from electronic research records by one reviewer, then a random sample of 5 cases in addition to all surviving cases were independently verified by a second reviewer. Records were reviewed for general information such as the NWTs study, and year of diagnosis. Demographics and clinical characteristics including gender, ethnicity, race, pattern of metastasis (axial, appendicular, or both), number of bone metastases when WTBM was first noticed, family history of WT, presenting symptoms, location(s) of bone metastasis, age at diagnosis, and presenting stage (local and overall renal tumor stage) were abstracted from the research records. Pattern of metastasis was defined as either axial, appendicular, or both. Date at diagnosis was defined as the date of primary surgical tumor resection or original biopsy. Bone metastasis was categorized into two different points of initial presentation: at diagnosis or in progression/relapse. Diagnosis of bone metastasis was established based on clinical presentation combined with imaging (x-ray, CT, MRI, bone scan), and/or tissue biopsy. Surgical details including initial surgical approach to renal tumor (biopsy versus nephrectomy), biopsy method (closed or open needle), if the tumor was resected in one piece, and whether there was tumor rupture, spill reported, positive margins, or peritoneal implants were collected. Treatment information including chemotherapeutic regimen, surgical approach to bone metastasis (if any), site(s) of irradiation and dose, chemotherapy details at relapse, and morbidity of local control strategies for bone metastasis was collected. Lastly, disease specific details including site(s) of other metastasis, histology (favorable and anaplastic, all diagnosed pre-chemotherapy), relapse, all dates of relapse, site(s) of relapse, serious adverse events, survival, second malignancy, and cause/date of death (if applicable) were abstracted from the research record. Favorable histology included any WT histology that was not focal/diffuse anaplastic.

Statistical Analysis

We calculated the overall survival (OS) following presentation of bone metastasis (at diagnosis or at disease progression/relapse) until death or time of last contact. The Kaplan-Meier method was used to draw the OS curve. Survival rates were compared using the Fisher's Exact test. Percentages and counts were reported to describe the clinical variables including histology, highest radiation dose to bone, chemotherapeutic regimen, timing of bone metastasis (at diagnosis or progression/relapse), and pattern of bone metastasis.

RESULTS

Bone metastasis occurred in 38/8,609 (0.44%) patients with WT enrolled on NWTS 1–5. Three, four, five, sixteen and ten of these cases occurred in NWTS 1, 2, 3, 4, and 5, respectively. Cohort demographics are summarized in Table 1. This table also describes whether bone metastasis was present at diagnosis or in progression/relapse. The median age at diagnosis of WT in the study cohort was 65 months (range 24 – 247), 42% of patients were male, and 82% were white - reflecting the expected variance of race in the study population. Bone metastasis most commonly occurred in progression/relapse (29/38, 76% of patients). Diagnosis of bone metastasis was made by biopsy in 50% (19/38) of cases, imaging (i.e. x-ray, CT, MRI) in 29% (11/38) of cases, bone scintigraphy in 13% (5/38) of cases, and was unclear in 8% (3/38) of cases. The vast majority of patients with bone metastasis had advanced disease, 36/38 patients with WTBM also had metastases to other sites (e.g. lung, liver, brain, mediastinum). Figure 1 displays the Kaplan-Meier OS curve of the patients on study. Mean time to first relapse was 24.1 months.

In Table 2, we present survival statistics overall and as a function of when BM presented, WT histology, highest dose of radiation to bone, and pattern of metastasis. Overall, 13% (5/38) of patients with WTBM survived. The vast majority of deaths were related to progressive tumor (29/33, 88%); four deaths were caused by tumor and toxicity. Of those who died, the median survival following presentation of bone metastasis was 10.9 months (range 0.49 to 61.4 months). Four of nine (44%) patients with bone metastasis presenting at diagnosis and 3% (1/29) in progression or relapse survived ($p=0.0075$). Nineteen percent (5/26) of patients with favorable histology and 0% (0/12) with anaplastic histology survived ($p=0.16$).

Since multiple doses of radiation are often given over the course of treatment for patients with WTBM, only the highest dose of radiation given to bone was used to classify patients into three categories: 0–2,000, 2,001–3,000, and >3,000 cGy (Table 2). Twenty percent (3/15) of patients with only axial bone metastasis, 0% (0/9) with only appendicular metastasis, and 14% (2/14) with both axial and appendicular metastases survived. Ten percent (3/29) of patients with one bone metastasis, 17% (1/6) with two bone metastases, and 33% (1/3) with 3 or more bone metastases when bone metastases were first identified survived.

In Table 3 we present the relevant characteristics of the 5 survivors on study. In this group, median follow-up was 14 years (range 6.7 to 23.8 years); the one surviving male (diagnosed at relapse) was still living with disease at last follow-up. Local tumor stage in 4 of 5

survivors was 3, and 4 of 5 survivors had BM at diagnosis of WT. Radiation was used in 3 of 5 survivors. All survivors were registered on either NWTS 4 or 5. Overall, 19% (5/26) of patients on NWTS 4 and 5 with WTBM survived, and no patients with WTBM (0/12) survived if registered on NWTS 1–3. Chemotherapeutic approach was extracted from the research records for all patients; however, no chemotherapeutic regimen consistently appeared to be associated with a better disease outcome.

DISCUSSION

This study sought to describe the clinical characteristics for patients with WTBM to inform physicians regarding optimal treatment strategies. Thirty-eight patients with WTBM were identified out of 8609 patients in the NWTS database. This prevalence (0.44%) differs from the prevalence rates of 1.3% and 3.5% reported in the studies by Marsden et al. and Bond et al., respectively.^{6,7} A portion of the cases classified as WT in the study by Bond et al. were later shown to be CCSK. Therefore, some discrepancy can be accounted for by advancement in pathological interpretation. Other differences in prevalence could be explained by population variation, ascertainment bias or sample size, and advances in detection.

Our study showed that WTBM is associated with poor prognosis, with only a 13% survival rate. In comparison, the overall survival of stage 4 WT taking into account both favorable and unfavorable histology is at most 73%, as estimated from previously published data.^{13,16,17,19,22,24} As shown in Table 1, 76% (29/38 patients) of patients enrolled presented with WTBM at relapse or progression. Often, these patients had advanced disease at this point with several metastatic sites. Patients with WTBM at relapse or progression (1/29 survivors) appeared to have worse outcomes than patients with bone metastasis at initial diagnosis (4/9). This result may be due to the lower likelihood of chemotherapy-resistant tumor cells in WTBM presenting at diagnosis than at relapse.

Although the prognosis for WTBM is poor, it seems that survival has improved over time. Two previous studies that investigated WTBM observed a survival rate of 0% and 2.2% out of 18 and 45 patients, respectively.^{6,7} In this patient cohort, survival was 0% in patients enrolled on NWTS 1–3 and 19% in patients enrolled on NWTS 4–5.

The rarity of WTBM and its poor survival makes it difficult to draw conclusions about prognostic factors, but some clinical observations could be deduced. Histology appeared to be a strong predictor of survival in WTBM. In accordance with previous studies, anaplastic histology worsened prognosis.³ Thirty-two percent (12/38) of patients with WTBM presented with anaplastic histology. This proportion is several times higher than the prevalence of anaplasia in patients with WT (6–10%).^{25–27} No patients with anaplasia and WTBM (0/12) survived. This low survival is in line with published literature as the 10 year overall survival of stage IV anaplastic WT is only 33%.²² Therefore, the high rate of anaplasia likely played a role in the very poor outcome of patients with WTBM. Favorable histology WTBM was associated with a better prognosis, having a 19% (5/26) rate of survival. This remains inferior to the recently reported estimated overall survival outcomes for both favorable histology stage IV WT (85%) or relapse (approximately 50%).^{12,17}

Pattern of bone metastasis, dose of radiation to the bone metastasis, number of bone metastases when first noticed, and chemotherapeutic regimen did not appear to be related to survival. We observed that no patients (0/9) survived with appendicular BM while 20% (3/15) survived with axial metastasis. This difference did not appear meaningful as 14% (2/14) of patients with both appendicular and axial metastasis survived. Similarly, survival did not appear to have any relation to radiation dose to bone, as survivors were split between the lowest (0–2000 cGy) and highest (>3000 cGy) doses. We report the number of initial bone lesions by one, two, or more than two, but the numbers are too small to be meaningfully examined with respect to survival. Lastly, no NWTS chemotherapeutic approach consistently demonstrated better outcomes in patients with WTBM.^{12,22} Until more definitive evidence emerges, clinicians may consider the therapeutic approaches used in recently closed Children's Oncology Group (COG) studies: Regimen M for patients with FH and Regimen UH-1 for patients with anaplastic histology. Although radiation was not always recorded as being given to survivors, WT is sensitive to radiation and thus delivery of bone metastasis radiation would appear prudent in this higher risk situation. Patients with relapsed disease may be considered for experimental therapies and novel local control strategies such as cryoablation or radiofrequency ablation.^{3,28,29}

As this was a retrospective chart review, the study had several limitations. These include: long interval of data collection (5 decades), varying stringency of reporting in the research records, and varying therapeutic protocols across institutions and over time. Method of WTBM diagnosis presents another study limitation. Regardless of imaging modality sensitivity, tissue biopsy remains the gold standard of WT diagnosis. In 50% of cases on study, methods other than biopsy were used to establish a diagnosis of bone metastasis. While x-ray, CT, and MRI have a high specificity for diagnosing bone metastasis, bone scintigraphy has a low specificity and was used as the sole diagnostic means in 5 cases.³⁰ In the 3 cases where method of WTBM diagnosis was unclear, location was clearly documented. Strengths include the relatively large size of this very rare population, and central review of all cases, augmenting consistency in classification and pathological diagnostic expertise. Additionally, while the data were abstracted by one reviewer, a random sample of 5 cases and all 5 surviving cases were verified by a second reviewer.

Wilms tumor with bone metastasis was found to be a rare clinical presentation of WT predicting a very poor prognosis. Presentation of bone metastasis at progression or relapse, and anaplastic histology are the strongest predictors of poor prognosis, while radiation dose to bone, pattern of metastasis, number of bone metastases when first noticed, and chemotherapeutic regimen did not appear to be associated with prognosis. From this work, clinicians confronted with this uncommon presentation can provide families with prognostic information. Continued investigation as to the optimal management of this poor prognosis clinical situation is warranted.

Acknowledgements

The authors would like to acknowledge Dalhousie Medical School for project funding, the NWTS for documenting and reviewing thousands of Wilms Tumor cases, and the patients and families who consented to participation in these studies. We would also like to acknowledge Dr. Dan D'Angio, Dr. Daniel Green, and Dr. Paul Grundy who

were chairs of the successive NWTs studies and to the many investigators who contributed review and patient data to these studies.

Supported by grants from the National Institutes of Health to the National Wilms Tumor Study Group (CA-42326), the National Wilms Tumor Study Group Late Effects Study (CA-54498), and to the Children's Oncology Group (U10CA180886, U10CA180899, U10CA098543). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Also supported by St. Baldrick's Foundation.

Abbreviations

CCSK	Clear Cell Sarcoma of the Kidney
COG	Children's Oncology Group
NWTS	National Wilms Tumor Study
NWTSG	National Wilms Tumor Study Group
OS	Overall Survival
SIOP	International Society of Pediatric Oncology
WT	Wilms Tumor
WTBM	Wilms with Bone Metastasis
UKCCSG	United Kingdom Children's Cancer Study Group

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Figure 1.
Kaplan-Meier overall survival curve of the 38 patients with Wilm's tumor and bone metastasis on study.

Table 1.

Demographics of patients identified with Wilms tumor with bone metastasis on NWTS 1–5 overall and as a function of when bone metastasis presented.

Variable	Overall / Number	When Bone Metastasis Presented	
		Diagnosis	Progression/Relapse
No. of Patients	38	9	29
Male	16	1	15
Age at Diagnosis (months)			
Median	65	113	80
Range	24 – 247	42 – 247	24 – 215
Race			
White	31	9	22
Black	4	0	4
Hispanic	2	0	2
Other	1	0	1
Mean Time to First Relapse (months)	24.1	15.6 (n=1)	24.5 (n=20)

Table 2.

Characteristics of patients identified with Wilms tumor with bone metastasis on NWTs 1–5.

Variable	Count (%)	Number of survivors (%)	Range in survival time (days)	Number of anaplastic patients (%)
Overall	38	5 (13%)	15 – 8711	12 (32%)
When BM Presented				
Diagnosis	9 (24%)	4 (44%)	39 – 8711	2 (22%)
Progression/Relapse	29 (76%)	1 (3%)	15 – 1868	10 (35%)
Histology				
Favorable	26 (68%)	5 (19%)	39 – 8711	0 (0%)
Anaplastic	12 (32%)	0 (0%)	15 – 865	12 (100%)
Radiation (n = 30)				
0 – 2000 cGy	14 (47%)	2 (14%)	15 – 8711	5 (36%)
2001– 3000 cGy	6 (20%)	0 (0%)	71 – 1868	2 (33%)
>3000 cGy	10 (33%)	3 (30%)	81 – 7960	2 (20%)
Pattern of Metastasis				
Axial	15 (39%)	3 (20%)	15 – 918	5 (33%)
Appendicular	9 (24%)	0 (0%)	54 – 7960	2 (22%)
Both	14 (37%)	2 (14%)	39 – 8711	5 (36%)
Number of Bone Metastases when First Noticed				
One	29 (76%)	3 (10%)	54 – 7960	10 (34%)
Two	6 (17%)	1 (17%)	15 – 8711	2 (33%)
Three or More	3 (8%)	1 (33%)	39 – 2461	0 (0%)

* Range of survival time/last contact following identification of bone metastasis.

Table 3.

Characteristics of patients with bone metastasis who survived on NWTS 1–5.

NWTS Study	Age at Dx / months	Histology	Overall Stage	Local Stage	When BM Presented	Location(s) of BM	Chemotherapy	XRT to BM / cGy
4	66	Favorable	5	3	Diagnosis	Both **	DD	0
4	41	Favorable	4	3	Diagnosis	Axial	DD4A	3030
4	54	Favorable	4	3	Diagnosis	Axial	DD	0
5	139	Favorable	4	3	Diagnosis	Both **	DD4A	5070
5	75	Favorable	5	2	Relapse	Axial	Multiple	5940

* Indicates patient was still living with disease at last follow-up.

** Both - axial and appendicular

Dx - diagnosis, BM - bone metastasis, XRT - radiation therapy, cGy - centigray

DD: vincristine/standard, dactinomycin, doxorubicin/radiation therapy

DD4A: vincristine/pulse intensive dactinomycin, and doxorubicin/radiation therapy