

Chapter 2

The Clinical Relevance of Age at Presentation in Nephroblastoma

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Abstract

The most important prognostic factors for Wilms tumor (WT) patients seem to be stage, histological subtype, and 1p/16q loss of heterozygosity (LOH) in chemotherapy-naive WTs.

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Over the last decade, age at diagnosis also was suggested to be an important risk factor for WT recurrence in Children's Oncology Group (COG), United Kingdom (UK), and International Society of Pediatric Oncology (SIOP) studies. Several studies have analyzed age as a prognostic factor; these studies revealed age <2 years as a favorable prognostic factor, while age >4 years has been described as an adverse prognostic factor. In adults (>18 years of age), WT represents less than 1% of all diagnosed renal tumors; therefore, diagnosis of WT in adults is often unexpected and poorly recognized, thereby inducing treatment delay with subsequent adverse outcome. One explanation for the higher risk of recurrence with increasing patient age is the higher frequency of anaplasia at higher age. Other suggested reasons are delay in diagnosis, advanced tumor stage at presentation, and intrinsically different biological behaviors. Whether age is really an *independent* risk factor, and whether age is a stronger prognostic factor than stage, histology, and LOH 1p/16q, needs to be further explored. This may provide some insight into whether older patients need to be treated more intensively, as is already advised for adult WT patients.

Key words: Age; Prognostic factor; Wilms tumor

Introduction

Wilms tumor (WT) is the most common type of childhood renal cancer. It affects approximately one child per 10,000 worldwide before the age of 15 years (1). The median age at diagnosis of WT is approximately 3.5 years (1). The two treatment approaches (European and North America) available for children with WT result in comparable overall survival rates, currently reaching 90%. The International Society of Pediatric Oncology (SIOP) in Europe advocates chemotherapy before nephrectomy, whereas the Children's Oncology Group (COG) in North America recommends immediate surgery (2).

The most important prognostic factors for WT patients seem to be stage, histological anaplastic subtype and blastemal subtype (the latter in chemotherapy-pretreated nephroblastoma cases only), and 1p/16q loss of heterozygosity (LOH) in chemotherapy-naive WTs (3–5). Tumor stage is the original prognostic factor for WT, while tumor histology is perhaps the most powerful prognostic factor for WT; (diffuse) anaplasia is associated with adverse outcome in both the COG and SIOP histologic classification systems, while the adverse prognostic effect of residual blastemal cells after pre-operative chemotherapy is only recognized in the SIOP classification system (4, 5). LOH of 1p/16q is found in around 5% of favorable-histology WTs, and it has been demonstrated to be significantly correlated with less favorable outcome (3).

Over the last decade, age at diagnosis also was suggested to be an important risk factor for WT recurrence in COG, UK (United Kingdom), and SIOP studies (6–9).

The clinical relevance of age

General

Cooperative studies have shown that increasing age is associated with an increased risk of recurrence of nonmetastatic WT (6, 7, 9–11). This is only partly explained by the fact that the occurrence of anaplasia increases with age (12); even in patients with favorable histology, older age seems to be associated with less favorable outcome. It still needs to be determined what the exact age threshold is at which outcome starts to deteriorate.

Infants

The “chemotherapy before surgery strategy” has been under debate internationally for years. SIOP protocols recommend to treat patients >6 months with preoperative chemotherapy; this has the clear evidence-based benefit of downstaging tumors, thereby sparing survivors the late effects of doxorubicin or radiotherapy (14). However, in young infants, the so-called non-WTs tend to occur up to a substantial proportion in the younger age group (13). This initiated a study on all renal tumors in infants (under the age of 7 months at presentation) on a global level, based on data in 750 children, treated in UK, COG, and SIOP protocols, showing that above 2 months of age at presentation, WT is the most common tumor type, while congenital mesoblastic nephroma occurred more often than WT under the age of 3 months at presentation (Figure 1) (13). In addition, the biologically more aggressive malignant rhabdoid tumor of the kidney has a high propensity in this young age group. This has forced

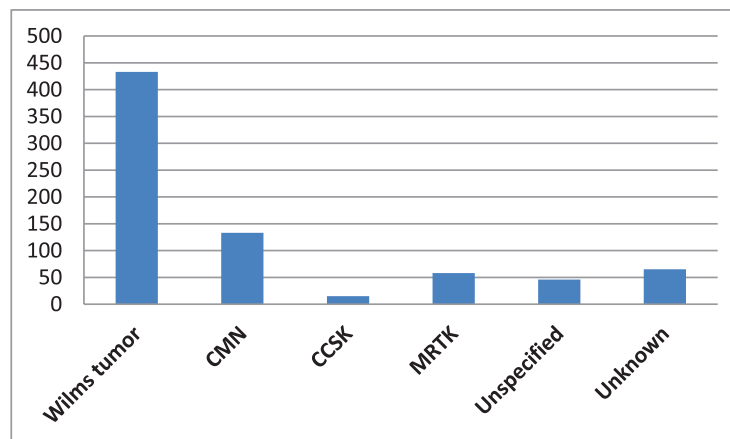


Figure 1. Distribution of renal tumors in children aged 7 months or less (13). CMN: congenital mesoblastic nephroma; CCSK: clear cell sarcoma of the kidney; MRTK: malignant rhabdoid tumor of the kidney.

an international recommendation to, even in the SIOP community, immediately perform surgery instead of pre-operative chemotherapy in these young children with renal tumors.

Survival rates for WT patients below the age of 7 months are very good (5-year overall survival 93.4%). In addition, the incidence of metastatic WT in this age group is very low (<1%) (13).

Children >6 months of age

Several studies have analyzed age as a prognostic factor (Table 1). These studies revealed age <2 years as a favorable prognostic factor, while age >4 years has been described as an adverse prognostic factor. One study specifically addressed the adverse outcome in teenagers (10–16 years of age) (15).

Currently, age is already incorporated into the risk stratification of COG studies (AREN0532); it is predicted that children under the age of 2 years with small tumors (<550 g) and stage I favorable-histology WTs can benefit from surgical treatment only (nephrectomy alone without adjuvant chemotherapy). As stage and histology are considered to be stronger prognostic markers, age is not used for risk stratification in the SIOP trials.

Adults

In adults (>18 years of age), WT represents less than 1% of all diagnosed renal tumors (17–22). The most common type of adult renal cancer is renal cell carcinoma (approximately 85%); therefore, diagnosis of WT in adults is often unexpected and poorly recognized, thereby inducing treatment delay with subsequent adverse outcome (23). This treatment delay, rather than more aggressive biology seems to determine the worse outcome in adults with WT as compared to in children (17–22, 24, 25). More recent data indicate the potential for improvement in adults when pediatric treatment approaches, including multimodality chemo- and radiotherapy adapted from the pediatric treatment protocols, are used (18, 19, 21, 22, 24, 25).

Multiple factors, including the unfamiliarity of adult oncologists with WT, lack of standardized treatment, delay in initiating the appropriate therapy and also a possible more biologically aggressive tumor type, may contribute to poor outcome (22).

This prompted several representatives of the renal tumor committees of the COG and the SIOP to develop, together with adult urologists, medical oncologists, and radiotherapists, a consensus “best practice” guideline for the management of WT in adults (26). The aim of this international consensus recommendation is to further improve outcome by shortening adjuvant treatment delay and by using standardized treatment (26).

Age in correlation with other prognostic factors

One explanation for the higher risk of recurrence with increasing patient age is the higher frequency of anaplasia at higher age. Anaplasia is only very rarely seen in WT diagnosed

Table 1. Age as a prognostic factor

Report	Study	Result	Multivariate analysis	Outcome measures
Green et al. (JCO 1993) (6)	NWTS1, NWTS2, NWTS3	Age <2 y as favorable prognostic factor in small (<550 g) stage I favorable-histology tumors	Not performed	4 y EFS
Pession et al. (EJC 2008) (16)	AIEOP 1989–1998	Age ≤2 y as favorable prognostic factor	Age <i>not</i> an independent prognostic factor	OS
Pritchard-Jones et al. (JCO 2003) (7)	UKW2, UKW3	Age >4 y as adverse prognostic factor in stage I favorable-histology tumors	Age an independent prognostic factor	4 y EFS and OS
Irtan et al. (EJC 2015) (10)	UKW3	Age >4 y as adverse prognostic factor	Age an independent prognostic factor	EFS
Shamberger et al. (Ann Surg 1999) (9)	NWTS4	Age >4 y as adverse prognostic factor	Age <i>not</i> an independent prognostic factor	EFS
Reinhard et al. (Oncol Rep 2008) (8)	SIOP-GPOH 1989–2003	Age >4 y as adverse prognostic factor	Age <i>not</i> an independent prognostic factor	OS
Breslow et al. (Cancer 1991) (11)	NWTS3	Age 0–23 m, 5.4% relapse; age 24–47 m, 9.5% relapse; age 48+ m, 16.3% relapse	Not performed	EFS
Popov et al. (Ped and Dev Pathology 2011) (15)	UKW3, SIOP 2001	Age 10–16 y as adverse prognostic factor	Not performed	5 y OS

NWTS: National Wilms Tumor Study; AIEOP: Associazione Italiana Ematologia ed Oncologia Pediatrica; UKW: United Kingdom Wilms Tumour Study; SIOP: International Society of Pediatric Oncology; GPOH: Gesellschaft für Pädiatrische Onkologie und Hämatologie; y: year; m: month; EFS: event-free survival; OS: overall survival.

during the first year of life and is also rare in the second year of life (12). Nevertheless, even in the group of patients with favorable histology, older age seems to be correlated with a higher risk of relapse and death, although prognostic factors such as stage or histology seem to be more powerful (7). Other suggested reasons for the adverse survival rates in older children are delay in diagnosis, advanced tumor stage at presentation, and intrinsically different biological behaviors (7).

While age has been described as an independent risk factor in two (UK) studies, it did not remain significant after multivariate analysis in other studies (Table 1). It is important to stress that studies reported are heterogeneous with respect to design, outcome measures, and treatment regimens. Whether age is really an *independent* risk factor, and whether age is a stronger prognostic factor than stage, histology, and LOH 1p/16q, needs to be further explored. This may provide some insight into whether older patients need to be treated more intensively, as is already advised for adult WT patients.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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