

**Congenital mesoblastic nephroma fifty years after its recognition: A narrative review**

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1 **Congenital mesoblastic nephroma fifty years after its recognition: A narrative review**

2 *Running head: Review on congenital mesoblastic nephroma*

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27

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36

37 **Abbreviations key**

CMN	Congenital mesoblastic nephroma
BWS	Beckwith-Wiedemann syndrome
AV	Actinomycin and vincristine

38

39 **Abstract**

40 Congenital mesoblastic nephroma (CMN) is a rare pediatric renal tumor with low malignant  
41 potential that most commonly occurs early in infancy. Treatment strategies are based on the few  
42 published CMN series, while a significant number of CMN patients have been described in case  
43 reports. The aim of this narrative review was to create an up-to-date overview of the literature.  
44 Complete surgical removal is curative in most cases. The risk of treatment-related mortality  
45 (both surgery- and chemotherapy-related) is relatively high in the first weeks of life, indicating  
46 that these young patients deserve special attention with respect to timing and type of treatment.

47

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## 48 **Introduction**

49 Congenital mesoblastic nephroma (CMN) is a rare tumor with low malignant potential, which  
50 represents approximately 3% of all pediatric renal tumors [1-3]. It is the most common renal  
51 neoplasm diagnosed in the first month of life [4,5]. CMN is frequently recognized before or at  
52 time of birth, illustrating the embryonal character of the disease.

53 Bolande was the first to use the term ‘congenital mesoblastic nephroma’ in 1967, though decades  
54 earlier this tumor was already described using different terminologies including fetal renal  
55 hamartoma and leiomyomatous renal hamartoma [3,6-9]. The histological classification of CMN  
56 includes three subtypes, i.e. the classic, cellular and mixed type [10-12]. Recurrent genetic  
57 aberrations described in CMN include somatic trisomy 11 and t(12;15)(p13;q25), resulting in a  
58 fusion of *ETV6* and *NTRK3* [13,14].

59 The vast majority of CMN patients seems to present with local disease. Complete nephrectomy  
60 is considered the standard of care for children with CMN, although use of adjuvant  
61 chemotherapy and even radiotherapy has been reported [2,15,16]. These treatment strategies are  
62 mainly based on the few published CMN series with substantial numbers. A significant number  
63 of CMN patients have been described in case reports and to date a comprehensive review is not  
64 available. The aim of this narrative review was to gain insight into the clinical characteristics,  
65 histological subtypes, genetic aberrations, treatment modalities and outcome of patients with  
66 CMN, in order to develop future treatment strategies.

67

## 68 **Methods**

69 For this review, databases of PubMed, Embase, Web of Science, Scopus and Google scholar  
70 were searched using search terms “mesoblastic nephroma”, “mesoblast” within 3 words of  
71 “nephrom”, “non-Wilms” or “not-Wilms” (mesoblastic nephroma\*[tw] OR (mesoblast\*[tw]  
72 NEAR/3 nephrom\*[tw])) OR non-Wilms\*[tw] OR not-Wilms\*[tw]). After removal of double  
73 articles, 984 articles published before 1 December 2015 remained (Fig 1). Thirteen articles were  
74 added after hand searching. Articles were selected on the basis of title and abstract by two  
75 independent reviewers (S.L.G. and T.D.) (Fig 1). To be eligible for inclusion, a study had to (1)  
76 contain well-described CMN patients <18 years of age, (2) be an original article, (3) be reported  
77 after the study by Bolande et al (1967), (4) be written in English language and (5) be available in  
78 full-text. In case of doubt about the histological diagnosis or in case the tumor was described

79 under a different name, the paper was reviewed extensively by an expert pathologist (G.J.V.)  
80 before inclusion in the current review.

81

## 82 **Results**

83 A total of 200 articles met the inclusion criteria (Fig. 1). Of these, 25 articles reported series of  
84  $\geq 10$  patients which included 628 patients in total (Table 1, Supplemental Table S1). Where more  
85 than one paper reported on the same or overlapping cohorts, the report with the most detailed  
86 information on the largest number of individuals was used; eventually 12 non-overlapping series  
87 including 306 patients were selected for the analysis in this review (Table 1).

88 In addition to these series, 174 case reports described 270 cases in total (Supplemental Table S2).  
89 Data of these case reports were only included in the analysis of this review if they provided well  
90 documented data and relevant additional information, such as the correlation between genotype  
91 and histology and characteristics of stage III or relapsed CMN patients.

92

### 93 **Clinical characteristics**

94 Median age at diagnosis ranged from 0 days (newborn) - 2.3 months (median age  $\leq 1$  month in  
95 63% of series) and overall age ranged from prenatal - 3.8 years (Table 1). Prenatal detection of  
96 the tumor was reported in 16% of the patients [15,17-19]. The male to female ratio was 1.5:1  
97 (Table 1). The most commonly reported presenting symptom was an abdominal mass, described  
98 in 76% of the cases (Table 1). Other repeatedly reported symptoms were hypertension (19%) and  
99 hematuria (11%) (Table 1). Case reports additionally reported polyhydramnios in 40/270 cases  
100 (15%), hypercalcemia in 12/270 cases (4%) and hyperreninemia in 3/270 cases (1%)  
101 (Supplemental Table S2). Both hypercalcemia and hyperreninemia completely resolved with  
102 removal of the tumor in all cases [5,20-34].

103 Congenital anomalies were reported in 11 patients described in series; genitourinary anomalies  
104 were described in 6 patients, gastrointestinal malformations in 2 patients, polydactyly in 1  
105 patient, hydrocephalus in 1 patient and 1 patient was described to be diagnosed with the  
106 Beckwith-Wiedemann syndrome (BWS) [2,15,18,35]. In case reports, 2 additional patients with  
107 BWS were diagnosed with CMN [5,36].

108

## 109 Pathology

110 CMN is classified into three histological subtypes: classic, cellular and mixed type. Classical  
111 type CMN shows a leiomyomatous pattern resembling infantile fibromatosis composed of  
112 interlacing bundles of spindle cells and low mitotic activity, no capsule, infiltrative growth into  
113 the renal parenchyma and/or perirenal fat, and entrapped islands of parenchyma [37]. The  
114 cellular type, identical to infantile fibrosarcoma, shows dense cellularity, a strong  
115 hemangiopericytous vascular pattern and a high mitotic activity but less infiltrative growth into  
116 the renal parenchyma [10,37]. Mixed type CMN shows a mixture of these two patterns in any  
117 proportion [37]. Information on histological subtype was available for 231 patients; the classic  
118 type occurred in 91 patients (39%), the cellular type in 96 patients (42%), the mixed type in 23  
119 patients (10%) and classic/mixed type (no discrimination) in 21 patients (9%) (Table 1). In three  
120 series a significant difference in age between classic (median age ranging between 6-17 days)  
121 and cellular type CMN (median age ranging between 3.7-5 months) was reported [15,16,19]. The  
122 median age of mixed type CMN was described in only one series, i.e. 1.9 months [16].

123 Information on stage was available for 251 patients; stage I/II disease was found in 208 patients  
124 (83%) and stage III disease in 42 patients (17%) (Table 1). Reasons for stage III disease were  
125 positive surgical margins (n=13), tumor rupture (n=12) or a combination of positive surgical  
126 margins and tumor rupture (n=11), while in 8 patients the reason for stage III was unknown  
127 [2,10,15-18,38-40]. One patient was described to have stage IV disease because of 'suspected'  
128 malignant cells in the bone marrow, however these cells were not histologically proven to be  
129 CMN cells, so we consider this case not being stage IV [35]. In case reports, another case was  
130 described to have stage IV disease at diagnosis (lesions in the right tibia on CT scan, however no  
131 histological confirmation available) [41]. Bilateral (stage V) disease has never been reported.  
132 Stage in relation to histological type is presented in Figure 2.

133 Data on immunohistochemistry were described in one series, showing immunoreactive renin  
134 (intense staining in vessels within areas of the trapped cortex) in 10/12 studied cases [38,39].  
135 Case reports provided information on immunohistochemical staining in 53 cases. In these cases,  
136 in total 27 different immunohistochemical markers were used. No marker specific for CMN  
137 could be identified (Supplemental Table S3).

138

## 139 Genetics

140 The most commonly reported genetic aberrations in CMN are t(12;15)(p13;q25), leading to a  
141 fusion of the genes *ETV6* and *NTRK3*, and trisomy 11 (both somatic). In Table 2, information on  
142 stage, histological type and outcome is provided for cases harboring t(12;15)(p13;q25) and cases  
143 harboring trisomy 11. In series, t(12;15)(p13;q25) and trisomy 11 were identified in 29% and  
144 54% of the analyzed cases, respectively [13,18,19,40]. No clear relation between stage and  
145 genetic subtype could be identified. Both genetic aberrations occurred in mixed/cellular type  
146 CMN only, and never in the classic type of CMN (Table 2). Median ages of patients harboring  
147 t(12;15)(p13;q25) and patients harboring trisomy 11 were both 1 month.

148 Other recurrently reported genetic aberrations in CMN (in case reports) are trisomies 8 (n=9), 17  
149 (n=4), 20 (n=4), 7 (n=3), 10 (n=3), 18 (n=2), 2 (n=2) and 9 (n=2) (Supplemental Table S2); all  
150 identified aberrations only occurred in mixed/cellular type CMN.

151

## 152 **Treatment**

153 Treatment details were available for 263 patients. Pre-operative chemotherapy was administered  
154 in only 9 patients, consisting of actinomycin and vincristine (AV) in 8 patients and unknown  
155 type of treatment in one patient [15,16,18]. Information on response to pre-operative  
156 chemotherapy was described in 6 cases; 5 cases treated with AV showed a reduction in tumor  
157 size of at least 30% and one case treated with AV had a significant increase in tumor size, but  
158 histology at time of surgery showed 80% necrosis [15,16].

159 All patients underwent surgery (179 complete nephrectomy, 6 partial nephrectomy (re-excision  
160 n=3), 77 unknown type of surgery), except for one patient who died before surgery could be  
161 applied.

162 Post-operative chemotherapy had been administered in 50 patients, consisting of AV in 21 cases,  
163 actinomycin alone in 11 cases, AV and doxorubicin in 3 cases, AV and cyclophosphamide in 1  
164 case, etoposide/cyclophosphamide/doxorubicin/carboplatin in one case and in 13 cases type of  
165 post-operative chemotherapy was unknown [2,10,15,16,18,35,38,39,42]. Radiotherapy was  
166 applied in nine cases [2,10,15,35].

167

## 168 **Outcome**

169 Information on outcome was available for 276 patients described in series (Table 1). Of these,  
170 264 patients survived (96%) and 12 patients died (4%). Causes of death in these 12 patients were

171 disease-related in 5 cases and treatment-related in 7 cases (5 surgery-related, 2 chemotherapy-  
172 related) (Supplemental Table S4). Median age at diagnosis of patients who died of disease was 6  
173 months, while median age at diagnosis of patients who died of treatment-related causes was 0  
174 days (newborn). Surgery-related causes of death included post-operative sepsis (n=2), post-  
175 operative necrotizing enterocolitis (n=1), intra-operative bleeding (n=1) and 'not specified'  
176 (n=1). Chemotherapy-related causes of death consisted of severe neutropenia and sepsis (n=2).  
177 Information on occurrence of relapse was available for all 306 patients described in series.  
178 Relapses occurred in 12 patients (4%) (9 local, 2 metastatic in lung and bone, 1 location  
179 unknown) (Supplemental Table S5). The histological subtype was known in 11 relapsed cases (8  
180 cellular, 1 classic, 2 mixed). Information on outcome after relapse was available in 10 cases; 6  
181 achieved a second complete remission and 4 patients died of disease (Supplemental Table S5).

182

### 183 **Prognostic value of stage, histologic subtype and genetic aberrations**

184 Information on outcome according to stage was available for 145 patients described in series. Of  
185 125 patients with stage I/II disease, 4 patients (3%) suffered from a relapse and 6 patients (5%)  
186 died (3 of treatment-related toxicity and 3 of disease) (Supplemental Table S4 and S5). Of note,  
187 only 1 of 100 (1%) stage I/II patients treated with surgery alone, developed a relapse. Of 34  
188 patients with stage III disease, 6 patients (18%) had a relapse (4 cellular, 1 mixed, 1 unknown  
189 histology) and 2 patients (11%) died of tumor progression (both cellular) (Supplemental Table  
190 S4 and S5). As this is only a small set of patients, we also analyzed stage III patients as described  
191 in case reports. Stage III patients reported in case reports (n=22), together with stage III patients  
192 reported in series (n=34) are described in Supplemental Table S6; 15/56 stage III patients (23%)  
193 suffered from a relapse (73% cellular subtype) and 4/56 patients (6%) died of disease (all cellular  
194 subtype).

195 Information on outcome according to histological subtype was available for 156 patients  
196 described in series. Of 74 patients with classic type CMN, 1 patient (1%) (stage II) had a relapse  
197 and another patient (1%) (stage II) died of surgical complications (Supplemental Table S4 and  
198 S5). Of 59 patients with cellular type CMN, 6 patients (10%) (1 stage I, 1 stage II, 4 stage III)  
199 had a relapse and 4 patients (7%) (1 stage I, 1 stage II and 2 stage III) died of disease  
200 (Supplemental Table S4 and S5). Of 23 patients with mixed type CMN, one patient (4%) (stage  
201 III) had a relapse, but was alive after treatment (Supplemental Table S5 and S6).



202 Outcomes of patients harboring t(12;15)(p13;q25) and trisomy 11 are described in Table 2.

203

## 204 **Discussion**

205 The aim of this narrative review was to present a comprehensive and up-to-date overview of  
206 clinical characteristics, optimal treatment strategies and outcome of different histological and  
207 genetic subtypes of CMN, thereby serving future treatment guideline development for this rare  
208 tumor.

209 Most studies reporting on CMN have not been based on (inter-)national registries. Therefore, the  
210 prevalence of CMN and its histological subtypes is hard to analyze. Large series have suggested  
211 that CMN comprises 3.5-4% of all pediatric renal tumors, but it is conceivable that perinatal  
212 diagnosed cases may have been considered benign, and therefore not have been included in renal  
213 tumor registries [15,16]. The frequency of the cellular subtype and classic subtype seems to be  
214 similar, while the mixed subtype occurs remarkably less often ( $\pm 10\%$ ) [15,16,19].

215 CMN most commonly occurs early in infancy and over 15% of the cases are detected prenatally  
216 [13,15,16,35,38,39]. Although CMN has been reported in 26 adult patients in literature, it  
217 remains uncertain whether these cases are real CMN's [43-62]. It is believed that most of these  
218 so-called adult mesoblastic nephromas are now recognized to have represented other tumors,  
219 such as metanephric stromal tumor, cystic hamartoma of the renal pelvis or mixed epithelial and  
220 stromal tumor [63,64]. For this reason, adult cases have been excluded from the current review.

221 Two major genetic variants have recurrently been described in CMN; t(12;15)(q13;q25),  
222 resulting in a fusion of *ETV6* and *NTRK3*, and trisomy 11 [13,18,19,40]. These genetic  
223 aberrations were only identified in cellular and (less common) mixed type CMN. Of interest, the  
224 other recurrently but rarely reported genetic aberrations (i.e. trisomy 2/8/9/10/17/18/20) also only  
225 occurred in mixed and cellular type CMN [30,65-72]. This clonality may be illustrative for more  
226 malignant disease as these are the subtypes that seem to behave more aggressively. However, no  
227 biological studies have been performed to functionally verify this, as yet. We assume that all  
228 aforementioned genetic aberrations are somatic, since no germline genetic aberrations associated  
229 with CMN have been described. This is in line with the observation that bilateral CMN has never  
230 been reported. Besides the diagnosis of Beckwith-Wiedemann syndrome in 3 CMN patients, no  
231 association with genetic predisposition syndromes has been reported up until now [5,18,36].  
232 Occurrence of CMN in two siblings has been reported once [73].

233 Overall survival of CMN patients was excellent (5-year overall survival  $\pm$ 95%). Nevertheless, it  
234 was not 100% as suggested in earlier reports [16,42]. It is remarkable that causes of death were  
235 treatment-related in about half of the cases and most of these patients were very young (median  
236 age at diagnosis: 0 days, newborn) [2,10,13,15,17,18,35,38,39]. This underscores that these  
237 infants with renal tumors deserve special attention with respect to timing and type of treatment,  
238 and need a dedicated expert pediatric oncology setting. Relapses were described in only 4% of  
239 the patients [2,13,15,18,19,35]. Virtually all relapses occurred within 12 months after diagnosis,  
240 indicating that close monitoring of all cases should be advised for at least 1 year following end of  
241 treatment. Most relapses occurred locally, however also metastatic relapses have been reported  
242 (Supplemental Table S5). About 69% of the relapsed patients survived after relapse treatment  
243 consisting of individualized combinations of surgery, chemotherapy and radiotherapy  
244 (Supplemental Table S5) [2,13,15,18,19,35].

245 Factors that seem to negatively influence outcome of CMN patients were stage III disease and  
246 cellular subtype (Supplemental Table S4, S5 and S6) [15]. In addition to these factors,  
247 Furtwangler et al. described age  $\geq$  3 months to be associated with the occurrence of relapse based  
248 on a univariate analysis of 50 CMN cases, which can probably be attributed to the observation  
249 that the more aggressive cellular subtype occurs most often in older patients [15]. According to  
250 the current review, patients with relapse indeed seemed to be slightly older (median age  
251 approximately 3.8 months) compared to patients without relapse (median age <1 month)  
252 (Supplemental Table S5). In contrast, most deceased CMN patients were relatively young  
253 (median age 0 days, newborn), mainly due to the high incidence of treatment-related mortality  
254 among these very young patients (Supplemental Table S4). It is currently not possible to  
255 elucidate the prognostic value of t(12;15)(p13;q25) and trisomy 11 in CMN patients due to lack  
256 of published data [13,18,19].

257 Designing a standard of care for CMN patients is a challenge based on the limited available  
258 evidence. It is obvious that patients with stage I/II disease, representing over 80% of the CMN  
259 patients, benefit from a surgery only strategy [15,16,74]. Particularly in CMN cases, removing  
260 perirenal fat during surgery is considered the golden standard, as CMN tumors often show  
261 infiltrative growth into the perirenal fat [1]. Throughout the world immediate surgery is  
262 recommended for renal tumors in patients under 6 months of age due to the higher probability of  
263 pathology other than Wilms' tumor in this age group [4,75]. However, consideration of pre-

264 operative chemotherapy (AV) may be justified in a small subset of these young patients, when  
265 imaging or clinical symptoms suggest a high risk of operative or anesthetic complications or  
266 inoperability, even by an experienced surgical team. Partial nephrectomy or nephron-sparing  
267 surgery has only been performed in a small subset of patients and in 3 of 6 such cases, re-  
268 excision was necessary [15]. It is important that, especially in the neonatal setting, the risk of  
269 surgery should be weighed carefully against the risk of pre-operative chemotherapy.

270 Stage III CMN patients represent a challenging subgroup with respect to the development of  
271 proper guidelines. For most of the cases surgery only seems to be sufficient, especially for stage  
272 III cases of the classic or mixed histological subtype. Of 12 well-documented classic and mixed  
273 type stage III patients treated without additional chemotherapy, one patient (8%) suffered from a  
274 relapse, but survived after relapse treatment (Supplemental Table S6). In contrast, 7/12 (58%)  
275 stage III cases of the cellular type treated with surgery only suffered from a relapse, while 4/14  
276 (29%) stage III cellular type cases treated with adjuvant chemotherapy developed a relapse.  
277 Hence, evidence that additional chemotherapy is reasonable for stage III cellular type cases is not  
278 available due to a small dataset including selected subjects (Supplemental Table S6) [15,16,18].  
279 Chemosensitivity is documented in CMN patients; treatment of patients with pre-operative  
280 actinomycin/vincristine resulted in a reduction in tumor size or necrotizing of the tumor in all  
281 reported patients [15,16]. In addition, Loeb *et al* described three patients with recurrent cellular  
282 CMN who showed a complete response to different combinations of chemotherapy  
283 (Supplemental Table S5) [76]. However, based on the results of this review, caution with respect  
284 to chemotherapy-related toxicity is important in these young children (Supplemental Table S4).  
285 Targeted therapy might be an option for cases with progressive disease that do not respond to  
286 chemotherapy. In particular Crizotinib, an ALK inhibitor which proved to be of benefit for acute  
287 lymphoblastic leukemia patients harboring the ETV6-NTRK3 transcript, resulting from the same  
288 t(12;15)(p13;q25) as described in CMN cases, could be considered as a potential compound in  
289 highly selected aggressive cases [77]. The role of radiotherapy for CMN patients is uncertain,  
290 and considering the fact that late effects of radiotherapy are suspected to be substantial in this  
291 relatively young group of patients, radiotherapy should be reserved for highly selected,  
292 aggressive and chemotherapy resistant cases only.

293 Because of the small number of relapsed CMN patients and the different treatment regimens  
294 applied in these patients, designing evidence-based treatment guidelines for relapsed CMN is not

295 possible. Treatment of such patients requires an individualized approach in dedicated centers for  
296 pediatric oncology.

297 Based on this overview, we conclude that CMN is a disease that presents at young age, most  
298 commonly in the first months of life. Most CMN patients present with stage I/II disease, for  
299 which surgery only is the recommended treatment. Based on the very limited available data,  
300 partial nephrectomy or nephron-sparing surgery is currently not recommended for CMN patients.  
301 There is insufficient evidence for recommending adjuvant chemotherapy in patients with stage  
302 III disease, due to the small number of reported cases and lack of clinical trials. Histologically  
303 confirmed stage IV or stage V CMN cases have not been described. Although initial surgery is  
304 recommended for renal tumors in patients under 6 months of age, consideration of pre-operative  
305 chemotherapy may be justified in a small subset of young patients, when imaging or clinical  
306 symptoms suggest a high risk of operative or anesthetic complications. Survival rates of reported  
307 CMN patients were excellent (approximately 95% overall survival). Factors that seemed to be  
308 associated with occurrence of relapse were stage III disease and cellular histology. The  
309 prognostic value of  $t(12;15)(p13;q25)$  and trisomy 11, only described in cellular and mixed type  
310 CMN, is hard to elucidate based on the small number of series with available data. Despite the  
311 excellent outcome of patients diagnosed with CMN, the risk of treatment-related complications  
312 (both surgery and chemotherapy related complications) seems to be relatively high, especially  
313 when the tumor appears in the first weeks of life. This indicates that these very young patients  
314 deserve special attention with respect to the timing and type of treatment, that they need a  
315 dedicated expert pediatric oncology setting, and that close monitoring of toxicity is needed. It is  
316 recommended to discuss rare challenging individual CMN cases (such as (cellular) stage III and  
317 relapsed cases) with steering committees of pediatric renal tumor boards, such as SIOP  
318 (International Society of Pediatric Oncology) and COG (Children's Oncology Group). The  
319 results of this review have guided the design of new CMN treatment recommendations, which  
320 will be included in the international SIOP RTSG 2016 UMBRELLA protocol, however they  
321 illustrate that longitudinal prospective registries that include histology as well as molecular  
322 diagnostics are necessary for further evidence-based treatment and guideline development for  
323 patients with CMN.

324

325

326 **Conflict of interest statement**

327 The authors declare no conflict of interest.

328

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521 **Legends**

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523 **Figure 1:** Selection of articles524 **Figure 2:** Stage according to histological subtype (reported in non-overlapping series  $\geq 10$   
525 cases)

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527 **Table 1:** Non-overlapping series reporting  $\geq 10$  CMN patients528 **Table 2:** Stage, histology and outcome of reported CMN cases harboring t(12;15)(p13;q22)  
529 or trisomy 11

530

531 **Supplemental Table 1:** Available series reporting  $\geq 10$  CMN patients532 **Supplemental Table S2:** CMN patients described in case reports533 **Supplemental Table S3:** Immunohistochemical staining of 53 CMN patients described in  
534 case reports535 **Supplemental Table S4:** Characteristics and treatment of reported deceased CMN patients536 **Supplemental Table S5:** Characteristics, treatment and outcome of reported relapsed CMN  
537 patients538 **Supplemental Table S6:** Characteristics, treatment and outcome of reported stage III CMN  
539 patients

540

**Table 1.** Non-overlapping series reporting  $\geq 10$  CMN patients

Author, year	M/F	L/R	Median age (range)	Presenting symptoms				Stage			Treatment				Histologic patterns			Genetics		EFS	OS	Median follow-up (range)
				AM	HT	HE	Other	I/II	III	IV	Pr-CT	S	P-CT	RT	Cl	M	Ce	t(12;15)	Trisomy 11			
1. Howell, 1982	33/18	26/25	2.3m	48	2	9	6	39	12	0	-	51	28	4	NA	-	20	NA	NA	98%	98%	3.2y (4m-11.5y)
2. Sandstedt, 1985	11/18	13/16	NA	18	-	5	5	21	8	0	-	29	5	1	9	-	20	NA	NA	93%	93%	> 4y
3. Cook, 1988 / Malone, 1989 †	9/3	3/9	3d (1d-2.5y)	11	4	1	NA*	11	1	0	-	12	1	-	NA	-	-	NA	NA	83%	83%	7.3y †
4. Barrantes, 1991	8/5	9/4	0d (0d-19m)	NA*	-	-	-	12	0	1 <sup>#</sup>	-	13	4	3	9	1	3	NA	NA	85%	85%	5.8y
5. Leclair, 2005	NA	NA	NA	NA	-	-	-	25	1	0	-	26	-	-	21	-	5	NA	NA	96%	96%	$\pm$ 3.5y
6. Anderson, 2006	NA	NA	2m (0d-11m)	NA	-	-	-	11	2	0	-	13	-	-	3	6	4	3/13	NA	85%	100%	NA
7. Furtwaengler, 2006	34/16	21/29	18.5d (0d-2.6y)	27	16	1	6	41	9	0	5	50	6	1	29	-	21	NA	NA	94%	95%	4.2y (0.8-8.3y)
8. Watanabe, 2007	7/6	NA	30d (5d-7m)	NA	-	-	-	NA	-	-	NA	NA	NA	NA	4	1	8	8/12	7/13	92%	92%	NA
9. Bayindir, 2009	7/3	5/5	3.1m (6d-5.5m)	9	7	2	4	7	3	0	2	9	2	-	2	2	6	2/10	NA	70%	90%	3.6y (6m-7y) †
10. Chaudry, 2009	15/15	14/16	NA	NA*	-	-	-	NA	-	-	NA	30	NA	NA	12	3	15	6/30	NA	93%	NA	NA
11. England, 2011	28/19	23/24	1m (0d-3.8y)	NA*	NA*	-	-	41	6	0	2	47	2	-	23	10	14	NA	NA	100%	100%	4.4y (1m-10y)
12. Saula, 2012	7/5	NA	NA	12	2	-	2	NA	-	-	-	12	2	-	NA	-	-	NA	NA	92%	100%	5-10y
<b>Total</b>	<b>159/108</b>	<b>114/128</b>	<b>Range 0d-2.3m</b>	<b>125</b>	<b>31</b>	<b>18</b>	<b>23</b>	<b>208</b>	<b>42</b>	<b>1</b>	<b>9</b>	<b>292</b>	<b>50</b>	<b>9</b>	<b>91</b>	<b>23</b>	<b>96</b>	<b>16/52</b>	<b>7/13</b>	<b>94%</b>	<b>95%</b>	<b>Range 3.5-5.8y</b>

**Abbreviations** AM: abdominal mass, BM: bone marrow, Ce: cellular type, Cl: classic type, d:days, EFS: event free survival, F: female, HC: hypercalcaemia, HE: hematuria, HT: hypertension, L: left, M: male, M: mixed type, m: months, NA: not available, NB: newborn, OS: overall survival, PH: polyhydramnion mother, P-CT: post-operative chemotherapy, Pr-CT: pre-operative chemotherapy, R: right, RT: radiotherapy, S: surgery, y: years

† Cook et al (1988) and Malone et al (1989) described the same series of CMN patients with different endpoints

# Suspected malignant cells in bone marrow, no histological confirmation of CMN

\* Symptom reported, number of patients unknown

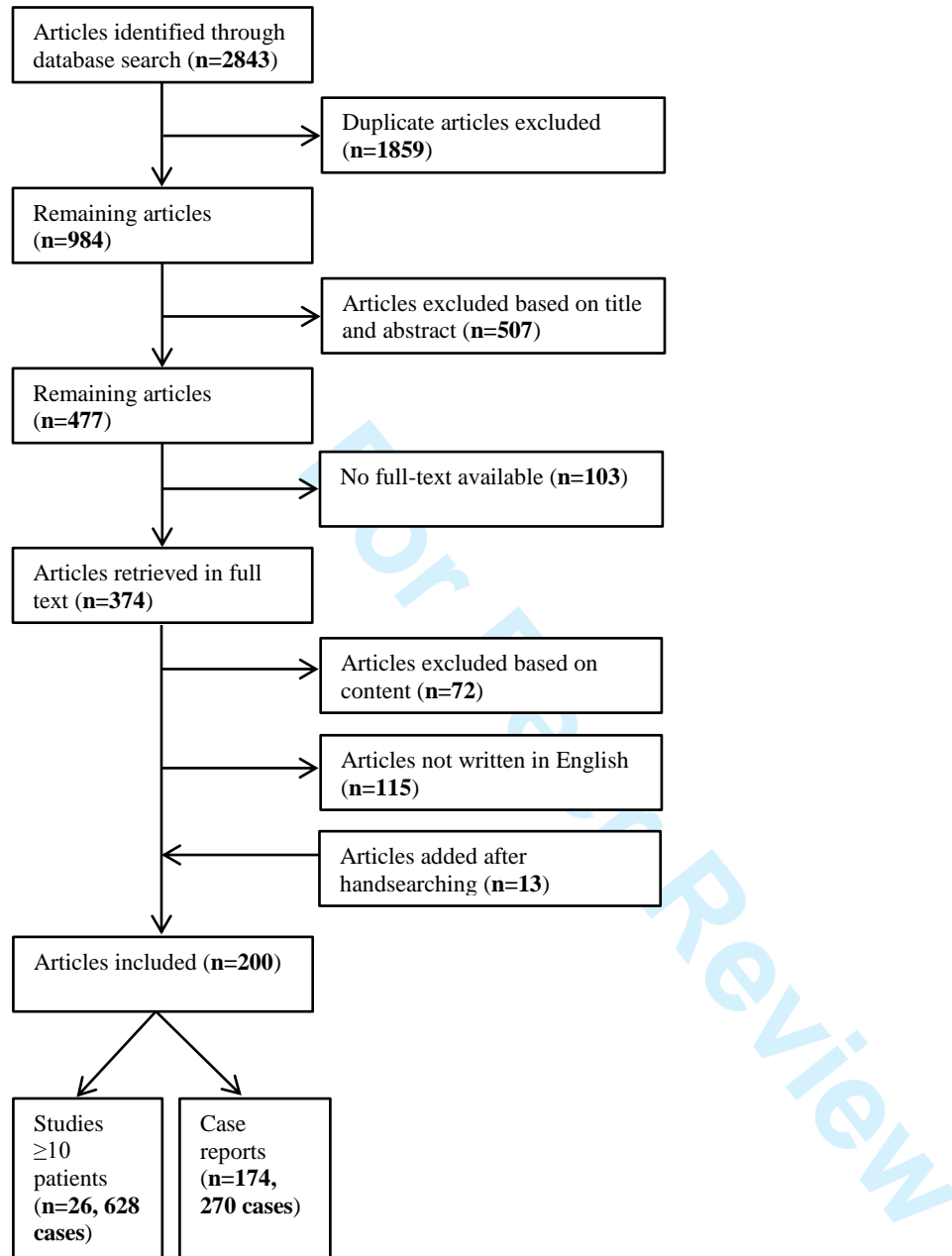
† Mean follow-up instead of median follow-up

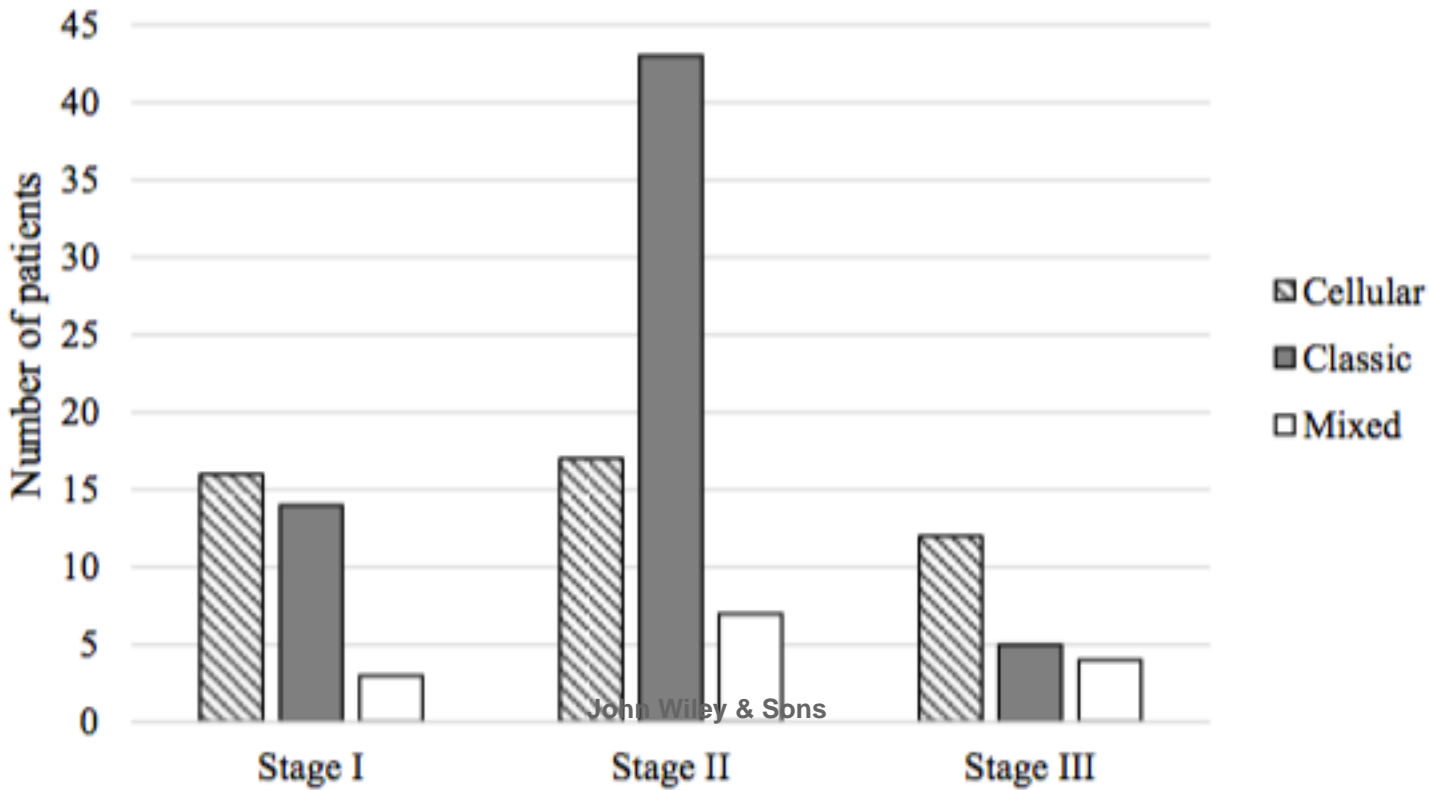
**Table 2.** Stage, histology and outcome of reported CMN cases harboring t(12;15)(p13;q22) or trisomy 11

	<b>t(12;15)(p13;q22) *</b>		<b>Trisomy 11 *</b>	
	<b>Series ≥ 10 patients</b>	<b>Case reports **</b>	<b>Series ≥ 10 patients</b>	<b>Case reports **</b>
<b>Number of cases analyzed</b>	65	NA	13	NA
<b>Number of positive cases</b>	19	16	7	15
<b>Stage</b>	I/II: 3 III: 1 Unknown: 15	I/II: 5 III: 4 Unknown: 7	I/II: 0 III: 0 Unknown: 7	I/II: 7 III: 2 Unknown: 6
<b>Histology</b>	Classic: 0 Mixed: 0 Cellular: 19 Unknown: 0	Classic: 0 Mixed: 4 Cellular: 10 Unknown: 2	Classic: 0 Mixed: 0 Cellular: 7 Unknown: 0	Classic: 0 Mixed: 3 Cellular: 9 Unknown: 3
<b>Outcome data available</b>	n = 13	n = 5	n = 7	n = 4
<b>Outcome</b>	Relapse: 2/13 Dead of disease: 1/13	Relapse: 2/5 Dead of disease: 0/5	Relapse: 0/7 Dead of disease: 0/7	Relapse: 0/4 Dead of disease: 0/4

\* Six cases described in series ≥ 10 patients and 11 cases described in case reports harbored both t(12;15)(p13;q22) and trisomy 11

\*\* Case reports also included in series ≥ 10 patients were removed from this table





Supplemental Table S1. Available series reporting ≥ 10 CMN patients

Author, year	M/F	L/R	Median age (range)	Presenting symptoms				Stage			Treatment				Histologic patterns			Genetics		EFS	OS	Median follow-up (range)
				AM	HT	HE	Other	I/II	III	IV	Pr-CT	S	P-CT	RT	CI	M	Ce	t(12;15)	Trisomy 11			
<b>NON-OVERLAPPING SERIES</b>																						
1. Howell, 1982	33/18	26/25	2.3m	48	2	9	6	39	12	0	-	51	28	4	NA			NA	NA	98%	98%	3.2y (4m-11.5y)
2. Sandstedt, 1985	11/18	13/16	NA	18	-	5	5	21	8	0	-	29	5	1	9	-	20	NA	NA	93%	93%	> 4y
3. Cook, 1988 / Malone, 1989 <sup>†</sup>	9/3	3/9	3d (1d-2.5y)	11	4	1	NA*	11	1	0	-	12	1	-	NA			NA	NA	83%	83%	7.3y †
4. Barrantes, 1991	8/5	9/4	0d (0d-19m)	NA*	-	-	-	12	0	1 <sup>#</sup>	-	13	4	3	9	1	3	NA	NA	85%	85%	5.8y
5. Leclair, 2005	NA	NA	NA	NA				25	1	0	-	26	-	-	21		5	NA	NA	96%	96%	±3.5y
6. Anderson, 2006	NA	NA	2m (0d-11m)	NA				11	2	0	-	13	-	-	3	6	4	3/13	NA	85%	100%	NA
7. Furtwaengler, 2006	34/16	21/29	18.5d (0d-2.6y)	27	16	1	6	41	9	0	5	50	6	1	29	-	21	NA	NA	94%	95%	4.2y (0.8-8.3y)
8. Watanabe, 2007	7/6	NA	30d (5d-7m)	NA				NA			NA				4	1	8	8/12	7/13	92%	92%	NA
9. Bayindir, 2009	7/3	5/5	3.1m (6d-5.5m)	9	7	2	4	7	3	0	2	9	2	-	2	2	6	2/10	NA	70%	90%	3.6y (6m-7y) †
10. Chaudry, 2009	15/15	14/16	NA	NA*	-	-	-	NA			NA	30	NA	NA	12	3	15	6/30	NA	93%	NA	NA
11. England, 2011	28/19	23/24	1m (0d-3.8y)	NA*	NA*	-	-	41	6	0	2	47	2	-	23	10	14	NA	NA	100%	100%	4.4y (1m-10y)
12. Saula, 2012	7/5	NA	NA	12	2	-	2	NA			-	12	2	-	NA			NA	NA	92%	100%	5-10y
<b>Total</b>	<b>159/108</b>	<b>114/128</b>	<b>Range 0d-2.3m</b>	<b>125</b>	<b>31</b>	<b>18</b>	<b>23</b>	<b>208</b>	<b>42</b>	<b>1</b>	<b>9</b>	<b>292</b>	<b>50</b>	<b>9</b>	<b>91</b>	<b>23</b>	<b>96</b>	<b>16/52</b>	<b>7/13</b>	<b>94%</b>	<b>95%</b>	<b>Range 3.5-5.8y</b>
<b>PARTIALLY OVERLAPPING SERIES</b>																						
Bogdan, 1973 <sup>^1</sup>	14/5	NA	4w (0d-2.5y)	15	-	-	4	NA			2	15	5	8	NA			NA	NA	68%	68%	1.8y (0m-34y)
Shen, 1980 <sup>^1</sup>	5/5	7/3	5d (1d-8m)	10	1	2	1	NA			-	10	4	-	5	3	2	NA	NA	90%	90%	4.5y (3.3-10y)
Snyder 1980 <sup>^1</sup>	8/3	NA	0d(0d-6m)	NA*			3	11	0	0	-	11	-	5	9	-	2	NA	NA	73%	73%	NA (3-26y)
Hartman, 1981 <sup>^1</sup>	9/11	NA	2w (0d-16y)	NA				NA			NA				NA			NA	NA	NA	NA	NA
Chan, 1987 <sup>^1</sup>	9/8	NA	CI:5.3d (1-21d) Ce:5.3m (1-18m)	NA*	14	3	6	17	0	0	-	17	3	2	9	8		NA	NA	100%	100%	10y †
Pettinato, 1989 <sup>^1</sup>	7/9	9/4	CI: 16d M:2.3m Ce:5.3m	NA*	2	2	3	15	1	0	0	14	1	-	6	3	7	NA	NA	81%	81%	5.3y †
Schofield, 1993 <sup>^1</sup>	8/9	NA	7d (1d-2y)	NA				NA			0	17	5	-	6	5	5	NA	7/17	88%	88%	Range 8m-22y
Mascarello, 1994 <sup>^1,10</sup>	NA	NA	NA	NA				NA			NA				11	12		NA	9/23	NA	NA	NA
O'Malley, 1996 <sup>^1</sup>	9/6	NA	NA(2d-2y)	NA				NA			-	15	1	-	1	6	9	NA	NA	NA	NA	NA
Knezevich, 1998 <sup>^9,10</sup>	8/7	NA	1m (1d-3y)	NA				NA			NA				4	2	9	10/15	9/14	NA	NA	NA
Shao, 2004 <sup>^1,9,10</sup>	NA	NA	NA	NA				NA			NA				5	-	7	NA	NA	NA	NA	NA
Abosoudah, 2008 <sup>^10</sup>	8/6	NA	12d (3d-2y)	NA*	-	-	-	NA			NA				4	1	9	9/10	NA	86%	93%	NA
Vd Heuvel-Eibrink, 2008 <sup>^7</sup>	NA	NA	< 7m	NA				98	17	0	NA				NA			NA	NA	94%	96%	NA
<b>Abbreviations</b> AM: abdominal mass, BM: bone marrow, Ce: cellular type, CI: classic type, d:days, EFS: event free survival, F: female, HC: hypercalcaemia, HE: hematuria, HT: hypertension, L:left, M: male, M: mixed type, m: months, NA: not available, NB: newborn, OS: overall survival, PH: polyhydramnion mother, P-CT: post-operative chemotherapy, Pr-CT: pre-operative chemotherapy, R: right, RT: radiotherapy, S: surgery, y: years <sup>^</sup> Overlap of patients with other series (number of overlapping series is depicted, for example <sup>^1</sup> means overlap with the study by 1. Howell, 1982) <sup>†</sup> Cook et al (1988) and Malone et al (1989) described the same series of CMN patients with different endpoints <sup>#</sup> Suspected malignant cells in bone marrow, no histological confirmation of CMN * Symptom reported, number of patients unknown † Mean follow-up instead of median follow-up																						

Supplemental Table S2. CMN patients described in case reports

Study (year)	Sex	Age at diagnosis	Side	Presenting symptoms	Congenital abnormalities	Tumour rupture	Operative procedures	Overall stage	Histological type	Volume at diagnosis	Genetics	Event-free survival (status)	Overall survival (status)	Overall survival (months)	Cause of death	
Adem -1 (2001)	F	NA	NA	NA	NA	NA	NA	NA	Cellular	NA	t(12;15)(p13;q25)	NA	NA	NA	NA	
Adem -2 (2001)	NA	NA	NA	NA	NA	NA	NA	NA	Classic	NA	trisomy 11	NA	NA	NA	NA	
Al-Turkistani (2008)	F	PN: GA 26 w	R	Fetal abdominal mass*, polyhydramnios*	No	NA	Total nephrectomy 4 weeks after birth	NA	Mixed	4x5x4.5cm	NA	NA	NA	NA	NA	
All (1994)	M	PN: GA NA	L	Fetal abdominal mass*	NA	NA	Total nephrectomy 3 days after birth	NA	Cellular	NA	NA	Relapse	Died	9	Tumor progression	
Angulo (1991)	M	14 D	R	Congenital hypertrophic pyloric stenosis, renal tumor found during pyloromyotomy	NA	No	Total nephrectomy	I	Cellular	NA	NA	No relapse	Alive	108	-	
Angulo (1991)	M	PN: GA 37 w	R	Stillborn	No	NA	No surgery (stillborn)	NA	Classic	NA	NA	Stillborn	Died	0	Stillborn (hydrops fetalis) Patient died due to complications of prematurity, tumor found at	
Anurobi (2014)	F	0 D (NB)	L	Stillborn, abdominal mass, polyhydramnios*	NA	NA	No surgery	NA	Classic	5x6x3cm	NA	Died	Died	1 day	-	
Arnsman (1980)	M	4 D	L	Left flank mass	No	Yes	Total nephrectomy	III	NA	NA	NA	No relapse	Alive	24	-	
Argani -1 (2000)	M	14 Mo	NA	NA	NA	NA	Tumor resection (total nephrectomy?)	II	Cellular	NA	t(12;15)(p13;q25)	Relapse	Alive	84	-	
Argani -2 (2000)	M	11 Mo	NA	NA	NA	NA	Total nephrectomy	NA	Cellular	980 gram	t(12;15)(p13;q25)	NA	NA	NA	NA	
Bandyopadhyay -1 (2009)	F	3 Mo	NA	Abdominal mass	NA	NA	Total nephrectomy	I	Classic	8.5x5x4cm	NA	No relapse	Alive	24	-	
Bandyopadhyay -2 (2009)	M	2.5 Mo	NA	Abdominal mass	NA	NA	Total nephrectomy	I	Classic	9x6x4cm	NA	No relapse	Alive	24	-	
Bandyopadhyay -3 (2009)	F	3 Mo	L	Abdominal mass, vomiting, Abdominal distention, vomiting, diarrhea,	NA	NA	Total nephrectomy	I	Cellular	8x5x4cm	NA	No relapse	Alive	24	-	
Bauer (1979)	F	3 Mo	R	hyperreninemia	NA	NA	Total nephrectomy	II	NA	9.5cm (diameter)	NA	No relapse	Alive	18	-	
Becroft (1995)	F	1 Mo	L	Abdominal mass Low-grade fever, abdominal distention, diarrhoea, general malaise	No	NA	Tumor resection (total nephrectomy?) Partial resection (infiltration of duodenum and colon)	II	Mixed	8x7x5.5cm	54XX, +del(1p13), trisomy 2/7/8/12/15/17, biallelic expression	No relapse	Alive	48	-	
Bell (2002)	F	9 Mo	R	Abdominal mass	No	NA	Total nephrectomy	III	Mixed	16x6x7cm	NA	Relapse	NA	NA	NA	
Bendre -1 (2014)	M	2 Mo	R	Abdominal mass	NA	No	Total nephrectomy	NA	Classic	9.3x3x3cm	NA	No relapse	Alive	22	-	
Bendre -2 (2014)	M	3 Mo	R	Abdominal mass, hypertension	NA	No	Total nephrectomy	NA	Classic	NA	NA	No relapse	Alive	24	-	
Bernstein (1994)	F	5 w	L	Abdominal distention, crying, decreased appetite	No	NA	Nephrectomy (95% of the tumor removed)	III	Cellular	14x10x6cm	50XX, +der(6)del(6)(p23) add(6)(q11), trisomy 8/10/11, add(17)(p130)	NA	NA	NA	NA	
Biscaglia (2000)	F	0 D (NB)	R	Abdominal mass Abdominal mass, polyhydramnios*, premature delivery at 32 weeks gestation	No	NA	Total nephrectomy 1 month after birth	II	Classic (with some features: high mitotic index- of cellular variant)	3cm (diameter)	Flow cytometry: euploid DNA content	No relapse	Alive	72	-	
Blank -1 (1978)	M	0 D (NB)	R	Abdominal mass, polyhydramnios*	No	NA	Total nephrectomy 4 days after birth	NA	NA	NA	NA	No relapse	Alive	6	Fatal tear in inferior vena cava during nephrectomy	
Blank -2 (1978)	M	0 D (NB)	R	Abdominal mass, polyhydramnios*	No	NA	Total nephrectomy (timing unknown)	NA	NA	NA	NA	Died	Died	0	-	
Blank -3 (1978)	F	0 D (NB)	R	Abdominal mass, polyhydramnios*	NA	NA	Total nephrectomy 8 days after birth	NA	NA	NA	NA	No relapse	Alive	12	-	
Bolande -1 (1967)	M	0 D (NB)	R	Abdominal mass, transient hyperbilirubinemia	NA	NA	Total nephrectomy 1 week after birth	NA	NA	NA	NA	No relapse	Alive	72	-	
Bolande -2 (1967)	F	0 D (NB)	L	Abdominal mass	NA	NA	Total nephrectomy 5 days after birth	NA	NA	NA	NA	No relapse	Alive	12	-	
Bolande -3 (1967)	F	0 D (NB)	NA	Abdominal mass, respiratory distress, sepsis, hyperbilirubinemia	NA	NA	Total nephrectomy 3 weeks after birth	NA	NA	NA	NA	No relapse	Alive	72	-	
Bolande -4 (1967)	M	3 Mo	R	Abdominal mass	NA	NA	Total nephrectomy	NA	NA	NA	NA	No relapse	Alive	72	-	
Bolande -5 (1967)	F	0 D (NB)	R	Abdominal mass	NA	NA	Total nephrectomy 2 days after birth	NA	NA	NA	NA	Died	Died	0.4	Pseudomonas sepsis on 12th post-operative day	
Bolande -6 (1967)	F	0 D (NB)	L	Abdominal mass	NA	NA	Total nephrectomy in first week after birth	NA	NA	NA	NA	No relapse	Alive	60	-	
Bolande -7 (1967)	M	0 D (NB)	R	Abdominal mass	NA	NA	Total nephrectomy in first week after birth	NA	NA	NA	NA	No relapse	Alive	36	-	
Bolande -8 (1967)	F	0 D (NB)	L	Abdominal mass	NA	NA	Total nephrectomy 2 months after birth	NA	NA	NA	NA	No relapse	Alive	180	-	
Campagnola (1998)	M	4 Mo	L	Abdominal distention	NA	NA	Total nephrectomy	NA	Cellular	17x17cm	NA	No relapse	Alive	48	-	
Campos (2001)	NA	0 D (NB)	R	Abdominal mass	NA	NA	Total nephrectomy 6 days after birth	I	Cellular	NA	NA	46X,X, trisomy 11	No relapse	Alive	24	-
Carpenter (1993)	F	PN: GA 36 w	L	Fetal abdominal mass*	NA	NA	Total nephrectomy (timing unknown)	I	Mixed	8x6x4.5cm	t(12;15)(p13;q25)	No relapse	Alive	19	-	
Celik (2009)	M	PN: GA 28 w	L	Fetal abdominal mass*, polyhydramnios*	NA	No	Total nephrectomy 3 days after birth	NA	Cellular	6x5.5x4.5cm	NA	NA	NA	NA	NA	
Chan (1995)	F	3 D	R	Abdominal mass, vomiting	NA	No	Total nephrectomy	III	Cellular	6.5cm diameter	NA	No relapse	Alive	12	-	
Chan -1 (2002)	NA	PN: GA 30 w	NA	Fetal abdominal mass*	NA	No	Total nephrectomy after 1 course of vincristine	NA	NA	NA	NA	No relapse	Alive	84	-	



**Supplemental Table S3.** Immunohistochemical staining of 53 CMN patients described in case reports

Staining	Positive				Negative			
	Classic	Mixed	Cellular	NA	Classic	Mixed	Cellular	NA
Vimentin	7	5	17	3	1	2		
Desmin				3	3	2	9	2
(Smooth muscle) actin	3	3	5	3	2	1	5	
(Cyto)keratin	1		2		3	1	7	
S-100		1			2	1	3	
Neuronspecific enolase					1		1	
TrkC antibody			1					
Epithelial membrane antigen	3	3	3		2		7	
AE1/AE3	2	2	2		1	1	1	
PTHrP		1	1					
c-kit				2	1			
Ki-67	1		4		1			
CD34	1				2		4	
Myoglobin							1	
Alpha-fetoprotein							1	
Bcl-2							1	
CD99							1	
INI1			4					
Fibronectin	1	1	2					
Laminin					1	1	2	
TP					2	3	2	
PHA					3	2	2	
THP	1		1		1	2	1	
AH	3	3	2					
PSA	1	1	1		2	2	1	
WT1-GP			1	1				
Renin								1

**Supplemental Table S4.** Characteristics and treatment of reported deceased CMN patients

Type of report	Report	Age	Stage	Histologic subtype	Tx at diagnosis	Relapse	Cause of death
Series ≥ 10 patients	Furtwangler 2006	6m	III	Cellular	PN, CN (rupture)	Yes	Tumor progression
	Furtwangler 2006	2.7y	I	Cellular	Pre-op CT, CN, post-op CT	Yes	Tumor progression
	Bayindir 2009	3.9m	III	Cellular	Pre-op CT	No	Tumor progression
	Watanabe 2007	1.1y	II	Cellular	CN, post-op CT (NWTS-3 regimen K)	Yes	Tumor progression
	Leclair 2005	NB	I/II	Cellular	CN	No	Toxicity (surgery)
	Barrantes 1991	NB	II	Classic	CN, RT	Yes	Tumor progression
	Barrantes 1991	NB	II	Classic	CN	No	Toxicity (surgery)
	Howell 1982	NB	III	NA	CN (rupture), AMD	No	Toxicity (chemotherapy)
	Sandstedt 1985	NA	NA	NA	NA	No	Toxicity (surgery)
	Sandstedt 1985	NA	NA	NA	NA	No	Toxicity (surgery)
	Cook 1988 /Malone 1989	1d	III	NA	CN (rupture), post-op CT	No	Toxicity (chemotherapy)
	Cook 1988 /Malone 1989	3d	I/II	NA	CN	No	Toxicity (surgery)
Case reports	Ali 1994	NA	NA	Cellular	CN	Yes	Tumor progression
	Cheol 2007	NB	NA	Cellular	None	No	Tumor progression
	Jones 2007	1d	III	Cellular	CN	Yes	Tumor progression
	Joshi 1986	10m	III	Cellular	CN, post-op CT (AVD), RT	Yes	Tumor progression
	Santos 2011	2.8y	NA	Cellular	CN, post-op CT	Yes	Tumor progression
	Vujanic 1993	1.2y	III	Cellular	Surgery, post-op CT (AV)	Yes	Toxicity (chemotherapy)
	Angulo 1991	NB	I	Classic	None	No	Stillborn (hydrops fetalis)
	Chen 2003	NB	NA	Classic	None	No	Died directly after birth (hydrops fetalis)
	Anunobi 2014	NB	NA	Classic	None	No	Died 13 hours after birth (prematurity, polyhydramnios mother)
	Correia 1995	7m	I	Classic	CN	No	Toxicity (peritonitis due to peritoneal dialysis)
	Favara 1968	NB	NA	Classic	None	No	Died 8 hours after birth (respiratory distress)
	Kumar 1985	0m	NA	Classic	NA	NA	Toxicity (sepsis)
	Walker 1973	3m	NA	Classic	CN, post-op CT (ACT)	Yes	Tumor progression
	De Paepe 2011	NB	NA	Mixed	None	No	Intra-uterine death (intra-tumoral hemorrhage, early non-immune hydrops)
	Heidelberger 1993	NB	NA	Mixed	CN	Yes	Tumor progression
	Gray 1989	NB	NA	NA	None	No	Intra-uterine death (hydrops fetalis)
	Kotani 2010	NB	NA	NA	CN	No	Toxicity (surgery)
	Liu 1996	NB	NA	NA	None	No	Died directly after birth (ascites, pleural effusions, pericardial effusion, subcutaneous oedema)
	Meenal 2003	NB	NA	NA	None	No	Stillborn
	Blank 1978	NB	NA	NA	CN	No	Toxicity (surgery)
	Bolande 1967	NB	NA	NA	CN, post-op CT (ACT)	No	Toxicity (surgery)
	Larson 1978	NB	NA	NA	None	No	Tumor progression and advanced hyaline membrane disease
	Wigger 1969	NB	NA	NA	CN	No	Toxicity (surgery)
	Wigger 1969	NB	NA	NA	CN	No	Toxicity (surgery)

**Abbreviations** CN: complete nephrectomy, NA: not available, NB: newborn, PN: partial nephrectomy, post-op CT: post-operative chemotherapy, pre-op CT: pre-operative chemotherapy, Tx: treatment

**Supplemental Table S5.** Characteristics, treatment and outcome of reported relapsed CMN patients

Source	Report	Age	Stage	Histologic subtype	Initial treatment	Time to relapse	Location of relapse	Treatment of relapse	Outcome (follow-up time)
<b>Series ≥ 10 patients</b>	Furtwaengler 2006	3m	III	Cellular	CN (rupture)	NA	Local	S, CT (AVD)	Alive (5.6y)
	Furtwaengler 2006	6m	III	Cellular	PN, CN (rupture)	NA	Local	CT (AVI)	Died of tumor progression (1y)
	Furtwaengler 2006	2.7y	I	Cellular	Pre-op CT, CN, post-op CT	NA	Local	CT (ICED), RT, S	Died of tumor progression (1.5y)
	Bayindir 2009	5m	III	Cellular	Pre-op CT (AV), CN (incomplete), post-op CT (AV)	2m	Local	S, CT (VCD/VP-16/IFO), RT	Alive (7y)
	Chaudry 2009	NA	NA	Cellular	CN	<6m	Local	NA	NA
	Chaudry 2009	NA	NA	Cellular	CN	<6m	Local	NA	NA
	Watanabe 2007	1.1y	II	Cellular	CN, post-op CT (NWTS-3 regimen K)	NA	Bone (ilium, humerus, vertebrae)	NA	Died of tumor progression (1.3y)
	Anderson 2006	NB	III	Cellular	CN	6m	Local	S, CT (VCR/IFO/ACT)	Alive (NA)
	Barrantes 1991	NB	II	Classic	CN, RT	NA	NA	None	Died of tumor progression (9m)
	Bayindir 2009	3m	II	Mixed	CN	6m	Lung	S, CT (VCD)	Alive (4.5y)
Anderson 2006	8m	III	Mixed	CN	8m	Local	S, CT (AVD+ICE)	Alive (NA)	
Howell 1982	4m	NA	NA	CN (spill), AV	7m	Local	S, CT (DOX/CYC)	Alive (1.6y)	
<b>Case reports</b>	Ali 1994	NB	NA	Cellular	CN	3m	Local, brain	S, CT (type NA)	Died of tumor progression (9m)
	Jones 2007	NB	III	Cellular	CN	6m	Local	S	Alive (7m)
	Argani 2000	1.2y	II	Cellular	S (type unknown)	12m	Lung	S	Alive (7y)
	Glick 2004	3.5m	II	Cellular	CN	6m	Lung	S, CT (type NA)	Alive (6m)
	Gonzalez-Crussi 1980	7m	NA	Cellular	CN	3m	Lung	S, RT, CT (ACT)	Alive (5.5y)
	Jones 2007	1d	III	Cellular	CN (rupture)	6m	Local	S, CT (AVD/CYC/CIS)	Died of tumor progression (1.6y)
	Joshi 1986	10m	III	Cellular	CN, post-op CT (AVD), RT	13m	Local	S, CT (AVD)	Died of tumor progression (1.6y)
	Loeb 2002	1y	III	Cellular	CN (rupture)	3m	Local	CT (AVD), RT	Alive (18y)
	Loeb 2002	3m	III	Cellular	CN (rupture), post-op CT (AVD)	5m	Local	CT (IFO/CARBO/VP-16), RT	Alive (9y)
	Loeb 2002	NB	III	Cellular	CN (rupture)	5m	Local	S, CT (VCD)	Alive (2y)
	Patel 2003	9m	II	Cellular	Pre-op CT (AV), CN	2.5m	Liver	CT (VCR/IFO/DOX/VP-16), S	Alive (1.5y)
	Santos 2011	2.8y	NA	Cellular	S (type unknown), post-op CT (type NA)	8m	Local	S, CT (type NA)	Died of tumor progression (1.2y)
	Steinfeld 1984	4m	NA	Cellular	CN	2m	Local, lung	CT (AVD/CYC), RT, S	Alive (1.6y)
	Vujanic 1993	1.2y	III	Cellular	S (type unknown), post-op CT (AV)	5m	Lung, heart	S, CT (IFO/VCR)	Died of pneumonia (2y)
	Wang 2014	1.5m	I	Cellular	TE	8m	Local	CT (AVD), S	Alive (4y)
	Walker 1973	3m	NA	Classic	CN, post-op CT (ACT)	4m	Local	S, RT	Died of tumor progression (4m)
	Heidelberger 1993	NB	NA	Mixed	CN	7m	Brain	S, CT (type NA)	Died of tumor progression (14m)
	Ko 2013	NB	III	Mixed	CN	7w	Local, liver	CT (AVC)	Alive (7m)
	Bell 2002	9m	III	Mixed	Pre-op CT, PN, post-op CT	3m	Liver	S, CT (type NA)	NA
	Joshi/Fu 1973	1d	III	NA	CN	4m	Local	RT, CT (AV)	Alive (15m)

**Abbreviations** ACT: actinomycin, AVC: actinomycin/vincristine/cyclophosphamide, AVD: actinomycin/vincristine/doxorubicin, AVI: actinomycin/vincristine/ifosfamide, CIS: cisplatin, CN: complete nephrectomy, CT: chemotherapy, CYC: cyclophosphamide, DOX: doxorubicin, ICE: ifosfamide/carboplatin/etoposide, ICED: ifosfamide/cyclophosphamide/etoposide/doxorubicin, IFO: ifosfamide, m: months, NA: not available, NB: newborn, RT: radiotherapy, S: surgery, TE: tumor enucleation, VCD: vincristine/cyclophosphamide/doxorubicin, VCR: vincristine, VP-16: etoposide, y: years

Supplemental Table S6. Characteristics, treatment and outcome of reported stage III CMN patients

Type of report	Study	Age	Gender	Histology	Initial therapy	Reason for stage III	Relapse	Relapse treatment	Outcome
Series ≥ 10 patients	Furtwaengler 2006	3m	Female	Cellular	CN	Tumor rupture	Yes (local)	Surgery, AVD	Alive (5.6y)
	Furtwaengler 2006	3m	Female	Cellular	PN, 2 <sup>nd</sup> look surgery, CN, post-op CT	Margin+, tumor rupture	No	-	Alive (7.2y)
	Furtwaengler 2006	6m	Female	Cellular	PN, 2 <sup>nd</sup> look surgery, CN	Margin+, tumor rupture	Yes (local)	AVI	DOD (1y)
	Furtwaengler 2006	8m	Female	Cellular	CN, 2 <sup>nd</sup> look surgery, post-op CT	Margin+, tumor rupture	No	-	Alive (5.8y)
	Furtwaengler 2006	2y	Female	Cellular	CN, post-op CT	Margin+, tumor rupture	No	-	Alive (1.9y)
	Bayindir 2009	4m	Female	Cellular	Biopsy, pre-op CT (AV), CN (incomplete), post-op CT (AV)	Margin+	Yes (local, liver)	Surgery, VCD+VP-16/IFO, RT (10.5 Gy)	Alive (7y)
	Anderson 2006	NB	NA	Cellular	CN	Tumor rupture	Yes (local)	Surgery, VCR+ACT+IFO	Alive (NA)
	Bayindir 2009	2m	Male	Cellular	CN, post-op CT	Margin+	No	-	Alive (2.5y)
	Bayindir 2009	3m	Male	Cellular	Biopsy, pre-op CT	Margin+	No	-	DOD (6m)
	England 2011	NB	NA	Cellular	CN	Margin+, tumor rupture	No	-	Alive (4y)
	England 2011	2d	NA	Cellular	CN	Margin+	No	-	Alive (1.2y)
	Leclair 2005	NA	NA	Classic	CN	Tumor rupture	No	-	Alive (2y)
	Furtwaengler 2006	NB	Male	Classic	CN	Margin+	No	-	Alive (2.2y)
	Furtwaengler 2006	1w	Female	Classic	CN	Margin+	No	-	Alive (2.7y)
	Furtwaengler 2006	2w	Female	Classic	CN	Margin+	No	-	Alive (2.4y)
	Furtwaengler 2006	3m	Female	Classic	PN, 2 <sup>nd</sup> look surgery, CN	Margin+	No	-	Alive (1.1y)
	England 2011	7w	NA	Classic	CN	Margin+	No	-	Alive (5.3y)
	Anderson 2006	8m	NA	Mixed	CN	Tumor rupture	Yes (local)	Surgery, AVD+ICE	Alive (NA)
	England 2011	1d	NA	Mixed	CN	Margin+	No	-	Alive (2.2y)
	England 2011	2d	NA	Mixed	CN	Margin+	No	-	Alive (2y)
	England 2011	11m	NA	Mixed	CN, post-op CT	Tumor rupture	No	-	Alive (5.4y)
	Howell 1982	1d	NA	NA	CN, post-op CT	Margin+, tumor rupture	No	-	Alive (2.5y)
	Howell 1982	2d	NA	NA	CN, post-op CT	Margin+, tumor rupture	No	-	Alive (6.5y)
	Howell 1982	2d	NA	NA	CN, post-op CT	Tumor rupture	No	-	Died of sepsis (2w)
	Howell 1982	3w	NA	NA	CN	Tumor rupture	No	-	Alive (1.5y)
	Howell 1982	3w	NA	NA	CN	Tumor rupture	No	-	Alive (1.7y)
	Howell 1982	1m	NA	NA	CN	Margin+, tumor rupture	No	-	Alive (2.2y)
	Howell 1982	4m	NA	NA	CN, post-op CT, RT	Margin+, tumor rupture	No	-	Alive (2.5y)
	Howell 1982	4m	NA	NA	CN, post-op CT	Margin+, tumor rupture	No	-	Alive (5.5y)
	Howell 1982	4m	NA	NA	CN, post-op CT	Margin+, tumor rupture	Yes (local)	Surgery, CYC/ADR	Alive (2.2y)
	Howell 1982	5m	NA	NA	CN, post-op CT	Margin+	No	-	-
Howell 1982	16m	NA	NA	CN, post-op CT, RT	Margin+	No	-	-	
Howell 1982	9y	NA	NA	CN, post-op CT, RT	Tumor rupture	No	-	-	
Cook 1988/Malone 1989	3d	Male	NA	CN, post-op CT	Tumor rupture	No	-	-	Died of sepsis (3w)
Case reports	Jayabose 1988	2m	Female	Cellular	CN, AVD	Margin+	No	-	Alive (1.8y)
	Jones 2007	1d	Female	Cellular	CN	Margin+	Yes (local)	Surgery, AVCD + cisplatin	DOD (1.5y)
	Joshi 1986	10m	Male	Cellular	CN, AVD, RT	Margin+	Yes (local)	Surgery, continuation AVD	DOD (1.5y)

Matsumara 1993	NB	Male	Cellular	CN	Tumor rupture	No	-	Alive (2y)
Jones 2007	NB	Female	Cellular	CN	Margin+	Yes (local)	Surgery	Alive (7m)
Chan 1995	3d	Female	Cellular	CN, VCR	Surgical biopsy	No	-	Alive (1y)
Gormley 1989	2m	Female	Cellular	CN, AV	Tumor rupture	No	0	Alive (9m)
Kalidasan 1994	5m	Male	Cellular	CN	Tumor rupture	No	-	Alive (7y)
Kelly 1985	8m	Female	Cellular	CN, AV	Tumor rupture	No	-	Alive (11m)
Loeb 2002	12m	Female	Cellular	CN	Tumor rupture	Yes (local)	AVD, RT	Alive (18y)
Loeb 2002	3m	Female	Cellular	CN, AVD	Tumor rupture	Yes (local)	ICE, RT	Alive (9y)
Loeb 2002	NB	Female	Cellular	CN	Tumor rupture	Yes (local)	Surgery, VCD	Alive (2y)
McCahon 2003	NB	Female	Cellular	AVC	Surgical biopsy	No	-	Alive (2.5y)
Vujanic 1993	14m	Female	Cellular	CN, AV	Margin+	Yes (lungs, heart)	Surgery, IV	Died of pneumonia (2y)
Whittle 2010	NB	Female	Cellular	CN	Surgical biopsy	No	-	Alive (1y)
Irsutti 2000	NB	Male	Classic	CN	Margin+	No	-	Alive (10m)
Walterhouse 1990	2d	Male	Classic	CN	Margin+	No	-	Alive (2y)
Bell 2002	9m	Female	Mixed	Pre-op CT, CN, post-op CT	Margin+	Yes (liver)	Surgery, CT (type unknown)	
Arensman 1980	4d	Male	NA	CN	Tumor rupture	No	-	Alive (2y)
Ehman 1983	NB	Male	NA	CN	Margin+	No	-	Alive (1y)
Goldberg 1994	5m	Male	NA	CN	Tumor rupture	No	-	Alive (1y)
Joshi/Fu 1973	1d	Female	NA	CN	Margin+	Yes (local)	Surgery, AV	Alive (12.5y)

**Abbreviations** ADR: adriamycin, AV: actinomycin/vincristine, AVC: actinomycin/vincristine/cyclophosphamide, AVCD: actinomycin/vincristine/cyclophosphamide/doxorubicin, AVD: actinomycin/vincristine/doxorubicin, CN: complete nephrectomy, CT: chemotherapy, CYC: cyclophosphamide, DOD: died of disease (tumour progression), ICE: ifosfamide/carboplatin/etoposide, IV: ifosfamide/vincristine, NB: newborn, PN: partial nephrectomy, post-op CT: post-operative chemotherapy, pre-op CT: pre-operative chemotherapy, VCD: vincristine/cyclophosphamide/doxorubicin, VCR: vincristine, VIE: vincristine/ifosfamide/etoposide