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Paediatric Oncology Update

Wilms' Tumour

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WILMS' TUMOUR is the paradigm for the treatment of a malignant solid tumour of children and adolescents. Dramatic improvements in survival have occurred as the result of advances in anaesthetic and surgical management, radiation therapy technique and the availability of several very effective chemotherapeutic agents. Despite these successes, additional questions are still to be addressed in three areas—epidemiology and molecular biology, pre-therapy staging and identification of minimal necessary therapy.

EPIDEMIOLOGY AND MOLECULAR BIOLOGY

Wilms' tumour is the most common malignant renal tumour in children. The incidence rate of Wilms' tumour is 8.1 cases per million in Caucasian children less than 15 years of age [1]. In 1996, the total incidence was estimated at 470 cases per year [1, 2]. The incidence rate is approximately three times higher for blacks in the United States and Africa than for East Asians, with rates for Caucasian populations in Europe and North America intermediate between these extremes [3].

Wilms' tumour in the U.S. is slightly less frequent in boys than in girls. The male:female ratio for those with a unilateral tumour is 0.92:1.00, and for those with bilateral tumours is 0.60:1.00 [4]. The tumour presents at an earlier age among males, with the mean age at diagnosis for those with unilateral tumours being 41.5 months compared with 46.9 months among females. The mean age at diagnosis for those who present with bilateral tumours is 29.5 months for males and 32.6 months for females [4].

Children with Wilms' tumour may have aniridia, hemihypertrophy, cryptorchidism and/or hypospadias [5–8]. Children with pseudohermaphroditism and/or renal disease (glomerulonephritis or nephrotic syndrome) who develop Wilms' tumour may have the Denys–Drash syndrome [9, 10], which is associated with mutations within the same chromosomal segment as that involved in the WAGR (Wilms' tumour, aniridia, genitourinary malformation, mental retardation) syndrome [11, 12]. Hemihypertrophy may be an isolated anomaly, or a component of the Beckwith–Wiedemann syndrome (BWS), which includes macroglossia, omphalocele and visceromegaly [13]. Wilms' tumour has occurred in patients with other overgrowth syndromes, including the Perlman [14, 15], Simpson–Golabi–Behmel [16, 17] and Soto syndromes [18]. It has also been described in patients with genetic instability syndromes, including Bloom syndrome [19] and incontinentia pigmenti [20]. Although cases of Wilms' tumour have been reported in children with neurofibromatosis [21, 22], it is not clear whether they are at increased risk of this tumour [23–25].

The aetiology of Wilms' tumour was thought to follow the two-event model proposed by Knudson to explain the pattern of retinoblastoma, in which approximately 10% of patients with sporadic unilateral tumours, and all patients with bilateral tumours, carry a germline mutation of the retinoblastoma tumour-suppressor gene (*RB1*) [26]. This mutation could be either a new germinal mutation transmitted from the father [27, 28] or a mutation transmitted from a carrier or affected parent [29]. In either case the result is loss of function of one of the alleles of the *RB1* gene. A tumour arises only if a second event occurs, with loss of function of the remaining normal *RB1* allele. This loss occurs via one of several mechanisms, all of which result in complete absence of the normal *RB1* gene product within the affected retinal cell [30].

At least three genes are associated with Wilms' tumour. The Wilms' tumour-suppressor gene located at 11p13, *WT1*, was isolated in 1990 [31–33]. There is a constitutional deletion of *WT1* in WAGR patients, and constitutional mutations within the *WT1* gene have been identified in patients with Wilms' tumour who have the rare Denys–Drash syndrome [34], and in patients with sporadic bilateral [35, 36] and sporadic unilateral [37–39] Wilms' tumours. However, specific mutations of *WT1* have been found in only 10% or less of sporadic Wilms' tumours [38, 39].

A second Wilms' tumour locus (*WT2*) maps to chromosome 11p15.5, based on tumour-specific loss of heterozygosity restricted to this region, which does not include *WT1* [40, 41]. The BWS, which carries a predisposition to embryonal tumours including Wilms' tumour, also maps to this location [41]. It is not known whether a single or adjacent genes are involved in both the tumour and the syndrome. Interestingly, in tumours with loss of heterozygosity,

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it is invariably the maternal copy of 11p15 which is lost [40, 42], suggesting that the two copies of *WT2* are not functionally equivalent. This phenomenon is thought to be due to genomic imprinting, a process whereby one allele is marked or imprinted in a parental-specific manner to be functionally inactive. Among tumours which have lost heterozygosity for 11p15, most have been shown to have not lost the insulin-like growth factor II gene (*IGFII*) imprint [43, 44]. It is not yet known what role, if any, *IGFII* actually plays in Wilms' tumorigenesis. However, the fact that GPC3, the product of the Simpson–Golabi–Behmel syndrome gene [45], binds IGFII, suggests that this gene may have a role.

Linkage studies of rare, but large, Wilms' tumour pedigrees have excluded linkage to 11p13 and 11p15 [46, 47] and to 16q [48], suggesting the existence of an as yet unidentified locus where a mutation may predispose to tumour formation. A recent report suggests that a familial Wilms' tumour gene is located at 17q12-q21 [49]. In addition, a new Wilms' tumour associated suppressor gene has been mapped to chromosome 7p13 [50].

PRETHERAPY STAGING

Pretherapy staging includes both the diagnostic imaging evaluation performed prior to exploratory laparotomy, and the staging performed at the time of surgical exploration.

DIAGNOSTIC IMAGING EVALUATION

The initial imaging study is an abdominal ultrasound examination, which will usually allow determination of the organ of origin of the abdominal mass, identify a contralateral kidney, and demonstrate the presence or absence of a tumour thrombus within the inferior vena cava. The inferior vena cava of children with Wilms' tumour has been demonstrated by ultrasonography in 77% of 18 patients in one report [51]. When a tumour thrombus is identified within that vessel, the proximal extent must be established prior to operation. Extension of the thrombus to the right atrium may not be suspected pre-operatively, since there may be few, if any, clinical signs [52, 53]. Exceptionally, sudden death has been reported following dislodgement and mobilisation of the tumour lying within the draining vessels at laparotomy [54].

Contrast enhanced computed tomography of the abdomen, performed to evaluate further the nature and extent of the mass, may suggest apparent extension of the tumour into adjacent structures such as the liver, spleen and or colon. However, most children identified by computed tomography as having possible invasion of the liver are found by surgical exploration to have hepatic compression rather than invasion [55]. In addition, the examination may demonstrate small lesions which may be nephrogenic rests or Wilms' tumour in the opposite kidney [56]. Small superficial or intrarenal lesions are frequently missed even when computed tomography is employed [56, 57].

Plain chest radiographs should be obtained to determine if pulmonary metastases are present. Computed tomography has been compared to conventional radiographic studies in Wilms' tumour patients in two studies. In the first, only 9.4% (11/117) of the computed tomography scans demonstrated densities not identified on a plain chest radiograph—none of these patients underwent open lung biopsy for confirmation of the histology of the pulmonary lesions [58]. In the other, only 2.4% (2/83) of the computed tomography scans demonstrated densities not identified using chest radiography—one of the lesions was shown pathologically to be a granuloma, not a metastasis [59]. Others have reported that eight of ten biopsied lesions from the lungs of children with Wilms' tumour identified only by computed tomography, were, in fact, pulmonary metastases [60, 61].

A radionuclide bone scan and X-ray skeletal survey should be obtained postoperatively on all children with clear cell sarcoma of the kidney. Both studies are necessary because plain radiographs of the bones involved with clear cell sarcoma of the kidney can demonstrate lytic lesions that may not be seen on bone scan [62, 63].

Brain imaging, using magnetic resonance imaging (MRI) or computed tomography (CT), should be conducted on all children with clear cell sarcoma of the kidney or with rhabdoid tumour of the kidney, since both are associated with intracranial metastases [64, 65]. Second primary malignant brain tumours of various histological types, often arising in the posterior fossa, are also found in patients with rhabdoid tumour of the kidney [65–67].

SURGICAL STAGING

Surgical staging includes thorough examination of the contralateral kidney after opening Gerota's fascia, retroperitoneal lymph node sampling and palpation of the liver.

In the National Wilms' Tumor Study (NWTS)-1, bilateral disease was identified in only 56.6% of 30 children by intravenous urography [68]. In a review of patients with bilateral Wilms' tumour in NWTS-2 and NWTS-3, computed tomography of the abdomen was accurate in diagnosing synchronous bilateral Wilms' tumour in 83% of patients [69].

Recently, authors have argued that formal exploration of the contralateral kidney is not necessary because of the improved sensitivity of computed tomography and magnetic resonance imaging. These series have included small numbers of patients, and thus lack sufficient statistical power to support their conclusions [70–72]. Contralateral nephrogenic rests were correctly identified on magnetic resonance imaging scans of all 5 patients with a contralateral lesion, but only 57% of 14 nephrogenic rests, including the five contralateral lesions, were identified using this modality [73]. Thus, currently, no imaging technique is sufficiently sensitive and specific to replace the surgeon's inspection of the contralateral kidney.

Biopsy of suspicious lesions must include the junction between the abnormal tissue and normal kidney to facilitate accurate diagnosis of small lesions. The presence of a pseudocapsule at the boundary between the abnormal tissue and normal kidney supports the diagnosis of Wilms' tumour, whereas the diagnosis of nephrogenic rest is made when no pseudocapsule separates these [74].

The decision to not explore the contralateral kidney requires consideration of three issues:

(i) The frequency with which bilateral Wilms' tumour will be incorrectly diagnosed as unilateral Wilms' tumour: A recent review of 122 patients with synchronous bilateral Wilms' tumour enrolled in NWTS-4 noted that 7% of bilateral lesions were not identified by the pre-operative imaging studies [56]. Although the risk of contralateral relapse in this group of patients is not known, the data of Jones and colleagues suggest that misdiagnosis of synchronous

bilateral Wilms' tumour due to inadequate initial surgical evaluation was the primary aetiological factor of metachronous bilateral Wilms' tumour, a condition with a very poor prognosis [75] and a high risk of renal failure [76], due to the need for bilateral nephrectomy.

(ii) The risk of not identifying a nephrogenic rest in the contralateral kidney: The frequency of nephrogenic rests in the contralateral kidney at the time of the initial surgical exploration is not known. The presence of nephrogenic rests in the nephrectomy specimen is associated with an increased risk of metachronous bilateral Wilms' tumour [77]. This emphasises the need for more frequent evaluation of the remaining kidney in the course of postnephrectomy follow-up to facilitate early diagnosis of contralateral relapse in the one per cent of Wilms' tumour patients who will be so affected [78].

(iii) The possibility that contralateral renal exploration increases the surgical morbidity of children undergoing abdominal exploration for removal of a Wilms, tumour: In a recent review, Ritchey reported that the frequency of intestinal obstruction was 5.6% in patients who had not undergone contralateral renal fossa exploration after Gerota's fascia was opened [79], compared to 6.9% among all patients evaluated for surgical complications on NWTS-3 [56]. No patient suffered renal injury as the result of contralateral renal exploration [80].

The presence of tumour cells in retroperitoneal lymph nodes is an important prognostic factor for children with Wilms' tumour. Although a formal retroperitoneal lymph node dissection is not necessary, lymph node sampling should be performed. If no suspicious lymph nodes are identified, one or more apparently normal lymph nodes should be removed. Histological evidence of Wilms' tumour has been identified in 11.5% of removed lymph nodes that the operating surgeon evaluated as negative for tumour [81].

The staging system currently employed by the National Wilms' Tumor Study Group (NWTSG) is outlined in Table 1.

IDENTIFICATION OF MINIMAL NECESSARY THERAPY

Single dose drug administration

Previous success in treatment strategies allowed the design of a unique study, NWTS-4, with the primary aims of continuing to improve treatment results while decreasing the cost of therapy through modification of the schedule of drug administration. This study was based on experimental [82] and clinical [83–86] data demonstrating the safety and efficacy of actinomycin-D when administered in a single, moderately high dose.

The design of NWTS-4 (Figure 1) allowed the results of 'pulse-intensive' (PI) chemotherapy regimens employing single doses of actinomycin-D and doxorubicin to be compared with treatment regimens using divided dose regimens of each drug (STD). In addition, treatment durations of approximately 6 and 15 months were compared in patients with stages II–IV/favourable histology (FH) Wilms' tumour and stages I–IV clear cell sarcoma of the kidney (CCSK). Patients less than 16 years of age were stratified into low-risk (LR) and high-risk (HR) categories. Those with stages I–II/FH or stage I/focal anaplastic Wilms' tumour were classified as LR and those with stages III–IV/FH Wilms' tumour or stages I–IV/CCSK were classified as HR. Patients were randomised to treatment which included vincristine and either divided dose (STD) courses (5 days) or single dose (PI) treatment with actinomycin-D. HR patients also received either divided dose (STD) courses (3 days) or single dose (PI) treatment with doxorubicin.

Toxicity analyses confirmed that the PI regimens produced less haematological toxicity than the STD regimens, and that the administered drug dose-intensity was greater

Table 1. The staging of Wilms' tumour by the National Wilms' Tumor Study Group

Stage I	The tumour is limited to the kidney and is completely excised. The renal capsule has an intact outer surface. The tumour is not ruptured or biopsied prior to removal (fine needle aspiration biopsies are excluded from this restriction). The vessels of the renal sinus are not involved. There is no evidence of tumour at or beyond the margins of resection.
Stage II	The tumour extends beyond the kidney, but is completely excised. There may be regional extension of tumour (i.e. penetration of the renal capsule or extensive invasion of the renal sinus). The blood vessels outside the renal parenchyma, including those of the renal sinus, may contain tumour. The tumour is biopsied (except for fine needle aspiration), or there is spillage of tumour before or during surgery that is confined to the flank, and does not involve the peritoneal surface. There must be no evidence of tumour at or beyond the margins of resection.
Stage III	Residual non-haematogenous tumour is present, and confined to the abdomen. Any one of the following may occur: (1) lymph nodes within the abdomen or pelvis are found to be involved by tumour (renal hilar, para-aortic or beyond). (Lymph node involvement in the thorax, or other extra-abdominal sites would be a criterion for stage IV.); (2) the tumour has penetrated the peritoneal surface; (3) tumour implants are found in the peritoneal surface; (4) there is residual gross or microscopic tumour postoperatively (e.g. tumour cells are found at the margin of surgical resection on microscopic examination); (5) the tumour is not completely resectable because of local infiltration into vital structures; (6) tumour spill is not confined to the flank, occurring either before or during surgery.
Stage IV	Haematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdomino-pelvic region are present.
Stage V	Bilateral renal involvement is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease prior to biopsy or treatment.

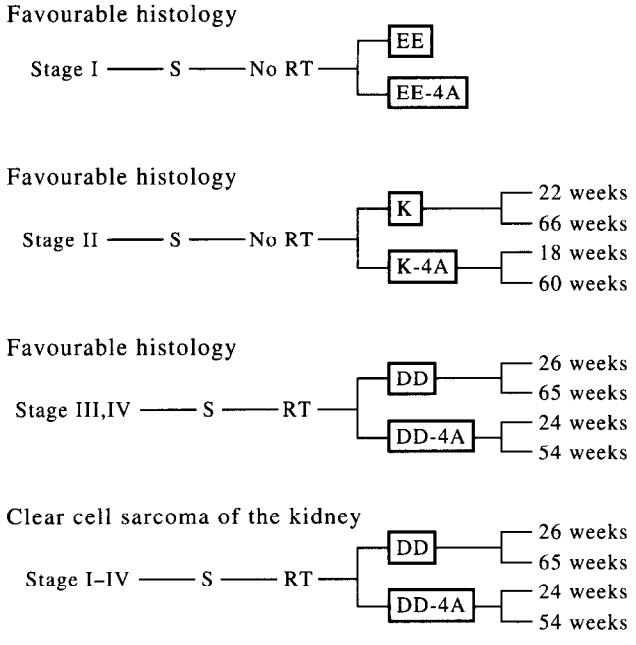

Figure 1. Treatment randomisation for National Wilms' Tumor Study-4.

on the PI regimens [87]. In addition, an analysis of the cost of chemotherapy treatment suggested that at least $790 000/year could be saved if all U.S. children with stages I–IV/FH Wilms' tumour were treated using the PI regimens [88]. The randomisation for children with stages I and II/FH and stage I/anaplastic Wilms' tumour was closed in February 1994, and that for children with stages III and IV/FH Wilms' tumour and stages I–IV/CCSK in September 1994.

The 2-year relapse-free survival (RFS) percentages for LR patients were 90.8 (±1.3) for 542 treated with PI and 91.2 (±1.3) for 554 treated with STD chemotherapy ($P = 0.89$). The 2-year RFS percentages for HR patients were 86.7 (±2.1) for 301 treated with PI and 89.1 (±2.0) for 291 treated with STD chemotherapy ($P = 0.73$) [89].

The minimal necessary treatment for patients with Wilms' tumour with focal or diffuse anaplasia [74, 90] was determined through a comparison between a three drug chemotherapy regimen that included vincristine, actinomycin-D and doxorubicin (regimen DD-RT) or these three drugs and cyclophosphamide (regimen J) [91]. The 4-year relapse-free survival percentage for 5 children with focal anaplasia who received regimen DD-RT was 80.0%, compared to 100.0% for 8 who received regimen J ($P = 0.68$). The 4-year relapse-free survival percentage for 29 children with diffuse anaplasia treated with regimen DD-RT was 27.2%, compared to 54.8% for 30 treated with regimen J ($P = 0.02$) [92].

RENAL PARENCHYMAL SPARING SURGERY

Successful therapy for children with unilateral, non-metastatic Wilms' tumour has included radical nephrectomy and combination chemotherapy for all patients, with the addition of abdominal radiation therapy to the treatment plan for those with stage III tumours.

Several authors have suggested that renal parenchymal sparing surgical procedures should be employed for the management of children with unilateral Wilms' tumour, to decrease their risk of late renal failure due to hyperfiltration injury. To determine the feasibility, one needs to define the candidates for this approach. Stringent criteria include: (1) tumour limited to one pole and occupying less than one-third of the kidney; (2) preserved renal function in the involved kidney; (3) no tumour invasion of the collecting system or the renal vein; and (4) clear margins between the tumour, kidney and surrounding structures. Using these criteria, investigators at St Jude Children's Research Hospital, determined that only 4.6% of 43 previously untreated patients would have been eligible at the time of diagnosis for partial nephrectomy [93]. Using similar criteria, investigators from the Emma Kinderzuikenhuis, Amsterdam, reported that 8.8% of 79 children who received prenephrectomy combination chemotherapy were candidates for partial nephrectomy [94], and investigators from the Austrian/Hungarian Wilms' Tumor Study reported that 8.1% of 37 similarly treated children with unilateral Wilms' tumour were candidates for partial nephrectomy [95].

The possible benefit of renal parenchymal sparing surgical procedures must be weighed against the potential risks of such procedures. Perilobar and/or intralobar nephrogenic rests were identified in 28.4% of 282 unilateral Wilms' tumour specimens. These rests are precursor lesions for Wilms' tumour, and are associated with metachronous bilateral Wilms' tumour [77]. Failure to include such microscopic lesions in the surgical specimen could increase the risk of intra-abdominal tumour recurrence in patients who have an excellent prognosis with current treatment approaches.

PRENEPHRECTOMY CHEMOTHERAPY

To decrease the need for post-operative abdominal radiation therapy for treating patients whose tumour ruptures during nephrectomy, the investigators of the International Society of Pediatric Oncology (SIOP) conducted a series of trials in which all patients received either chemotherapy or abdominal radiation therapy before the nephrectomy. Prenephrectomy abdominal irradiation decreased the percentage of nephrectomies complicated by tumour rupture from 33% (20/60) to 4% (3/72) [96]. In a subsequent randomised trial, the frequency of tumour rupture was nearly the same for patients treated with prenephrectomy abdominal irradiation and actinomycin-D (9%, 7/76) and for those treated with prenephrectomy chemotherapy with vincristine

Table 2. Loss of heterozygosity 16q

		Relapses		Deaths		% at 2 years	
	Number of patients	Obs	Exp	Obs	Exp	RFS	Alive
Absent	169	12	16.1	3	7.6	89.5	97.4
Present	35	7	2.9	6	1.4	77.6	84.4
		($P < 0.01$)		($P < 0.0001$)			

and actinomycin-D (6%, 5/88) [97]. The frequency of tumour rupture observed among the non-irradiated SIOP patients was higher than that reported among patients without haematogenous metastases entered on NWTS-1 (22%, 92/427) [98], NWTS-2 (12%, 76/626) [99] or patients with FH Wilms' tumour entered on NWTS-3 (13%, 195/1466) [100].

NWTSG investigators recommend immediate nephrectomy because the administration of prenephrectomy chemotherapy is associated with several risks, including: (a) administration of combination chemotherapy to a patient with a benign disease; (b) administration of combination chemotherapy to a patient with a different histological type of malignant tumour; (c) modification of tumour histology; and (d) loss of staging information.

The results of both the NWTS and the SIOP nephroblastoma trials demonstrated that 7.6% (40/522) [101] to 9.9% (44/442) [96] of patients with the prenephrectomy diagnosis of Wilms' tumour have a benign or malignant condition other than Wilms' tumour. Recent data suggest that, even with the use of modern imaging techniques, an incorrect diagnosis will be made in 4.8% of patients [102].

The effect of prenephrectomy chemotherapy on tumour histology has been evaluated in 140 patients with unilateral Wilms' tumour registered on the NWTS. The percentage of patients in this group with anaplastic tumours was 6.4% (9/140) [103] compared to 3.4% among the first 1700 patients entered on NWTS-3 [104], suggesting that the administration of prenephrectomy chemotherapy did not modify tumour histology to such an extent that the features diagnostic of anaplasia could not be identified. However, the available data raise other possibilities, including the induction of cytological changes consistent with anaplasia in tumours which, prior to treatment, may have had favourable histology, or the occurrence of an increased frequency of rapidly growing, invasive tumours within the anaplastic category.

The major concern regarding the management of children who receive prenephrectomy chemotherapy is the potential for loss of important staging information. This concern is exemplified by the recent experience reported by the investigators in SIOP. They designed a clinical trial in which patients treated with prenephrectomy combination chemotherapy, who were subsequently diagnosed as stage II Wilms' tumour without regional lymph node involvement were randomised either to receive no irradiation or abdominal irradiation postnephrectomy. All received postnephrectomy adjuvant chemotherapy which included vincristine and actinomycin-D. The trial was discontinued because an unexpected, statistically significant excess of intra-abdominal recurrences occurred in the non-irradiated patients [105]. This result suggested that prenephrectomy chemotherapy produced sufficient tumour response to destroy perinephric tumour extensions and/or tumour deposits which were present in regional lymph nodes [106].

The study recently completed by the NWTSG, NWTS-4 [89], and the current study of SIOP, SIOP Nephroblastoma Trial-9, employ abdominal irradiation and/or treatment with a combination chemotherapy regimen, which includes an anthracycline, for specific groups of patients. Those with stage II, lymph node positive Wilms' tumour on SIOP nephroblastoma trials are included in stage III in the NWTS. Employing the staging system developed by the NWTSG Study Committee, and placing SIOP patients with stage II, lymph node positive Wilms' tumour in stage III, one can demonstrate, using the stage distributions of patients entered on NWTS-3 and SIOP Nephroblastoma Trial-6, that approximately 50% more European than North American stage I–III FH Wilms' tumour patients will be treated with an anthracycline (SIOP-6: 45.5%, 201/442; NWTS-3: 29.3%, 449/1528), whereas approximately 50% more North American than European patients will be treated with abdominal irradiation (SIOP: 18.0%, 80/442; NWTS: 29.3%, 449/1528) [91, 105]. Thus, the efficacy of prenephrectomy treatment must be evaluated with respect to anthracycline exposure, with its risks of congestive heart failure [107] and carcinogenesis [108, 109], as well as the risk of tumour rupture and exposure to abdominal irradiation.

WHOLE LUNG RADIATION THERAPY

Patients with stage IV/FH Wilms' tumour with metastatic disease restricted to the lung(s) have an excellent prognosis, with more than 80% of such patients entered on NWTS-3 alive 4 years after diagnosis [91]. The treatment approach employed for patients with stage IV/FH Wilms' tumour in the NWTS includes immediate nephrectomy, followed by postnephrectomy whole lung irradiation. Abdominal radiation therapy is restricted to those patients who have a stage III primary tumour. All patients receive combination chemotherapy with vincristine, actinomycin-D and doxorubicin.

In NWTS-2, patients with stage IV/FH Wilms' tumour were randomised to treatment with vincristine and actinomycin-D (regimen C) or vincristine, actinomycin-D and doxorubicin (regimen D). All received abdominal and whole lung irradiation [110]. The 4-year, relapse-free survival percentages were 53.3% for those on regimen C and 57.7% for those on regimen D ($P = 0.63$). The 4-year survival rates were 53.3% for those on regimen C and 61.5% for those on regimen D ($P = 0.62$) [111].

Investigators in the United Kingdom Children's Cancer Study Group (UKCCSG) and SIOP evaluated different approaches to the management of patients with stage IV/FH Wilms' tumour. Both groups sought to avoid the use of whole lung irradiation, recognising the significant acute and long-term toxicity associated with such treatment [112]. Patients with stage IV Wilms' tumour entered on the UKCCSG Nephroblastoma Study-1 were treated with alternating courses of CVAd (cyclophosphamide, vincristine, doxorubicin) and CVActD (cyclophosphamide, vincristine, actinomycin-D) given every 3 weeks, either following nephrectomy or prior to nephrectomy, if the attending surgeon and paediatric oncologist determined that the tumour was inoperable. Those patients who had complete resolution of the pulmonary metastases after 12 weeks of chemotherapy did not receive whole lung irradiation. Chemotherapy was administered for 12 months from the date of complete remission, whether induced by the initial period of drug treatment or whole lung irradiation. The 6-year disease-free survival percentage was 50% for the 39 stage IV/FH Wilms' tumour patients so treated, 4 of whom received whole lung irradiation. The 6-year survival percentage was 65% [113].

Investigators from SIOP treated 36 patients with stage IV Wilms' tumour with 6 weeks of prenephrectomy chemotherapy consisting of vincristine, actinomycin-D and doxorubi-

cin. Postnephrectomy whole lung irradiation was administered only to those patients who did not have a complete response of the pulmonary metastases to the chemotherapy regimen with or without surgical excision of residual metastases. One third of the patients entered on this study had a solitary, unilateral metastasis. Seventy-five per cent of the patients had a complete response to the initial 6-week period of combination chemotherapy, including 10 of the patients with a solitary metastasis and 17 of those with multiple metastases. The relapse-free and overall survival percentage for these patients, 7 of whom received whole lung irradiation, was 83% [114]. The 4-year relapse-free survival rate was 85% for the patients who achieved a complete response of the pulmonary metastases to chemotherapy, and 78% for those who did not achieve a complete response to chemotherapy (Jan De Kraker, M.D., Emma Children's Hospital, Amsterdam, The Netherlands, 1990). The results of this limited institution pilot study need to be confirmed in a larger SIOP group-wide study.

The results of the studies conducted by the NWTSG suggest that some patients with stage IV/FH Wilms' tumour may be treated successfully without the use of an anthracycline, while those of SIOP and UKCCSG suggest that some may be treated successfully without whole lung irradiation. Evaluation of biological prognostic factors in this group of patients will allow identification of a group with favourable biological prognostic factors in whom a trial of therapy without an anthracycline or without whole lung irradiation could be conducted.

SURGERY ONLY

Recently, the need for any therapy after nephrectomy for a subgroup of children with stage I/FH Wilms' tumour has been questioned. Based on observations made by Garcia and coworkers [115], and a review by Green and Jaffe [116] of patients treated at the Dana-Farber Cancer Institute and staged according to the system suggested by Garcia [115] and Cassady [117], a prospective evaluation of eight patients with stage I (Cassady)/FH Wilms' tumour treated at the Dana-Farber Cancer Institute with nephrectomy only was undertaken. The results of this trial suggested that the risk of recurrence was similar to that of patients treated on the NWTS with nephrectomy, vincristine and acinomycin-D [118].

A review of children treated on NWTS-1, NWTS-2 and NWTS-3 supported the hypothesis that changes in the NWTS regimens had not improved upon the excellent prognosis of children who were less than 2 years of age at diagnosis whose tumours weighed less than 550 grams [119].

Weeks and his colleagues identified four features in stage I/FH Wilms' tumour patients, which appeared to be associated with an increased risk of relapse. The four factors were the presence of: (1) an inflammatory pseucapsule; (2) renal sinus invasion; (3) capsular invasion; and (4) intrarenal vessel invasion. When all four were absent, the risk of tumour recurrence was negligible [120]. Age at diagnosis less than 24 months, and tumour weight less than 550 g are highly correlated with the absence of adverse microsubstaging [121]. Thus, this group of children will be treated on NWTS-5 with nephrectomy only.

TREATMENT OF PATIENTS WITH RECURRENT WILMS' TUMOUR

Children with relapsed, FH Wilms' tumour have a variable prognosis, depending upon their initial stage, the site of relapse, the time from initial diagnosis to relapse and their previous therapy. Favourable prognostic factors include no prior treatment with doxorubicin, relapse more than 12 months after diagnosis, and subdiaphragmatic relapse in a patient not previously given abdominal irradiation [122].

Children in this more favourable group should be treated aggressively because they generally have a good response to retrieval therapy. Surgical excision of pulmonary metastases does not result in an increase in the number of children who do not have a second relapse [123], but surgical biopsy or excision of recurrence should, nonetheless, be performed to confirm histologically the presence of recurrent disease, and to document the site(s) of relapse, and, in the case of intra-abdominal recurrence, to reduce the tumour burden prior to the initiation of radiation therapy and combination chemotherapy. The optimal chemotherapy regimen has not been defined, but should include agents not previously employed, such as doxorubicin, cyclophosphamide, etoposide and carboplatin.

Patients who relapse after prior treatment with a regimen that included doxorubicin, or who develop a recurrence in the abdomen (including liver) after previous irradiation have a poor prognosis. The combination of etoposide and ifosfamide has rarely produced prolonged responses in these children [124, 125]. Several centres have suggested that a more aggressive approach, including the use of autologous bone marrow transplantation, should be employed in the management of patients with adverse prognostic factors at the time of relapse [126–128]. In general, these children should be referred to centres conducting research on the role of autologous bone marrow transplantation in the treatment of children with recurrent solid tumours. When this is not possible or desired by the family, these patients would generally be eligible for phase I or II studies.

BIOLOGICAL PROGNOSTIC FACTORS

Consistent genetic changes have been identified in Wilms' tumour tissue at 11p13, 11p15, 16q and 1p [129]. One or more genes within these regions may be involved in dysregulation of cellular proliferation, differentiation and/or localisation. Recently, Grundy and coworkers correlated treatment outcome with the presence of specific genetic abnormalities. In a study of 232 children with Wilms' tumour, registered on NWTS-3 and NWTS-4, it was shown that loss of heterozygosity of 16q, present in 17.2% of tumours from those with FH or anaplastic Wilms' tumour, was associated with statistically significantly poorer 2-year relapse-free and overall survival percentages (Table 2) [130]. The difference remained when the analysis was adjusted for stage or histology.

Loss of heterozygosity of chromosome 1p, present in 11% of Wilms' tumour, has been associated with poorer relapse-free and overall survival, although with borderline statistical significance ($P = 0.08$ and 0.12, respectively) [130]. By contrast, loss of heterozygosity for 11p or duplication 1q, present in 33% and 25% of cases, respectively, has not been associated with any difference in outcome.

CONCLUSION

The treatment of children with Wilms' tumour is very successful. Current clinical research is directed toward defining the minimal necessary therapy for successful treatment of children with Wilms' tumour by reducing the size of the group exposed to anthracyclines, using biological prognostic factors to identify stage III–IV/FH Wilms' tumour patients who have a low risk of relapse, increasing the amount of renal tissue remaining in children with bilateral Wilms' tumour, and confirming that children less than 24 months of age at diagnosis with stage I/FH Wilms' tumours weighing less than 550 g can be successfully treated with only nephrectomy. In addition, increased effort is being devoted to identifying and understanding the function of several Wilms' tumour-associated genes.

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