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ORIGINAL ARTICLE

Factors responsible for stage III disease in patients with Wilms tumor enrolled in the JWiTS-2 study

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Abstract

Background/objectives Treatment is more intensive for stage III Wilms tumor (WT) than for stages I and II non-metastatic WTs. Various factors including tumor spillage, unresectability, and lymph node metastasis are responsible for stage III disease. The present study aimed to not identify clinical factors associated with the features of stage III WT to establish new treatment strategies.

Design/methods Of 166 patients with non-metastatic WT enrolled in the Japan Wilms Tumor Study (JWiTS)-2, 51 patients had stage III disease. The treatment protocol for JWiTS-2 was essentially the same as that in the National Wilms Tumor study (NWTS)-5. Local hospitals were surveyed to collect details of clinical findings related to stage III disease, and data regarding 45 (88%) patients were obtained.

Results Nine patients with massive tumors underwent preoperative chemotherapy. Biopsy was performed in 6. Reduction in the tumor size was achieved in 8 of the 9 cases. Nephrectomy was finally performed in all of them. Thirty-six patients underwent primary nephrectomy. The reason for the stage III disease was lymph node metastasis ($n=9$, 25%), tumor spillage ($n=20$, 56%), and tumor extension/incomplete resection ($n=17$, 47%). Some patients had more than one of these factors. Most patients were treated with the DD-4A regimen, and 43 (95.6%) of the 45 patients received abdominal radiation therapy. Tumors recurred in three patients (local, 1; metastasis, 2), and two patients died. Overall and relapse-free survival rates were 95.2% and 90.8%, respectively.

Conclusion The prognosis of stage III WT was good. In the next stage, the doses of chemotherapy and radiotherapy should be reduced to avoid late effects. The high rate of tumor spillage after primary resection suggests that preoperative chemotherapy should be started instead of aggressive tumor resection in the large tumor cases with surgical risks

Keywords Wilms tumor · Stage III · JWiTS · Spillage

Introduction

The survival rates for patients with Wilms tumor (WT) have improved dramatically to almost 90% [1]. Improvements in survival have occurred because of advances in multimodality treatments, including surgical management, irradiation, and chemotherapy. Such advances were established in clinical trials conducted by a number of cooperative national and international groups, such as the National Wilms Tumor Study (NWTS) group (now a part of the Children's Oncology Group (COG) in the USA) [2] and the International Society of Pediatric Oncology (SIOP) [3]. In NWTS studies, primary surgical resection of the tumor was the initial treatment for most children, whereas chemotherapy was the initial treatment in the SIOP studies.

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In Japan, the Japan Wilms Tumor Study (JWiTS) group was founded in 1996, and a nationwide multicenter cooperative study was initiated to improve the outcomes of children with renal tumors [4, 5]. The protocol regimens used in JWiTS were similar to those of the NWTS-5 regimens. In these regimens, tumor stage is a major determinant of therapy. Treatment is more intensive for stage III than for stages I and II, and the increased treatment, such as additional doxorubicin and abdominal irradiation, increases the toxicity of therapy [6, 7].

In the COG staging system, clinical stage is determined after an initial surgical procedure (either tumor biopsy or unilateral nephrectomy and lymph node sampling). Stage III disease consists of the various clinical conditions shown in Table 1. These factors can be classified into the four clinical conditions: (1) positive lymph nodes; (2) tumor spillage/rupture; (3) residual disease/incomplete resection; and (4) initial chemotherapy due to unresectable tumor. However, previous studies have not shown which factor is most responsible for stage III disease. The objective of this study was to identify the clinical factors associated with the features of stage III WT to improve the treatment strategies.

Design/methods

Of the 166 patients with non-metastatic WT enrolled in the JWiTS-2 study (2006–2014), 51 had stage III disease. The treatment protocol of JWiTS-2 was essentially the same as that of NWTS-5, which was described previously [1–4]. Patients underwent nephrectomy before chemotherapy, unless the primary tumor was considered to be unresectable by the treating surgeon, in which case a biopsy was performed followed by initiation of chemotherapy. Tumor stage was assigned based on the surgical and pathologic findings after tumor resection.

Local hospitals were surveyed to collect details of the clinical findings related to stage III disease shown in Table 1, as well as radiological factors such as tumor size, vascular compression, and contralateral extension. Data regarding 45 patients (88%) were obtained and analyzed. Different criteria leading to stage III designation were assessed. Event-free survival (EFS) and overall survival (OS) were estimated using Kaplan–Meier methods [8].

This retrospective study was approved by the ethical review board of Hyogo College of Medicine (Approved No. 2006). Each institution obtained local institutional review board approval before enrolling patients into the JWiTS-2 study.

Results

Treatments

All patients were treated with the DD-4A regimen using vincristine, actinomycin-D, and doxorubicin. Abdominal radiation therapy was performed in 43 (95.6%) of the 45 patients. Thirty-six patients (80%) underwent primary nephrectomy, and 9 patients (20%) with massive tumors were considered to be unresectable and underwent preoperative chemotherapy. Of these patients who underwent initial chemotherapy, six underwent biopsy. Reduction in the tumor size was achieved in eight of the nine cases, and nephrectomy with complete tumor resection was finally performed in all nine cases.

Prognosis

Five-year EFS and OS estimates for the 45 patients with stage III tumor were 90.8% and 95.2%, respectively. Tumors recurred in three patients (local, 1; metastasis, 2), and two cases died of disease.

Table 1 Criteria of Stage III in the JWiTS-2 study

Stage III—residual non-hematogenous tumor present following surgery, and confined to the abdomen
Any one of the following may occur:
Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax or other extra-abdominal sites is a criterion for Stage IV)
The tumor has penetrated through the peritoneal surface
Tumor implants are found on the peritoneal surface
Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination)
The tumor is not completely resectable because of local infiltration into vital structures
Tumor spillage occurring either before or during surgery
The tumor is treated with preoperative chemotherapy (with or without a biopsy regardless of type, tru-cut, open, or fine-needle aspiration) before removal
Tumor is removed in greater than one piece (e.g., tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen). Extension of the primary tumor within the vena cava into the thoracic vena cava and heart is considered Stage III, rather than Stage IV even though it is outside the abdomen

Factors associated with stage III disease

Of the 36 patients who underwent primary nephrectomy, the reasons for stage III disease were LN metastasis in 9 (25%), tumor spillage/rupture in 20 (56%), and residual disease/incomplete resection in 17 (47%).

Factors associated with Stage III criteria in the cases with primary operation occurred in isolation or in combination with other stage III criteria (Fig. 1). Tumor spillage alone was the most frequent criterion for stage III designation (13 cases), followed by residual tumor alone (9 cases), LN involvement alone (6 cases), and spill and residual tumor (5 cases). Theoretically, tumor spillage should be occurring when there was a residual tumor, but surgeon in the local hospital considered that there was no tumor spillage.

Relationships between the criteria for stage III disease and tumor size, contralateral tumor extension, and compression of the great vessels were evaluated (Table 2). In the cases with unresectable tumor, spillage of tumor, or incomplete resection, the mean tumor diameter was around 11 cm, and contralateral tumor extension, as well as compression of the great vessels, was often observed, however, there was no statistical difference.

Discussion

The prognosis of patients with localized WT has been improving. In the present study, 5-year EFS and OS of patients with stage III tumor were 90.8% and 95.2%, respectively. The next goal of treatment is identification of approaches to minimize treatment-related toxicity while maintaining the excellent outcomes. If the localized WT is diagnosed as stage III, additional use of anthracycline chemotherapy and XRT substantially increases the risk of short- and long-term toxicities, such as congestive heart failure, coronary artery disease, impaired renal function, second malignancies, and adverse pregnancy outcomes [9–15]. Therefore, the present study examined which of the features of stage III disease is most responsible to improve the treatment of localized WT. Among the patients enrolled in the JWiTS-2 study, the most frequent factor associated with stage III disease was tumor spillage (56%), followed by residual tumor (46%). These results suggest that more than half of the tumors became stage III due to the surgical procedures.

Resection of large tumors sometimes results in intraoperative tumor rupture and spillage into the abdomen, which

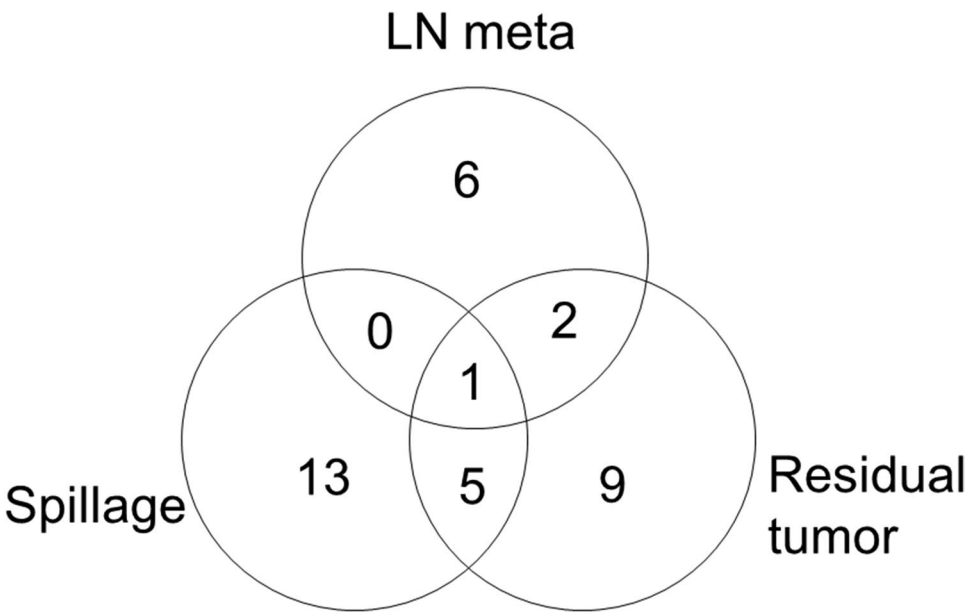

Fig. 1 Factors associated with Stage III criteria in the cases with primary surgery that occurred in isolation or in combination with other stage III criteria

Table 2 Relationships between the criteria for stage III disease and tumor size, contralateral tumor extension, and compression of the great vessels

Criteria of stage III	No	Tumor size (cm) Mean ± SD (range)	Contralateral extension	Compression of the great vessels
Unresectable	9	11.4 ± 1.9 (8.7–13.2)	9/9	8/9
Spillage	19	11.5 ± 2.9 (8.6–13.0)	13/19	15/19
Residual tumor	17	11.1 ± 2.5 (8.0–13.0)	9/17	12/17
Lymph node metastasis	9	10.3 ± 1.9 (8.0–13.0)	2/9	4/9

increases the risk of local abdominal relapse and a subsequent poor outcome [16]. Resection of extra-large tumor also increases the risk of residual tumor after operation. Such cases are considered to involve "surgical risks". If these patients had been treated with initial chemotherapy, reduction of tumor size would be achieved, and tumor may have been completely resected without spillage; thus, preoperative chemotherapy may be a better choice as the initial treatment. The relationship between tumor size and tumor spillage has been previously discussed. Gow et al. reported that a larger tumor size is a risk factor for intraoperative tumor spillage. Among the patients registered in the COG clinical trial, the overall rate of intraoperative tumor spillage was 11.9%, and the odds of intraoperative tumor spillage were 2.183 times higher for patients with a maximum tumor diameter of > 12 cm compared with < 12 cm [17]. Barber et al. reported that tumor volume greater than 1000 ml was significantly associated with intraoperative tumor spillage [18]. In the present study, mean tumor diameter in the cases with unresectable tumor or with tumor spillage was around 11.4 cm and 11.5 cm, respectively. Considering the observations of these reports, we recommend that cases with tumor size in excess of 12 cm or volume greater than 1000 ml should receive preoperative chemotherapy to reduce the surgical risks.

Recently, a pre-treatment risk classification system in cases with neuroblastoma was established by the International Neuroblastoma Risk Group (INRG) [19, 20]. In this INRG staging system (INRGSS), locoregional neuroblastomas are staged as L1 or L2 based on the absence or presence of imaging-defined risk factors (IDRFs), respectively. IDRFs were proposed by the INRG task force to predict the surgical risks of localized neuroblastoma, and they could be a tool for determining whether a patient should undergo surgery or chemotherapy at the time of diagnosis. However, in WT, these kinds of imaging-based surgical risk factors have not been established. Therefore, we performed a preliminary study to elucidate the preoperative imaging parameters to identify high-risk surgical cases [21]. Our data have shown that not only tumor size, but contralateral extension and compression of the great vessels, should also be included in the preoperative imaging-based surgical risk factors. In the present study, contralateral tumor extension was observed in all of the unresectable cases and in 13 of the 19 cases with spillage. Compression of great vessels was observed in 8 of 9 unresectable cases and 15 of 19 spillage cases. These findings indicate that most of the stage III cases could be predicted to have had surgical risks using the preoperative CT images. Patients with these surgical risk factors should receive preoperative chemotherapy to decrease tumor size, and they may then be easily resected.

According to both the JWiTS and the NWTS protocols, in unresectable cases, incisional biopsy is performed first, followed by three-drug chemotherapy and whole-abdomen radiotherapy. In the present study, eight cases were considered to be unresectable and received initial chemotherapy. The tumor was completely resected in every case after chemotherapy. In the NWTS/COG study, tumor biopsy was considered to increase the risk of intra-abdominal tumor spillage and tumor recurrence. Therefore, according to the current COG staging system, patients who undergo tumor biopsy should be classified as stage III so that doxorubicin and radiation therapy cannot be omitted.

In contrast, in the recent SIOP staging system, needle biopsy before chemotherapy is not included in the criteria of stage III. A recent report from the UK trial showed that needle biopsy is not associated with an increased risk of tumor relapse [22]. Therefore, we recommend that large tumor with surgical risks should be treated with the SIOP treatment strategy: needle biopsy and preoperative chemotherapy instead of primary tumor resection. If the tumor size decreases after chemotherapy, complete tumor resection can be easily performed without tumor spillage, and the tumor will become stage I or II. Finally, the number of cases with stage III will decrease, and reduction of anthracyclines or XRT may be considered to reduce long-term complications [14].

The prognosis of stage III WT was good. In the next stage, the doses of chemotherapy and radiotherapy should be reduced to avoid late effects. Our data revealed that the most reason of stage III disease was tumor spillage after primary resection. Therefore, we suggest that preoperative chemotherapy should be started instead of aggressive tumor resection in the cases with large tumor with surgical risks.

Limitations

The present study has some limitations. It was retrospective in nature, and multivariate analysis could not be performed because of the small sample size. Therefore, a study with a larger sample size should be conducted in the future.

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