Neoadjuvant Intraarterial Chemotherapy for Treatment of Malignant Vaginal Tumors in Children: A Single-Center Experience

De-Hua Wu, MS, Min-Ju Li, MD, Da-Xing Tang, MD, Shan Xu, MD, Yong Huang, MS, Jin-Hu Wang, MD, and Qiang Shu, MD

ABSTRACT

Six patients (aged 3–36 mo) with vaginal tumors (rhabdomyosarcoma and endodermal sinus tumor [EST]; n = 3 each) received intraarterial chemotherapy (IAC) and intravenous chemotherapy. Patients underwent internal iliac artery infusion with cisplatin, pirarubicin, and vindesine. Intravenous chemotherapy with vindesine, ifosfamide, and etoposide was administered after 3 weeks. Vaginal tumors disappeared in all patients after 2 or 3 cycles of alternating therapy. Two patients underwent resection of pelvic metastases. Intravenous consolidation chemotherapy was applied. Four patients were disease-free at a median follow-up of 5.8 years. One patient had pelvic recurrence treated with "salvage" therapy with IAC and surgery and was disease-free for 2.5 years.

ABBREVIATIONS

AFP = α-fetoprotein, EST = endodermal sinus tumor, IAC = intraarterial chemotherapy

Malignant tumors of the vagina in infants and children are extremely rare. Rhabdomyosarcoma and endodermal sinus tumor (EST) are the most common malignant tumors of the vagina in infants, and both are locally aggressive and capable of metastasis (1,2). The management of pediatric vaginal tumors has evolved from radical surgery to neoadjuvant chemotherapy followed by local control with surgery or radiation therapy (3,4).

Neoadjuvant intraarterial chemotherapy (IAC) has been reported to achieve favorable results in the treatment of locally advanced cervical cancer in adults (5–7). In the present retrospective observational study, we evaluate the feasibility and effect of neoadjuvant IAC combined with systemic chemotherapy for treatment of malignant vaginal tumors in children.

From the Divisions of Pediatric Urology (D.-H.W., D.-X.T., S.X., Y.H.), Pediatric Surgical Oncology (J.-H.W.), and Pediatric Surgery (Q.S.), Department of Pediatric Surgery (D.-H.W., M.-J.L., D.-X.T., S.X., Y.H., J.-H.W., Q.S.), Children's Hospital, Zhejiang University School of Medicine, Zhugan Xiang 57, Hangzhou 310003, China. Received July 25, 2015; final revision received March 12, 2016; accepted March 14, 2016. **Address correspondence to** M.-J.L.; E-mail: minjuli@qq.com

None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2016; 27:996–1000

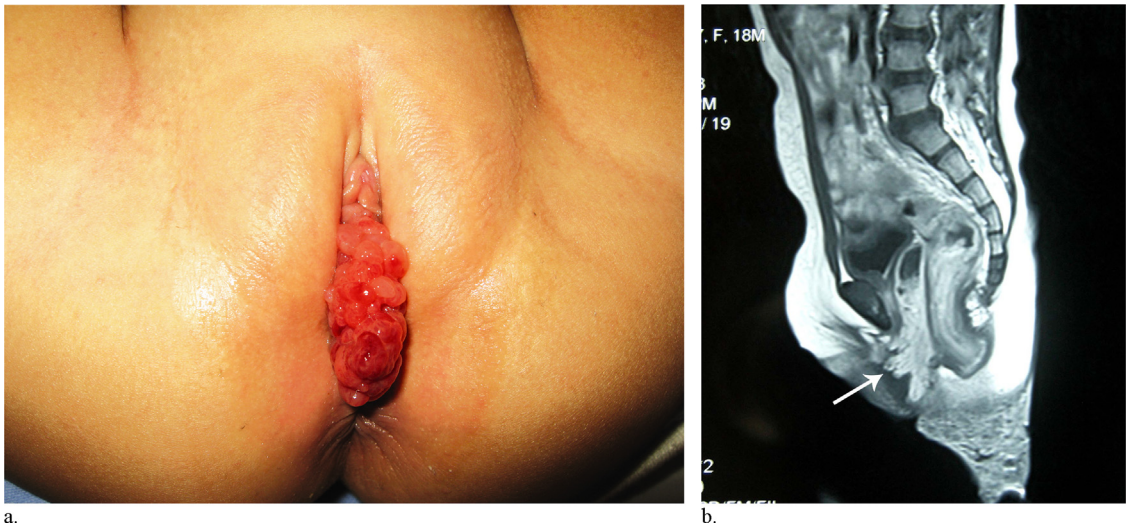
http://dx.doi.org/10.1016/j.jvir.2016.03.025

MATERIALS AND METHODS

From September 2002 to December 2013, six patients with malignant vaginal tumors were treated with neoadjuvant IAC and systemic chemotherapy at a single hospital. This study was approved by the institutional ethics committee, and informed consent was obtained from the children's parents before enrollment.

The median patient age at diagnosis was 1.27 years (range, 3–36 mo). All patients had the symptom of blood-tinged discharge from the vagina. Three patients had polypoid mass protruding from the vagina at admission. Contrast-enhanced magnetic resonance (MR) imaging, computed tomography (CT), and ultrasonography (US) showed a solitary mass in the vagina in each case (**Fig 1**). The tumor sizes ranged from 10 mm to 62 mm in maximum diameter (**Table**). Two patients presented with pelvic cavity tumor metastasis.

Biopsies were performed in all patients. Vaginoscopy was performed with the use of a pediatric cystoscope to visualize the vaginal tumor and obtain a biopsy specimen. The pathologic diagnosis was embryonal rhabdomyosarcoma of botryoid subtype in three cases and EST in three cases. All patients with EST had markedly elevated serum levels of α-fetoprotein (AFP; range, 916.9–10,446 μg/L). At the authors' institution, normal AFP levels in infants are 88 μg/L ± 87 at 3 months of age and 8.5 μg/L ± 5.5 at 8 months of age or more.



a. b.

Figure 1. Vaginal embryonal rhabdomyosarcoma of botryoid subtype in an 18-month-old girl. (**a**) A mass is seen protruding from the vagina. (**b**) Sagittal MR image shows a large tumor (arrows) in the vagina and protruding from the orificium vaginae.

The treatment consisted of alternating courses of IAC and systemic chemotherapy. IAC was performed under intravenous and caudal anesthesia. The femoral artery was catheterized via Seldinger technique with digital subtraction angiography guidance. A 5-F pigtail catheter (Cook, Bloomington, Indiana) was introduced into the abdominal aorta to perform aortography and iliac artery angiography. Tumor staining in the area of the vagina was visible (Fig 2a). A 4-F Cobra catheter (Cook) was placed in the anterior division of the internal iliac artery, with the tip of the catheter below the superior gluteal artery if possible (Fig 2b). The anticancer agents were then infused. The contralateral internal iliac artery intubation and drug infusion was performed via the same technique. The total amount of drugs infused was as follows: cisplatin 80 mg/m^2, pirarubicin 40 mg/m^2, and vindesine 3 mg/m^2. The drugs were mixed, diluted in 120–180 mL of normal saline solution, and injected by an external infusion pump over a period of 60 minutes. The procedure was performed bilaterally. The drug dose was divided depending on the predominant vascularization of the tumor. The drugs were infused with two thirds of the dose on the side of the predominant vascularization of the tumor and the remaining one third dose on the other side. To avoid ischemic necrosis of the viscera, no embolization agents were used. The catheter was removed after treatment. Intravenous hydration and alkalization were applied before, during, and after IAC. In addition, methylprednisolone and antiemetic agents were administered to prevent nausea and vomiting.

Intravenous chemotherapy was administered 3 weeks after IAC and consisted of vindesine 3 mg/m^2 on days 1 and 8 and ifosfamide 1,200 mg/m^2 and etoposide 100 mg/m^2 on days 2–4. Cycles of IAC and intravenous chemotherapy were repeated every 6 weeks. After two or three cycles of alternating IAC and intravenous chemotherapy, patients received four to six courses of intravenous chemotherapy as consolidation therapy. For the patients with rhabdomyosarcoma, two drug combinations were given at 3- or 4-week intervals: (*i*) alternating cycles of vindesine (3 mg/m^2 on days 1 and 8), carboplatin (300 mg/m^2 on day 2), and pirarubicin (20 mg/m^2 on days 3 and 4) and (*ii*) vindesine (3 mg/m^2 on days 1 and 8), ifosfamide (1,200 mg/m^2 on days 2–4), and etoposide (100 mg/m^2 on days 2–4). For the patients with EST, bleomycin (15 mg/m^2 on day 1), etoposide (100 mg/m^2 on days 1–3), and carboplatin (300 mg/m^2 on days 2 and 3) were given at 3- or 4-week intervals. The dosage of intraarterial and intravenous chemotherapy agents was reduced by 30% for patients with body weight of less than 10 kg.

During treatment, complete blood cell count and platelet count were repeated weekly; liver and kidney function tests, urinalysis, and toxicity evaluation were conducted before each treatment cycle. Toxicity was assessed according to World Health Organization criteria. MR imaging or CT scan, US, vaginoscopy and biopsy, chest radiography, and serum AFP measurement were repeated for every cycle of treatment to evaluate tumor response.

After treatment, all patients had regular follow-up visits at the outpatient department. Medical check-ups involved imaging examination of the pelvis, abdomen, and chest; complete hematologic analysis; renal and liver function tests; and serum AFP measurement.

RESULTS

There was no incidence of cardiologic toxicity, nephrotoxicity, hepatic dysfunction, or treatment-related death among all patients after IAC and intravenous chemotherapy. Grade II/III leukocytopenia occurred in three

Table. Clinical Characteristics, Treatment, and Outcomes in Six Patients with Malignant Vaginal Tumors

Pt. No.	Age at Diagnosis (mo)	First Symptom	Tumor Size (mm)	Histology	Serum AFP (μg/L)	Therapy	Outcome
1	36	Polyploid mass protruding from vagina	62 × 27 (pelvic cavity tumor metastasis)	RMS	Normal*	IAC/systemic chemotherapy, pelvic surgery/RT	Alive and disease-free at 11 y
2	3	Mass protruding from vagina	10 × 7.8	RMS	Normal*	IAC/systemic chemotherapy	Alive and disease-free at 9 y
3	18	Blood-tinged discharge from vagina	50 × 20	RMS	Normal*	IAC/systemic chemotherapy	Pelvic cavity recurrence 46 mo after vaginal tumor disappeared; repeat IAC/intravenous chemotherapy followed by resection; disease-free after 2.5 y
4	14	Mass protruding from vagina	40 × 13 (pelvic cavity tumor metastasis)	EST	916.9	IAC/systemic chemotherapy, pelvic surgery/RT	Alive and disease-free at 4 y
5	9	Blood-tinged discharge from vagina	48 × 32	EST	10,446.0	IAC/systemic chemotherapy	Vaginal EST recurrence 18 mo after disappearance of original tumor; parents declined further treatment
6	11	Blood-tinged discharge from vagina	44 × 20	EST	3,507.0	IAC/systemic chemotherapy	Alive and disease-free at 2 y

AFP = α-fetoprotein; EST = endodermal sinus tumor; IAC = intraarterial chemotherapy; RMS = rhabdomyosarcoma; RT = radiation therapy.
*Normal AFP levels in infants are 88 μg/L ± 87 at age 3 mo and 8.5 μg/L ± 5.5 at age ≥ 8 mo.

patients, grade I/II thrombocytopenia in two patients, and grade I/II nausea/vomiting in two patients. No muscle or skin complications were observed, but all patients experienced hair loss.

Vaginal tumors began to undergo necrosis and shrink 1 week after intraarterial infusion chemotherapy. CT, MR imaging, and US showed vaginal tumor disappearance after two or three cycles of IAC and intravenous chemotherapy in all six patients. Biopsy of the tumor site showed sclerosis, necrosis, and lack of viable malignant cells in the specimens. Serum AFP levels decreased to normal levels in patients with EST of the vagina.

One patient each with rhabdomyosarcoma and EST had pelvic metastasis at admission. The pelvic metastases shrank, and the patients underwent pelvic surgery after alternating IAC and intravenous chemotherapy (Fig 3a, b). One underwent ureter/bladder reimplantation as a result of obstruction at the ureterovesical junction caused by pelvic metastasis. Surgical specimens of the pelvic masses showed complete tumor necrosis by pathologic examination (Fig 3c). Bilateral ovarian transposition to the paracolic gutter was concomitantly performed during pelvic operation for the preservation of ovarian function, and postoperative pelvic external-beam radiation therapy was conducted in these two patients.

All six patients returned for regular follow-up visits until December 2013; the duration of follow-up ranged from 2 to 11 years (median, 5.8 y). Four patients remained recurrence-free as of the time of manuscript preparation. One patient had vaginal EST recurrence 18 months after disappearance of the original vaginal tumor. The parents declined further treatment, and the patient was lost follow-up. One of the patients with vaginal rhabdomyosarcoma had pelvic cavity recurrence 46 months after the vaginal tumor disappeared. This patient again underwent alternating arterial and intravenous chemotherapy for two cycles, and the pelvic metastatic lesion shrank significantly. The patient underwent pelvic tumor resection and partial cystectomy. Histologic examination showed complete necrosis of the metastatic tumor. Ovarian transposition was also performed during operation, and postoperative pelvic external-beam radiation therapy was conducted. As of the time of manuscript preparation, this patient had remained disease-free for 2.5 years after completion of this extensive therapy.

DISCUSSION

Gynecologic tumors in children are rare and represent fewer than 5% of all pediatric neoplasms. Malignant tumors of the vagina in infants and children are extremely rare, and rhabdomyosarcoma and EST are the most common types. Rhabdomyosarcoma in the vagina most commonly presents in patients before the age of

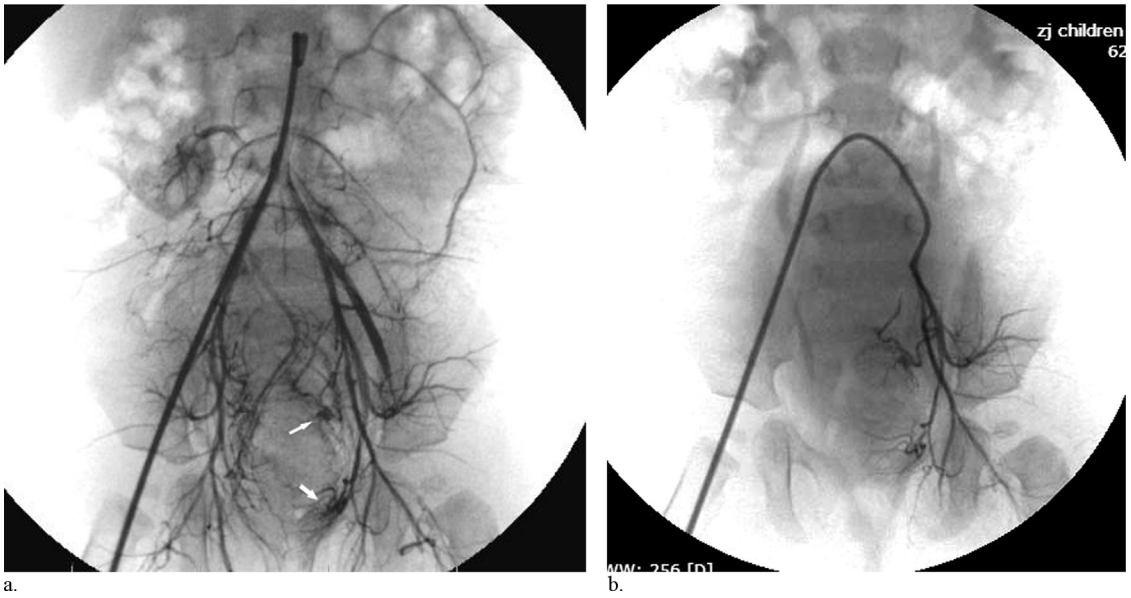


Figure 2. Images from a 14-month-old girl with a vaginal EST. **(a)** Aortography obtained before IAC revealed tumor staining (arrow) in the pelvic cavity. **(b)** The internal iliac artery was selected, and anticancer agents were slowly injected.

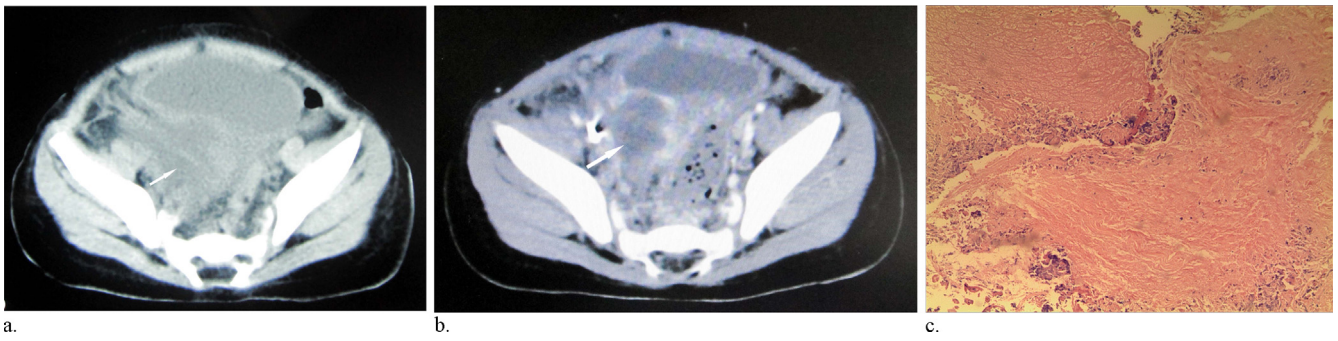


Figure 3. Pelvic cavity metastasis at admission in a 14-month-old girl with vaginal EST. **(a)** CT reveals a large mass in the pelvic cavity at admission (arrow). **(b)** The pelvic cavity metastasis shrank and had a clear margin after alternating IAC and systemic chemotherapy. The patient then underwent pelvic tumor resection and ureter/bladder reimplantation. **(c)** Histologic examination of the resected pelvic cavity metastatic tumor shows complete necrosis and partial calcification. (Hematoxylin and eosin stain; original magnification, ×40.)

2 years, and vaginal ESTs occur almost exclusively in girls younger than the age of 3 years (1–4).

Blood-tinged discharge and protruding vaginal mass are the most common clinical presentations of malignant vaginal tumors in children. US, CT, and MR imaging can be used to estimate the precise location and extent of the lesion. Histologic examination is required for diagnosis and differential diagnosis. Serum AFP level can be used as a tumor marker in the diagnosis of EST of the vagina, in evaluation of the response of treatment, and in surveillance for recurrence (8,9).

Traditionally, the typical treatment protocol for malignant vaginal tumors in children has consisted of aggressive operative excision followed by adjuvant radiation therapy and/or chemotherapy (10). Recent reports have described the use of vaginal preservation and chemotherapy. Surgical removal of the vagina is the last resort in an attempt to maintain fertility and sexual function in the future (11,12).

To increase the efficacy of chemotherapeutic drugs and to control local tumors, pelvic intraarterial chemotherapeutic drug administration has been proposed for the treatment of advanced cervical cancer in adults. Cisplatin is a well-known chemotherapeutic drug that is effective against various types of cancers (13). Intraarterial administration of cisplatin is considered ideal because the drug has a very high affinity for tissue protein, which leads to effective binding of cisplatin to tumor tissue during its first pass (14).

The vaginal artery is a branch of the internal iliac artery. The most common pattern of internal iliac artery branching is a bifurcation into anterior and posterior divisions. The divisions of the anterior branch include the inferior gluteal, obturator, internal pudendal, vesical, middle hemorrhoidal, and genital (uterine and vaginal) arteries (15). The benefits of IAC for vaginal tumors are based on the concept that the blood supply to the tumor comes from the anterior branch of the internal iliac

artery. The anticancer drugs are injected into the tumor-feeding artery, increasing the effect of the chemotherapy agent within the tumor while avoiding concomitant systemic toxicity. Our regimen of alternating IAC and systemic chemotherapy is also a combination chemotherapy regimen. This method is capable of inducing rapid tumor regression and reducing complications associated with antitumor drugs. It is not only effective for vaginal tumors, but also leads to shrinkage and necrosis of pelvic cavity metastases or recurrent pelvic tumors.

There are limitations to the present study, most notably that the series is too small to allow definitive conclusions to be drawn about the therapeutic effects of this treatment regimen. Nonetheless, in conclusion, the present preliminary results suggest that the use of neoadjuvant IAC and systemic chemotherapy may provide a promising choice in the treatment of malignant vaginal tumors in children. Further investigations are necessary.

ACKNOWLEDGMENT

We thank the children and their parents for allowing the use of the data for this research project. We also thank the staff of the department of pediatric surgery and department of radiology for their patient care and organization.

REFERENCES

1. Arora M, Shrivastav R, Jaiprakash M. A rare germ-cell tumor site: vaginal endodermal sinus tumor. Pediatr Surg Int 2002; 18:521–523.
2. Arndt CA, Donaldson SS, Anderson JR, et al. What constitutes optimal therapy for patients with rhabdomyosarcoma of the female genital tract? Cancer 2001; 91:2454–2468.
3. Walterhouse DO, Meza JL, Breneman JC, et al. Local control and outcome in children with localized vaginal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Pediatr Blood Cancer 2011; 57:76–83.
4. Handel LN, Scott SM, Giller RH, Greffe BS, Lovell MA, Koyle MA. New perspectives on therapy for vaginal endodermal sinus tumors. J Urol 2002; 168:687–690.
5. Kawase S, Okuda T, Ikeda M, et al. Intraarterial cisplatin/nedaplatin and intravenous 5-fluorouracil with concurrent radiation therapy for patients with high-risk uterine cervical cancer. Gynecol Oncol 2006; 102:493–499.
6. Tsubamoto H, Maeda H, Kanazawa R, et al. Phase II trial on neoadjuvant intravenous and trans-uterine arterial chemotherapy for locally advanced bulky cervical adenocarcinoma. Gynecol Oncol 2013; 129: 129–134.
7. Adachi S, Ogasawara T, Wakimoto E, et al. Phase I/II study of intravenous nedaplatin and intraarterial cisplatin with transcatheter arterial embolization for patients with locally advanced uterine cervical carcinoma. Cancer 2001; 91:74–79.
8. Liu Q, Yang J, Tao T, Cao D, Shen K. The clinical features and treatment of endodermal sinus tumor of vagina. Eur J Obstet Gynecol Reprod Biol 2012; 165:130–131.
9. Tao T, Yang J, Cao D, et al. Conservative treatment and long-term follow up of endodermal sinus tumor of the vagina. Gynecol Oncol 2012; 125:358–361.
10. Copeland LJ, Sneige N, Ordonez NG, et al. Endodermal sinus tumor of the vagina and cervix. Cancer 1985; 55:2558–2565.
11. Groff DB. Pelvic neoplasms in children. J Surg Oncol 2001; 77: 65–71.
12. Fernandez-Pineda I, Spunt SL, Parida L, Krasin MJ, Davidoff AM, Rao BN. Vaginal tumors in childhood: the experience of St. Jude Children's Research Hospital. J Pediatr Surg 2011; 46:2071–2075.
13. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol 2014; 740:364–378.
14. Chen HS, Gross JF. Intra-arterial infusion of anticancer drugs: theoretic aspects of drug delivery and review of responses. Cancer Treat Rep 1980; 64:31–40.
15. Pelage JP, Le Dref O, Soyer P, et al. Arterial anatomy of the female genital tract: variations and relevance to transcatheter embolization of the uterus. AJR Am J Roentgenol 1999; 172:989–994.