Current Developments in the Treatment of Genitourinary Rhabdomyosarcoma

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Rhabdomyosarcoma is the most common soft tissue sarcoma that is seen in children and makes up approximately 4 % to 8 % of malignant solid tumors [1]. Genitourinary rhabdomyosarcoma makes up 21 % of pediatric cases with approximately 5 % being retroperitoneal and 6 % pelvic. Until the 1960's, long-term survival with rhabdomyosarcoma was uncommon. Over the last 25 years, however, it has become evident that rhabdomyosarcoma responds both to chemotherapy with sarcoma-type agents and radiation therapy, albeit at quite high dosages. A real dilemma has evolved as to how to mix these two effective therapies with surgical excision. This article will touch on some of the current developments in management of this tumor.

Pathology

The most common type of rhabdomyosarcoma found in the genitourinary tract is embryonal, constituting about two-thirds of cases [2]. Sarcoma botryoids refers to a gross appearance of rhabdomyosarcoma protruding into a hollow organ and resembling a bunch of grapes. This is a polypoid form of embryonal rhabdomyosarcoma. Embryonal rhabdomyosarcoma is the most favorable form of the tumor. Less commonly found are the unfavorable forms, alveolar, pleomorphic and mixed.

In rhabdomyosarcoma, it is important to remember from a pathologic standpoint that under chemotherapy and radiation therapy treatment, the bulk of the lesion does not always correspond to the tumor burden present. Stroma at times appears to involute more slowly than do the malignant cells of the tumor. This is why histologic staging by biopsy is as important in the follow up of this tumor as imaging.

Presentation and diagnostic evaluation

The symptoms produced by genitourinary rhabdomyosarcoma depend on the size of the tumor and its site of origin [3]. Typically, a tumor involving the bladder base or urethra compromises the bladder outlet and the child presents with straining to void and occasionally urinary retention. For pelvic tumors that become large enough to encroach upon the bladder outlet, similar symptoms may be produced but are characteristically seen later in the course of the tumor development. If the tumor breaks through the lining of the urinary tract, hematuria may be seen as well. If the bladder outlet is not compromised, then the most common presentation is a large palpable mass and this is overall the most common presentation for rhabdomyosarcoma. In the female, the tumors arising in the bladder base or vagina may be seen as a polypoid vaginal mass.

In diagnostic evaluation, ultrasound provides an initial effective screening study. By filling the bladder or rectum with water, better ultrasound imaging may be achieved. While the CT scan has been helpful to define the extent of disease, recently the ability of magnetic resonance imaging to provide anatomic delineation of pelvic structures has come to be the most effective imaging modality for G-U rhabdomyosarcoma.

Histological diagnosis is established by biopsy often obtained by endoscopic technique with the pediatric resectoscope. It is important to be aware that the resectoscope loop electrode may cause sufficient coagulation of the specimen to make it uninterpretable. Accordingly, a cold cup biopsy forceps is generally more satisfactory in obtaining tissue. If a pelvic tumor cannot be biopsied by these means, needle biopsy techniques can be very useful. Only rarely is a laparotomy required.

Because approximately 20 % of genitourinary

rhabdomyosarcoma involves retroperitoneal lymph nodes at diagnosis [4], careful imaging and sampling if laparotomy is carried out is important. Evidence of dissemination to the chest is best detected by CT scan. Precise clinical staging is needed because of the effect on prognosis of dissemination and the need for more intensive treatment in that situation.

Clinical staging

There has been confusion in the area of staging because of changes which have occurred and differences between the European approach and that of the Intergroup Rhabdomyosarcoma Study (IRS). In Europe, the TNM staging system is widely used and has begun to be adopted for this tumor in the United States. The current modified system being used by the IRS is as follows [5]:

Stage I is confined to the organ of origin in favorable sites. In the genitourinary tract, that includes paratestis and vulvovaginal and uterine tumors, but excludes bladder prostate which is viewed as less favorable.

Stages II and III include patients with tumors at other sites but which are without distant metastases. In **Stage II**, the tumor is 5 cm in diameter or smaller. There is no regional node enlargement. **Stage III** are those with tumors greater than 5 cm in diameter, who have evidence of positive regional lymph nodes or both.

Stage IV disease has distant metastases beyond regional lymph nodes at diagnosis. Tragically, many children with rhabdomyosarcoma do have disseminated disease at presentation.

Treatment

Historically, the approach to rhabdomyosarcoma was through surgical excision of the primary tumor which, for genitourinary rhabdomyosarcoma, often involved an anterior or total pelvic exenteration. Long-term survival for patients treated by surgery alone varied from 40 % (vagina) to 73 % (bladder/prostate) [6]. The current approach to rhabdomyosarcoma began as it was realized that the tumor was also effectively treated by chemotherapy and radiation therapy. Unfortunately, the radiation therapy doses needed for local tumor control appeared to be quite high, in excess of 4,500 cGy [7]. A real dose response cure for this tumor, however, has never been established. Chemotherapy began with single agents but it has been recognized that the following drugs can be effective: Vincristine, Actinomycin D, Cyclophosphamide, Mitomycin C, Doxorubicin, Imidazole, Carboxamide, Cis-platinum and Etoposide [8].

Credit needs to be given to Pinkel and Pinkren who in 1961 suggested the coordination of initial aggressive surgery with postoperative radiation therapy and "prophylactic" chemotherapy [9]. This effort to try to improve outcomes by eliminating microscopic residual disease led to the first real progress with this tumor. Data from IRS Studies I and II showed approximately 50 % of the patients were alive with intact bladders [10]. However, the long-term follow up of bladder salvage was less satisfactory at 25 % at three years and unfortunately this was not improved when primary treatment was focused on chemotherapy and irridation [11].

Current recommended approach

Aggressive staging of the tumor is important. Today the emphasis continues on primary chemotherapy for genitourinary rhabdomyosarcoma. The current IRS approach is randomizing patients in Stages I, II and III among three drug combinations (Vincristine, Actinomycin D, Cyclophosphamide (VAC); Vincristine, Actinomycin D and Isophosphamide; and Vincristine, Etoposide and Isophosphamide). Radiation therapy is utilized after surgery to deal with residual nonmetastatic tumor. Fractionated treatment is being used in present protocols to see if toxicity can be lowered as the total dose needed continues to be high in the view of IRS investigators. For Stage IV patients with metastatic disease, survival in the past has been poor and current IRS investigation is looking a new combination of agents. Vincristine and Melphalan are being used in randomization with Isophosphamide and Etoposide for 6-12 weeks before the institution of standard therapy wih VAC. Surgical staging is carried out before the institution of radiation therapy because of the problem mentioned earlier of tumor at times involuting at a different rate from the stroma. Additionally, after the institution of radiation therapy, histology becomes very difficult to interpret as viable and non-viable residual tumor may be impossible to separate.

The role of surgery continues to evolve. It is my personal view that an effort to completely excise the tumor after maximal chemotherapeutic response continues to be essential. Any bulk lesion left behind too often results in recurrent tumor. A reasonably radical but non-exenterative approach is the surgical goal. Continued chemotherapy often with radiation therapy will complete management and lead to hopefully a better outcome than has been seen in the past.

If an anterior exenteration is needed surgically, the possibility of eventual continent reconstruction of the urinary tract should be borne in mind. We have favored utilizing a low end skin ureterostomy for each ureter. With careful technique, interdigitating a small skin flap into the spatulated ureter, this form of diversion can be carried out even when there is minimal or no ureteral dilatation. If the child is a long term survivor, continent reconstruction is possible by using one of the ureters as a continent catheterizable channel placed with a submucosal tunnel into an intestinal urinary reservoir. The ureter will be supported well on its blood supply from the skin anastomosis. The urinary tract is reconstituted by carrying out a high trans-ureteroureterostomy and then the distal second ureter is used as the one for anastomosis to the intestinal urinary reservoir with an anti-refluxing technique. In this way, a very satisfactory continent urinary reservoir may be created.

Paratesticular rhabdomyosarcoma

In closing this brief review, a special comment needs to be made about paratesticular rhabdomyosarcoma because this tumor's management has changed considerably in recent years. Because of the approximate 40 % incidence of retroperitoneal spread of this tumor, in the past a retroperitoneal node sampling procedure was standard in the diagnostic evaluation of the patients [12]. However, in recent years, it has become evident that microscopic disease in the retroperitoneum can be effectively eliminated by current chemotherapy. Additionally, through CAT scanning and MRI techniques, the retroperitoneum can be much more effectively evaluated for evidence of metastatic disease. If imaging is negative, these patients do very well with a radical inguinal orchiectomy followed by 32 weeks of Vincristine and Actinomycin D (current IRS protocol) [13].

If there is clear cut retroperitoneal disease, biopsy may be needed and radiation therapy used as an adjunct in treatment. Overall, 90 % of boys with paratesticular rhabdomyosarcoma should be long term survivors. Hopefully, in the future, we will find that other forms of genitourinary rhabdomyosarcoma lend themselves as satisfactorily to future treatment.

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