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Surgical aspects of the management of pediatric patients with rhabdomyosarcoma and related soft tissue sarcomas

- A review of the Intergroup Rhabdomyosarcama Study (U.S.) -

Daniel M. HAYS,*M.D., Walter LAAWRENCE, Jr., M.D., Eugene WIENER, *** M.D.**

** University of Southern California School of Medicine, Los Angeles, California, ** Medical College of Virginia, Richmond, Virginia, *** University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, U.S.A.*

Introduction

Rhabdomyosarcoma has not proved to be as sensitive to chemotherapeutic agents as nephroblastoma, nor as insensitive as neuroblastoma. However, management of this tumor has been radically altered by the use of effective chemotherapy regimens; and when occurrig in most sites, all three major modalities, i.e. surgery, irradiation, and chemotherapy have a significant part in current management.

Rhabdomyosarcoma would appear to be occurring with increasing frequency in pediatric patients; a trend noted for a decade. This probably represents the result of increasing ability to distinguish this specific tumor among the group of relatively undifferentiated mesenchymal tumors traditionlly referred to as "soft tissue sarcomas". The use of electron microscopy and immunocytologic techniques have established the diagnosis of rhabdomyosarcoma in many tumors which would formally have been labeled as undifferentiated sarcomas. Among young adults, a further transition has occurred, with many tumors formally regarded as rhabdomyosarcoma now falling in the category of malignant fibrous histiocytomas. This change has not occurred in pediatric patients.

Address: Daniel M. Hays M.D Professor of Surgery-Pediatrics University of Southern California School of Medicine, Los Angeles, California, U.S.A

There are no clinical tumor "markers" for rhabdomyosarcoma. Needle biopsy cores are frequently too small for detailed examination and cytologic studies too imprecise, so that the majority of these tumors are identified by direct biopsies through skin incisions or an endoscope.

The Intergroup Rhabdomyosarcoma Study (IRS): An Overview

This multiinstitutional study has been carried out during three time periods, with the first two completed, and the third (IRS-III) in progress [1,2]. IRS-I & II (1972-1984) admitted 1,688 patients with rhabdomyosarcoma, extra-osseous Ewing's, or undifferentiated small-cell sarcomas from institutions throughout the U.S.A., Canada, and several European countries. These patients were placed in randomized clinical trials on the basis of Clinical Groups (stage), which reflected both the extent of disease and the initial surgical procedure performed.

Division of these patients by Clinical Group was as follows: Clinical Group I -localized, completely resected tumors, 227 patients (13%); Clinical Group II localized tumors with gross resection but "microscopic residual" at the margin(s) and/or positive nodes, 346 patients (20%), Clinical Group III - localized tumors with gross residual disease at the pirimary site, 814 patients (48%); and Clinical Group IV - disseminated tumors, 301

patients (18%). The approximate three-year survival rates for patients in each of these Clinical Groups in IRS-I and II have been: Group I - 87%; Group II - 76%; Group III - 62%; and Group IV - 30%. Therapy regimens have included an initial attempt to excise the tumor when anatomically feasible, except in patients with lesions in orbital sites, some genitourinary categories and those in Clinical Group IV (distant metastases). Local radiotherapy is employed routinely except in Clinical Group I, with a dose range of 3000 cGy to 5500 cGy depending on patient age, site and regimen. Chemotherapy regimens, standard in all patients, consisting of vincristine and actinomycin-D (VA); VA + cyclophosphamide (VAC); or VAC + doxorubicin (VADRAC) [1,2].

Both site and histologic subtype are major and related factors influencing survival. Among patients with tumors of orbital, paratesticular, and superficial head and neck sites, survival rates have been 35-90% when treated by surgery, local irradiation (in some), and non-intensive chemotherapy regimens. This has included patients with paratesticular rhabdomyosarcoma with retroperitoneal node involvement. In contrast, other sites such as the perineum, retroperitoneal space, and the abdominal viscera have been associated with a mortality greater than 85%, even with intensive multimodal therapy. The influence of the histologic subtype, which is related to site but also an independent variable in some categories, was apparent. Patients with tumors in sites associated with low survival rates frequently exhibited a high incidence of the alveolar or undifferentiated histologic subtypes; while embryonal histology is generally associated with favorable outcome. In many sites, the alveolar subtype predicts early distant metastasis; while patients with tumors of the embryonal subtype, more frequently recur locally. In the following sections, surgical management is reviewed by site category. All reference, unless otherwise specified, is to data from the IRS.

Extremity Sites

Wide local excision remains the standard therapy for this site and is a major factor influencing survival [3,4]. Removing muscles from origin to insertion would appear to have no particular advantage over achieving wide margins in all directions about the tumor. The "compartmental" resections of entire muscle groups has not been demonstrated to be superior (or inferior) to less systematic but equally radical wide local excision. Rhabdomyosarcomas frequently have well demarcated "pseudocapsules" which do not represent the extent of the tumor and excision at this margin will almost always be followed by local recurrence unless very intensive local irradiation is employed. Such radiotherapy is frequently only practical in individuals who have achieved a major portion of their growth. Doses required to control rhabdomyosarcoma will produce major shortening of long bones in the lower extremities of children.

Extremity amputation has resulted in low survival rates in IRS-I, primarily because its use has been largely restricted to patients with advanced local disease, i.e. involvement of skin, bone, "neurovascular bundles", etc. In younger children with lower extremity tumors which are adjacent to the epiphysis of long bones, amputation may be indicated. "Limb saving" procedures employing arterial and venous grafts have been successful in some children. Thorough "sampling" of inguinofemoral nodes in lower extremity, and axillary nodes in upper extremity lesions, is necessary for accurate staging and to direct irradiation to the node groups when there is lymphatic involvement[5]. Radical regional node dissections, as carried out in adults with melanomas, etc., are not ordinarily employed in childhood. Intensive chemotherapy regimens are required in all of these patients, as well as local irradiation to the primary site and involved regional node groups. The overall survival rate among patients with primary extremity tumors is approximately 60% [4].

Trunk Sites

Primary tumors of the trunk will be discussed in theree categories, i.e. chest wall, abdominal wall, and paraspinal. Many chest wall tumors previously regarded as rhabdomyosarcomas are now

designated as Askin's tumors or peripheral neuroepitheliomas. This distinction does not affect the surgical approach but may substantially influence non-surgical therapy. Rhabdomyosarcoma of the chest wall characteristically occurs in older female children. Localized chest wall lesions should be excised with as wide a margin as possible, accepting some deformity during subsequent growth. Examination of the specimen often reveals these tumors to be incompletely excised. In such patients, reexcision should be attempted when feasible. The patient should receive irradiation (except possibly in infants and small children) and an intensive chemotherapy regimen. Apparently, making secondary resection feasible. Early dissemination frequently occurs in this group of patients.

Abdominal wall tumors are seen in younger patients of both sexes, and when localized have a relatively favorable prognosis. The paraspinal tumors are seen most frequently in younger male children, and have a significantly better prognosis, than the other categories, even when excision is incomplete. These tumors frequently destroy osseous structures and may invade the intrathecal space. Their initial management may raquire decompression of the cord, which is accompanied by an attempt to excise extraspinal portions of the tumor. Survival rates are high (>60%) when these patients are treated with subsequent intensive chemotherapy regimens, but the incidence of residual paraparesis is significant. The overall survival rate among patients with trunk primary sites approximately 50% [6].

Rhabdomyosarcoma in Pelvic Organs

The largest group of these patients have primary tumors in the bladder or prostate, and in males it is frequently impossible to determine the precise site of origin. Patients are predominantly infants, and the tumors almost entirely of the embryonal histologic type. Vaginal tumors occur in the same age group, while the rarer uterine rhabdomyosarcomas are seen in older children or young adults. By 1975, in the U.S., it had been demonstrated that when this group of patients were treated by radical cystectomy or anterior pelvic exenteration followed by local irradiation and two years of chemotherapy (primarily VAC), survival rates in patients without dissemination approached 90% [7]. During the next decade, dissatisfaction with the long-range results of this form of management relative to the quality of life with urinary diversion led to trials aimed at bladder preservation. These were carried out in centers throughout the world. The results of these attempts have, in general, been disappointing but have varied with primary tumor site and institution. Among patients with vaginal lesions, tumor response to chemotherapy is usually striking and the primary site may be excised, following reduction in tumor size, by either hysterectomy/partial vaginectomy, or in some by partial vaginectomy alone. These patients, treated with subsequent chemotherapy, with or without irradiation, have a long-range survival of >90%, and bladder preservation in 90% of survivors. In contrast, among the patients with tumors primary in the bladder-prostate region placed on chemotherapy regimens, although the initial response is similar, approximately 70% of the bladders have eventually been removed and the combined early and late mortality has climbed to 25%. The use of early irradiation in these patients is under stury (IRS-III). If partial cystectomy can remove the gross tumor, at any stage in therapy, this approach is effective. Secondary anterior pelvic exenterations for local relapse usually result in long-term survival [8,9]. Primary uterine sarcomas are more heterogeneous histologically and are probably best treated by initial hysterectomy followed by chemotherapy and irradiation [9].

Paratesticular Rhabdomyosarcoma

This tumor, once almost universally lethal, has proved to be among the most sensitive to chemotherapy regimens. Therapy usually begins with a radical orchidectomy. In the U.S. this has been followed by an ipsolateral retroperitoneal node dissection, which has been positive in 20%-40% of such cases [10]. When this procedure is positive, irradiation is omitted. Standard (non-intensive) chemotherapy regimens follow and survival rates approximate 90% [11]. If the initial approach to the tumor has been transscrotal, local

recurrence rates are higher and a secondary hemiscrotectomy, frequently carried out at the same time as the retroperitoneal node dissection, is recommended. In French studies, the node dissection and abdominal irradiation has been omitted in selected cases. This approach would appear to be associated with a higher rate of relapse in the retroperitoneum.

Head & Neck Sites

Orbital rhabdomyosarcomas, formerly treated by exenteration, usually remain within the confines of the orbit and these tumors have always been associated with a relatively favorable course. At present, they are treated effectively by biopsy and irradiation, with or without chemotherapy, resulting in survival rates >85%. Exenteration is reserved for recurrence [12].

Superficial non-orbital primary tumors, including those of the scalp, temporal musculature, face and oral cavity, are treated by standard surgical excisions, frequently irradiation, and chemotherapy in all patients. This therapeutic approach, which does not include either excessively radical surgery or intensive chemotherapy, results in survival rates >90% [13]. In some patients with deeper but non-parameningeal sites, such as the oropharynx and palate, complete surgical excision may be feasible and the prognosis is improved by such procedures. The other large group of patients are those with "parameningeal" lesions, designated by this term because of their proximity to the meninges, with the threat of extension and malignant meningitis. This complication is uniformly lethal. These primary tumors are not amenable to surgical excision. Their response to intensive chemotherapy/radiotherapy has been impressive with survival rates of approximately 60% when therapy is instituted before intrameningeal spread. Chemotherapy is usually both systemic and intrathecal [14].

Other Primary Sites

Rhabdomyosarcomas of the extra or intrahepatic biliary tract have the same gross and histologic "botryoid" appearance as the embryonal rhabdomyosarcomas of the bladder or nasopharynx [15]. When they occur in the choledochus or cystic duct they may sometimes be excised by radical surgery and log-range survivors have been reported following such procedures. Therapy has included chemotherapy universally and usually irradiation. Rhabdomyosarcomas of the intrathoracic and intraabdominal viscera have ordinarily been advanced at diagnosis and usually unresectable. The perianal and perineal rhabdomyosarcomas have a particularly poor prognosis despite excision. This may reflect the high incidence of alveolar histology and probably also the reluctance of surgeons to carry out radical abdominoperineal resections in childhood.

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