Rhabdomyosarcoma

- Rhabdomyosarcoma is a highly malignant soft tissue sarcoma that arises from unsegmented, undifferentiated mesoderm or myotome-derived skeletal muscle.
- Most frequently involved sites are the orbit.
Rhabdomyosarcoma is the most common of the childhood soft tissue sarcomas.

The male-to-female ratio is ~1.5:1.

Gender does not appear to carry prognostic significance.

Two peak age frequencies, at ages 2 to 6 and in adolescence.
✓ children <1 year and >10 years having inferior survival
✓ Adults with rhabdomyosarcoma have been reported to have poor outcomes, although there is evidence that when treated aggressively using pediatric-type protocols, the prognosis
may be similar to that of younger patients

✓ Rhabdomyosarcoma has been reported in association with several congenital disorders, including congenital pulmonary cysts, Gorlin's basal cell nevus syndrome, and neurofibromatosis.

✓ Relatives of children with rhabdomyosarcoma have
an increased frequency of breast cancer (embryonal rhabdomyosarcoma)

✓ Multiple tumors can occur in siblings and relatives of children with rhabdomyosarcoma, including adrenocortical carcinoma, brain tumors (particularly glioblastoma), lung cancer, breast cancer, and other sarcomas (This
occurrence is termed the Li-Fraumeni syndrome.)

✓ tumors arising in the urinary bladder and vagina occur primarily in infants and often are of the embryonal or botryoid histologic type

✓ Tumors arising in the trunk and extremity occur in adolescents and are often
alveolar or undifferentiated type

- Tumors of the head and neck area occur throughout childhood and are commonly of the embryonal type
- Overall risk of regional lymphatic spread is approximately 15%
- Lymph node metastases are rare in orbital tumors,
but they occur in approximately 15% of tumors at other head and neck sites, most commonly the nasopharynx.

Regional lymph node extension occurs in approximately 25% of children with paratesticular tumors and in 20% of patients with
extremity and truncal tumors

✓ Hematogenous metastases are detected at the time of presentation in approximately 15% of patients, particularly those with truncal and extremity primary tumors

✓ The most common sites of hematogenous
dissemination are lungs, bone marrow, and bone

- Head and neck
  - MRI or CT of primary tumor (with contrast)
  - Lumbar puncture with cytologic examination of fluid in parameningeal primary tumors

- Genitourinary
  - CT of MRI of abdomen-pelvis (with contrast)
  - Pelvic examination under anesthesia

- Extremity and truncal lesions
  - MRI or CT of primary lesion (with contrast)

- Plain films of area
- Dental films
- Paranasal sinus and skull films
- MRI of spine if cerebrospinal fluid is positive or patient is symptomatic
- Ultrasound of pelvis
- Cystoscopy
- Plain films of primary site
- Ultrasound
- Barium gastrointestinal contrast studies

- The site of primary tumor also has a significant impact on survival
The classic classification of rhabdomyosarcoma used by the IRS investigators consists of four histologic subtypes: embryonal, botryoid subtype of embryonal, alveolar, and pleomorphic.

Other variants including a solid alveolar pattern, considered a subtype of alveolar rhabdomyosarcoma, a spindle cell subtype of
embryonal rhabdomyosarcoma, and a diffuse anaplastic variant have also been described

✓ The superior-prognosis group, made up of two subsets (botryoid and spindle cell), carries a projected 5-year survival rate of 88% to 95%

✓ The botryoid subtype, a polypoid variant of embryonal
rhabdomyosarcoma, has a grapelike appearance

✓ The botryoid tumors are usually noninvasive and localized and occur in mucosal-lined organs such as the vagina, urinary bladder, middle ear, biliary tree, and nasopharynx

✓ Patients with embryonal rhabdomyosarcoma have intermediate outcome
loss of heterozygosity at the chromosome 11p15.5 locus suggests that this site is specific for the embryonal subtype

The embryonal histology occurs in 60% of cases and is found most commonly in the orbit, head and neck, and genitourinary sites.

The group with poor prognosis includes alveolar,
diffuse anaplastic, and undifferentiated sarcomas

✓ Alveolar histology is strongly associated with hyperdiploid content

✓ Approximately 80% of children with alveolar rhabdomyosarcoma exhibit a characteristic translocation involving chromosomes 2 and 13, t(2;13)(q35;q14), and
occasionally a 1;13 translocation

Table 85.4 International Classification of Rhabdomyosarcoma

I. Superior prognosis
   a. Botryoid rhabdomyosarcoma
   b. Spindle cell rhabdomyosarcoma
II. Intermediate prognosis
   a. Embryonal rhabdomyosarcoma
III. Poor prognosis
   a. Alveolar rhabdomyosarcoma
   b. Undifferentiated sarcoma
   c. Anaplastic rhabdomyosarcoma
IV. Subtypes whose prognosis is not presently evaluable
   a. Rhabdomyosarcoma with rhabdoid features

Intergroup Rhabdomyosarcoma Study Clinical Grouping

✓

✓
classification

Group I  Localized disease, completely resected

A  Confined to organ or muscle of origin

B  Infiltration outside organ or muscle of origin; regional nodes not involved

Group II  Compromised or regional resection

A  Grossly resected tumor with microscopic residual disease

B  Regional disease, completely resected, in which nodes may be involved or extension of tumor into adjacent organ may exist

C  Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual disease

Group III  Incomplete resection or biopsy with gross residual disease

Group IV  Distant metastases at diagnosis

✓ Orbit

✓ Most tumors in this site have embryonal histology
it is generally agreed that no surgical procedure should be used that may compromise vision.

In most patients, this means that biopsy only should be performed to provide the diagnosis.

Primary treatment usually consists of vincristine, actinomycin D, and Cytoxan (VAC) chemotherapy with
local radiotherapy beginning between the 3rd and 12th week of treatment

✓ Radiation doses of approximately 50 Gy are often used, although early results from the IRS-V study suggest that 45 Gy may be sufficient

✓ When radiation therapy alone was used, the entire orbit was considered to be at risk, and it
was recommended that the entire orbit be included in the treated volume
 ✓ with a combined-modality approach, radiotherapy can be directed to the tumor plus a margin without necessarily irradiating the entire orbit
 ✓ Photon irradiation with the eyelid open minimizes corneal dose when an anterior field is used and may be associated
with improved long-term functional outcome

Parameningeal Sites

✓ parameningeal sites
(nasopharynx, nasal cavity, paranasal sinuses, middle ear, pterygopalatine fossa, and infratemporal fossa)

✓ radiotherapy is essential for maximizing the chance of cure

✓ 35% of children with tumor arising in a parameningeal site
would later have meningeal extension,

✓ more recent studies demonstrate that whole-brain irradiation is not necessary, even in the presence of direct intracranial tumor extension

✓ Patients with known meningeal dissemination should receive craniospinal irradiation
✓ A radiation dose of 50.4 Gy in 28 fractions to the primary site is most commonly used
✓ improved local control in patients with intracranial tumor extension when radiotherapy is started within 2 weeks of diagnosis
✓ Aggressive surgery is rarely indicated because complete resection usually is not possible
 Delayed surgical resection has been proposed as beneficial for children with residual tumor after completing chemotherapy and radiotherapy.

Non-Parameningeal Sites have a better outcome than their parameningeal counterparts and require less-intensive chemotherapy.
These sites include the scalp, parotid, oral cavity, larynx, oropharynx, and cheek.

Radiotherapeutic management is based on the amount of residual tumor after surgery.

Draining regional lymph nodes are not routinely irradiated unless they contain metastatic tumor.

Bladder and Prostate Tumors
- Bladder and prostate primary tumors account for about half of all pelvic rhabdomyosarcomas.
- 75% of patients are age <5 years at presentation, and there is a strong male predominance.
- More than 90% of these tumors are of the embryonal histologic subtype, with
approximately one-third having a botryoid morphology

✓ In boys, it is often difficult to differentiate a tumor of prostatic origin from one of bladder origin because disease usually involves both structures

✓ patients with tumors arising in the prostate have significantly inferior survival
than those with tumor confined to the bladder (57).

✓ Historically, anterior pelvic exenteration (or partial cystectomy for small tumors arising from the dome of the bladder) combined with chemotherapy and irradiation for microscopic or gross residual disease

✓ More recently, emphasis has been on attempts to limit
radical surgery to preserve bladder function
✓ necessity of routine radiation therapy early in treatment

Paratesticular Tumors
✓ At presentation, the tumor usually is a painless scrotal or inguinal mass that does not transilluminate.
✓ Most boys with paratesticular rhabdomyosarcoma present with early-stage disease that
is amenable to complete resection and is associated with cure rates approaching 90%.

- The recommended surgical procedure for the primary tumor is inguinal orchietomy.

- If there is no evidence of invasion into the scrotum and the proximal spermatic cord is free of tumor, this procedure...
is considered equivalent to an amputation, and no further local therapy is necessary

✓ Surgical staging of retroperitoneal lymph nodes is controversial

✓ European investigators do not recommend retroperitoneal lymph node sampling for these patients

✓ In the IRS, recommendation for ipsilateral retroperitoneal
nerve-sparing node dissection for staging of all children >10 years of age

✓ Regional lymph node irradiation to the periaortic and ipsilateral iliac nodes is recommended when there is nodal involvement

✓ Surgical violation of the scrotum or tumor extension to the structure is an indication for
hemiscrotectomy or, less commonly, scrotal irradiation

Gynecologic Tumors

✓ Tumors arising in the vulva, vagina, cervix, and uterus are about one-third as common as bladder and prostate primary tumors and account for 4% of all rhabdomyosarcomas
Within this group, the vagina is the most common site of origin.

Patients with vaginal tumors are often much younger than those with other pelvic rhabdomyosarcomas, with most girls diagnosed before the age of 3 years.

Most present with a vaginal mass or discharge; botryoid morphology is common.
Initial surgery is used primarily for diagnosis, although gross tumor resection is occasionally possible without cosmetic or functional deformity.

These tumors are often quite sensitive to chemotherapy, and many may not require radical surgery or radiation therapy for local tumor control.
Even when surgery is used for persistent tumor after chemotherapy, preservation of bladder and sexual function is often possible with vaginal tumors.

Vulvar and uterine tumors may not be as amenable to organ-preserving therapy when surgery is necessary for local control.
Radiation therapy usually is reserved for patients with residual disease after resection or as part of a preoperative treatment regimen to help limit the extent of surgery.

Intracavitary and interstitial brachytherapy are useful irradiation techniques in these circumstances.
✓ disease control is excellent and late normal tissue effects are often significantly less than is seen with external-beam techniques.

✓ Permanent implants with iodine-125, temporary low-dose-rate, and high-dose-rate brachytherapy have all been used, and there are no clear differences between these.
techniques in terms of disease control or late effects
✓ When temporary implants are used, high-dose-rate brachytherapy has the practical advantage of minimizing radiation exposure to the family and medical personnel caring for the child.
✓ Children ages 1 to 9 years have a 98% 5-year survival.
Survival for infants and adolescents approaches 90%

**Other Pelvic Sites**
- These tumors include perianal, perirectal, and perineal primary sites
- Regional lymph node involvement may be high
- Combined chemotherapy and radiation therapy programs are favored over primary surgical procedures, if
excision demands exenteration with urinary and fecal diversion procedures

**Extremity**

✓ Tumors arising in the extremity are often of the alveolar or undifferentiated subtypes, large, deeply invasive, and associated with a high probability of lymphatic and hematogenous metastasis
when combined-modality treatment is given, these patients have an outcome approximating that for other tumor sites of similar TNM stage

recommend limb-salvage procedures including irradiation and chemotherapy

No data show that lymph node dissection offers a therapeutic advantage
✓ patients with lymph node involvement have a particularly poor prognosis
✓ If lymph node dissection is performed, it is for the purpose of staging, not for treatment
✓ Sentinel lymph node mapping and biopsy are being investigated for their diagnostic and prognostic value
Radiation therapy for extremity primary tumors requires careful immobilization techniques, sparing of nonirradiated skin for lymphatic drainage, and use of shrinking fields.

Routine physical therapy during and after radiation therapy is important for obtaining an optimal functional result.
Other Sites

✓ Patients with tumors arising in sites such as a paraspinal, retroperitoneal, or intrathoracic location have a poor outcome compared with other patients.

✓ Both local and distant relapse are common.

✓ These patients should be treated aggressively.
high-dose radiation therapy and multiagent chemotherapy

Metastatic Disease

✓ Intensive multiagent chemotherapy plays a major role in the treatment of these patients

✓ marrow ablative techniques have not improved efficacy compared with conventional chemotherapy approaches
• Local control of the primary tumor is site specific
• Metastatic sites should be treated with radiotherapy when feasible

**General Management**
• Multidisciplinary approach using surgery, irradiation, and chemotherapy is important in the management of rhabdomyo-sarcoma
Surgery

- The concept of reasonable surgery evolved; it involves removal of the bulk of tumor with maximal conservation of anatomic structures.
- 20% of patients have compromised surgical procedures, leaving microscopic residual disease.
- Patients with tumor amenable to complete excision fare...
better than those who have subtotal resection or biopsy alone
✓ combined-modality therapy provides good local control of the primary tumor even after subtotal excision
✓ the trend in recent years has been toward less-aggressive surgical resection, with more reliance on radiation therapy
and chemotherapy to provide local control

✔ Surgical excision is indicated if it can be done without compromise of function or cosmesis

✔ Normal tissue margins of at least 5 mm around the tumor are usually required to consider the resection complete
If microscopic disease remains after initial resection, a "primary re-excision" can be considered prior to beginning chemotherapy.

Amputation of an extremity, orbital exenteration, mutilating surgery of the head and neck area, therapeutic lymphadenectomy, and radical neck dissection are
procedures reserved in case initial therapy fails

✓ Second-look operations may be useful for converting partial responses after chemotherapy into complete responses

✓ Some investigators have used second-look operations in an attempt to eliminate radiotherapy, although this approach has resulted in
inferior local control and survival

✓ Second-look operations may be used to evaluate therapeutic response after chemotherapy and/or radiation therapy

✓ a clinical and/or radiographic evaluation indicating residual tumor after initial therapy may be misleading

Chemotherapy
The most extensive experience in combination chemotherapy is with VAC (vincristine, dactinomycin, cyclophosphamide) or VAC plus Adriamycin (VACA).

Patients with embryonal histology tumors in favorable sites who have no gross residual disease or lymph node involvement after the initial surgical resection.
appear to be adequately treated with VA (vincristine and dactinomycin) for 1 year, provided that irradiation is given for microscopic residual disease.

☑ Patients with unresectable pelvic tumors may benefit from the addition of Adriamycin and cisplatin to VAC.
tumors in other sites do not seem to benefit from the addition of these drugs compared with an intensive regimen of VAC alone.

Patients with metastatic rhabdomyosarcoma benefit from the addition of ifosfamide and etoposide to the standard VAC regimen.

High-dose chemotherapy with total-body irradiation and
autologous bone marrow transplantation has not improved the outcome in these high-risk patients

✓ response to induction chemotherapy “whether complete, partial, or no response” does not predict ultimate outcome

✓ When chemotherapy alone is used for tumors in sites such as the head and neck or
pelvis, omission of radiotherapy may result in inferior survival

- Even patients with only microscopic disease after initial resection (group II) require radiotherapy to achieve optimal local control

- In patients with group II disease, who routinely receive radiotherapy

Radiation Therapy
It is essential to evaluate the soft tissue extent of the primary lesion by computed tomography scan or magnetic resonance imaging.

Treatment portals usually are designed to encompass the involved region at the time of presentation (before chemotherapy) with margins that encompass surgical sites and biopsy tracts.
A biopsy should be performed of clinically suspicious lymph nodes, or they should be included in the radiation therapy portal.

Prophylactic lymph node irradiation is not necessary in children with clinically negative findings who will be receiving combination chemotherapy.
Patients with tumors at parameningeal sites have developed meningeal extension of tumor when inadequate irradiation portals were used.

Radiation therapy portals that cover the adjacent meninges in these patients can prevent meningeal relapse.

Even patients with advanced parameningeal tumors
presenting with cranial nerve palsies, base of skull erosion, or intracranial extension do not have significantly decreased 5-year survival rates, compared with those with less advanced parameningeal tumors, if appropriate irradiation portals are used.

✓ High-dose irradiation is necessary to ensure local
tumor control in patients who are unable to undergo complete surgical resection, even if concomitant multiagent chemotherapy is given.

✓ Local control of gross disease requires doses of at least 50 to 55 Gy, but microscopic disease can often be controlled with somewhat lower doses
local tumor control is greater for tumors <5 cm in diameter than for larger lesions
radiation doses of 40 to 41.4 Gy given in 4.5 weeks provide a 90% likelihood of local control of microscopic disease, with 50.4 to 55.8 Gy in 5.5 to 6 weeks recommended for gross residual disease
Early results of IRS-V data suggest that 36 Gy may be sufficient for microscopic residual, and in orbital primaries, 45 Gy may be sufficient for gross disease. The subset of group I patients with alveolar or undifferentiated histology had improved overall and failure-free survival when
Radiotherapy was given to the primary tumor site.

Current recommendations are to deliver 36 to 41.4 Gy to the operative bed of completely resected patients with alveolar or undifferentiated histology.

The standard of care for group III rhabdomyosarcoma continues to be
conventionally fractionated radiation with chemotherapy

✔ Three-dimensional conformal and intensity-modulated radiotherapy treatment planning techniques: The clinical target volume includes the gross tumor volume and any involved regional nodal chain, plus a 1-cm margin

✔ The planning target volume adds a patient-specific
margin, which is typically about 5 mm

Results of Therapy: Summary of Clinical Trials

In the first IRS study (IRS-I):

✔ For localized tumors amenable to complete resection (IRS group I), postoperative radiation therapy is unnecessary if the patient is given 2 years of VAC
Subsequent analysis has shown a benefit to postoperative radiation therapy for patients with group I tumors of alveolar or undifferentiated histology. VAC failed to improve results obtained with intensive VA for patients with group II disease if postoperative radiation therapy was given.
VACA provided no advantage over VAC for patients with group III disease (gross residual) or group IV disease (metastasis) if routine radiation therapy was used in addition.

Primary tumors of the orbit and genitourinary tract carried the best prognoses, and tumors of the
retroperitoneum had the worst.

✓ The alveolar histologic subset had a poor prognosis, especially in extremity lesions.

A second IRS study (IRS-II)

✓ Patients in group I (excluding alveolar extremity patients) had better disease-free status with VAC (82%) than those who received only VA (68%), but they had similar survival.
rates (82% and 88%) at 5 years

✓ Cyclophosphamide could not be withdrawn safely from the standard VAC regimen if irradiation was omitted from patients with group I disease

✓ Intensive (cyclic-sequential) VA therapy was as effective as repetitive pulse VAC therapy for patients with group II disease, if all patients
received postoperative irradiation

✓ Repetitive pulse chemotherapy for 2 years increased survival in children with group III disease but not in those with group IV disease

The third IRS study (IRS-III)

✓ Patients with group I favorable-histology tumors fared as well on a 1-year regimen of VA as did a
comparable group treated with VA plus cyclophosphamide

✓ Results for patients with group II favorable-histology tumors, excluding orbit, head, and paratesticular sites, were not improved with the addition of Adriamycin over VA chemotherapy — 1 year and radiation therapy.
✓ Patients with group III tumors, excluding those in special pelvic, orbit, and other
selected head sites (scalp, parotid, oral cavity, larynx, oropharynx, and cheek), fared better on the more intensive regimens of IRS-III than on pulsed VAC or VAC-VADR in IRS-II.

- Patients with group IV tumors did not benefit from the aggressive therapy of IRS-III.
- Patients with tumors in the bladder, vagina, and central pelvis in clinical group III had
significantly improved outcome as compared with IRS-II patients, primarily because of the routine administration of early radiation therapy

Patients with unfavorable histology, in clinical groups I and II, who received VADR-VAC + cisplatin and radiation therapy had improved outcome over patients in IRS-II receiving VA or VAC and irradiation.
Patients with favorable-histology group II paratesticular tumors and those with favorable-histology orbit and head tumors in groups II and III do not require cyclophosphamide when VA—1 year plus radiation therapy is used.

Whole-brain radiotherapy was omitted for patients with parameningeal primary tumors and cranial nerve palsy or base of skull erosion.
(although patients with intracranial extension of tumor still received this treatment)

The fourth IRS study (IRS-IV)

✔ For patients with group III tumors, hyperfractionated radiotherapy was no more effective than conventional radiotherapy for tumor control and survival
There was no difference in survival between VAC versus vincristine/actinomycin/ifosfamide versus vincristine/ifosfamide/etoposide in children with nonmetastatic disease.

Survival for patients with group I or II orbit/eyelid tumors was excellent when treated with VA and radiotherapy for group II disease.
Prognostic subsets of patients based on histologic subtype, stage and group could be identified as follows: Low-risk patients had embryonal histology and were stage 1 (all groups), or stage 2/3 and group I or II. All other patients with locoregional disease were intermediate-risk.

Survival for patients with metastatic disease was superior with the drug pair ifosfamide/etoposide when
compared with vincristine/melphalan.

✓ Whole-brain radiotherapy was omitted for all patients with parameningeal primary tumors except when there was cytologic evidence of cerebrospinal fluid involvement

The fifth IRS studies (IRS-V) were conducted from 1997 to 2005

✓ They studied a number of questions that included:
✓ Can a subset of the most favorable patients be treated without alkylation agents?
✓ Can radiation dose be reduced to 36 Gy for microscopic disease, and 45 Gy for gross tumor in the subset of patients with orbital primaries?
✓ Can radiation dose be reduced for group III patients after induction chemotherapy and second-look operation?
✓ What is the activity of topotecan and irinotecan in the
treatment of rhabdomyosarcoma?

Early results from the IRS-V studies support the elimination of alkylating agents from chemotherapy regimens for patients with a favorable prognosis, and the reduction of radiation dose to 36 Gy and 45 Gy for microscopic tumor and group III orbital primaries, respectively.

CWS Studies
The German-based Cooperative Weichteil Sarkom (CWS) studies:

- Duration of chemotherapy can be reduced to as little as 16 weeks for the most favorable patients.
- Ifosfamide gives improved response rates compared with cyclophosphamide.
- Hyperfractionated accelerated radiotherapy concurrent with chemotherapy as used in the study is tolerable and provided acceptable local control.
Sequelae of Treatment

- Moisturizers and steroid creams are effective symptomatic treatments for erythema and dry desquamation.
- Moist desquamation may be treated with aluminum acetate soaks or hydrocolloid dressings.
- Occasionally, a delay in radiation therapy is necessary to permit healing.
After orbital irradiation, an acute inflammatory reaction of the cornea and conjunctiva may be seen within weeks of completion of treatment. This can result in pain and photophobia. Topical steroids should be administered under the direction of an ophthalmologist for these symptoms.

Acute otitis externa or media with hyperemia and swelling of the membranes of the eustachian tube is common
during or soon after treatment of head and neck areas

✓ Acute otitis externa or media with hyperemia and swelling of the membranes of the eustachian tube is common during or soon after treatment of head and neck areas

✓ Erythematous mucositis leading to a patchy, fibrinous exudate is seen after head and neck irradiation, after
drug therapy, and almost universally if the two are used simultaneously

✓ Mouthwashes such as salt and soda, 1% hydrogen peroxide, or combinations of diphenhydramine elixir, hydrocortisone, and antibiotics partially alleviate the reaction

✓ Future Directions and Research

✓ Advances in molecular biology are now providing a more
comprehensive understanding of the biologic behavior of rhabdomyosarcoma and direct new research initiatives.

- Chromosome aberrations are common in rhabdomyosarcoma
### Head and Neck

- **MRI or CT of primary tumor (with contrast)**
- **Lumbar puncture with cytologic examination of fluid in parameningeal primary tumors**

### Genitourinary

- **CT of MRI of abdomen-pelvis (with contrast)**
- **Pelvic examination under anesthesia**

### Extremity and Truncal Lesions

- **MRI or CT of primary lesion (with contrast)**

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