Management of Rhabdomyosarcoma in Pediatric Patients

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KEYWORDS

• Rhabdomyosarcoma • Pediatric • Soft tissue sarcoma • Surgery

KEY POINTS

- Rhabdomyosarcoma is the commonest soft tissue sarcoma in children, requiring clinician vigilance to recognize the multitude of site-specific presentations.
- Biopsy enables pathologic, genetic, and biological characterization of the tumor, and accurate staging with imaging and surgical sampling informs risk-based therapy.
- A specialist multidisciplinary team assigns each patient to a risk group with treatment delivered by a risk-based approach.
- Patients always require chemotherapy and usually a combination of complex, site-specific surgery and/or radiotherapy.
- Outcomes for localized rhabdomyosarcoma continue to improve but locoregional relapse remains a problem, as does metastatic/metastatic relapsed disease, so new treatment approaches are required.

BACKGROUND

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, accounting for 4.5% of all childhood cancers. It follows neuroblastoma and nephroblastoma as the third most common extracranial solid tumor of childhood.[1] The incidence is 4.5 cases per million children/adolescents per year.[2] It is rare in adults, with an incidence of 0.9 cases per million per year, where soft tissue sarcomas constitute less than 1% of all malignancies, and RMS accounts for only 3% of all soft tissue sarcomas.[3]

RMSs are malignant tumors of mesenchymal origin and can therefore occur at any anatomic site and often show cellular differentiation toward muscle tissue. RMSs have

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Surg Oncol Clin N Am 30 (2021) 339–353
https://doi.org/10.1016/j.soc.2020.11.003
surgonc.theclinics.com

small round blue cells that usually mark positive immunohistochemically for the proteins desmin, vimentin, myoglobin, actin, and myoD.[4]

Childhood RMS is subdivided into 2 major subtypes, the commonest is PAX fusion–negative RMS (previously called embryonal RMS), occurring in 70%, and PAX fusion–positive RMS (previously called alveolar RMS). Spindle cell/sclerosing RMS is a third RMS subtype, whereas pleiomorphic RMS occurs exclusively in adults.[5,6] In adulthood, the distribution of subtypes differs, with most (65%) being adult-type RMS (pleiomorphic, spindle cell, and not otherwise specified).[3]

Most PAX fusion–negative RMSs show loss of heterozygosity at the 11p15 locus, the site of the IGF-II (insulin-like growth factor II) gene that has shown significant involvement in the pathogenesis of these tumors. PAX fusion–positive RMS is usually (80%) associated with one of several balanced chromosomal translocations, most commonly t(2;13) in approximately 60%, or t(1;13) in 20%, with the remaining 20% translocation negative. These chromosomal fusions result in expression of proteins (aberrant transcription factors) that induce cancer development.[7] PAX fusion–positive status in nonmetastatic disease is a poor prognostic marker (36.1% event-free survival [EFS] at 5 years); conversely, PAX fusion–negative status carries a better prognosis (70% EFS at 5 years).[8,9]

There are primary peaks of incidence in the 2-year-old to 6-year-old age group, with tumors generally within the head and neck and genitourinary tract, and in adolescents who present with extremity, truncal, or paratesticular tumors.

Outcomes in localized RMS have improved steadily and approach 80% survival; however, for patients who present with metastatic and relapsed disease, outcomes remain poor (<30%) and have not changed in several decades, prompting the need for new treatment approaches. Adult patients with RMS have a poorer overall survival than pediatric patients: 43% for localized RMS and 5% for metastatic RMS.[3,9–11]

PATIENT EVALUATION OVERVIEW

RMS occurs in multiple anatomic sites with the approximate distribution shown in **Table 1**.

Because of the variable sites of tumor origin, clinicians need vigilance to recognize patients with differing presenting signs and symptoms of RMS, as shown in **Table 2**.

Rarely (~5%), patients (PAX fusion negative) present with an underlying cancer-predisposition syndrome, such as neurofibromatosis, Li-Fraumeni syndrome, DICER1 syndrome, Rubinstein-Taybi syndrome, Gorlin basal cell nevus syndrome, Beckwith-Wiedemann syndrome, or Costello syndrome.[12,13] It is important to recognize any potential genetic predisposition to cancer so that genetic counseling, screening, surveillance, and timely treatment can be offered.[14]

Table 1
Distribution of rhabdomyosarcoma primary sites

Primary Tumor Site	Percentage
Head and neck	40
Genitourinary	20
Extremities	20
Trunk	10
Other	10

Table 2
Common presenting signs and symptoms by primary site

Primary Site	Symptoms and Signs
Head and neck	Painless or painful swelling Proptosis Ptosis Ophthalmoplegia Headache Vomiting Cranial nerve palsy Other cranial nerve palsies Nasal discharge Nasal/sinus congestion Trismus Systemic hypertension
Limbs/trunk	Asymptomatic swelling
Genitourinary tract/pelvis	Painless scrotal lesions Hematuria Urinary retention/dribbling Vulval nodule Polypoid vaginal lesions Vaginal bleeding/discharge Constipation
Abdomen/liver/biliary	Asymptomatic swelling Abdominal pain Intestinal obstruction Jaundice Cholangitis
Metastatic disease (20% at diagnosis) • Bone • Bone marrow • Lung • Lymph nodes	Otherwise unexplained: Poor feeding Seizures Pain Irritability Pancytopenia

When RMS is suspected, the patient requires imaging and biopsy to confirm the diagnosis, followed by accurate staging and a treatment plan made by a specialist multidisciplinary team using a risk-based approach.

Imaging Studies

Initial ultrasonography of a suspicious lesion can be helpful to delineate whether the mass is solid or cystic and can also assess its vascular characteristics.

MRI is the optimal imaging modality to assess most primary lesions, with RMS usually, but not invariably, isointense to muscle on T1-weighted images, and intermediate to high intensity on T2-weighted images.[15] Computed tomography (CT) is excellent for assessing bone involvement, and can be performed when osseous invasion is suspected. Cross-sectional imaging of the primary tumor should include the regional draining lymph nodes for staging, and, in the case of extremity tumors, the entire limb (Fig. 1). Chest CT should be performed as part of staging for the detection of pulmonary metastases.

When available, either whole-body fluorodeoxyglucose (FDG) PET/CT or FDG-PET/MRI can be used for the assessment of disease burden, but these cannot be relied on

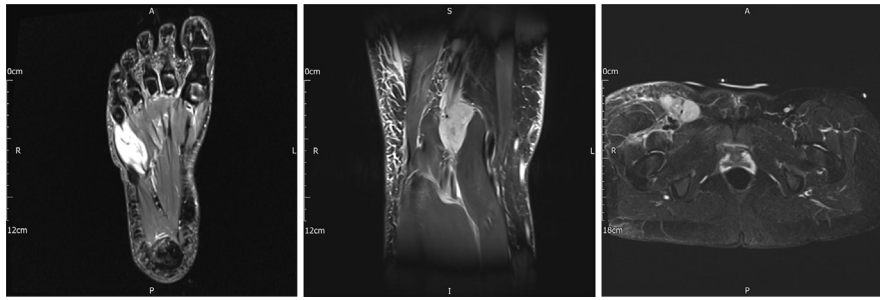

Fig. 1. MRI scans of a 15-year girl with a fusion-positive RMS of the right foot and lymph node metastases in the popliteal fossa and groin.

to give accurate representation of lymphatic metastasis.[16,17] Biopsy core needle or incisional biopsy should be the initial surgical procedure in all patients except when primary wide excision of the mass with adequate margins is possible without loss of function or excessive morbidity.[18,19] Fluorescence in situ hybridization (FISH) is performed on the biopsy tissue to detect the presence of a translocation and reverse transcription polymerase chain reaction (RT-PCR) is used to determine the specific fusion. Bone marrow biopsy should be performed in all intermediate-risk and high-risk patients to determine metastatic spread to the marrow.[20]

For parameningeal tumors, cerebrospinal fluid (CSF) cytology should be obtained to detect central nervous system involvement. Regional lymph nodes should be evaluated surgically in patients with tumors of the extremity, trunk, head and neck, perineal/perianal site, and patients more than 10 years old with paratesticular RMS, because lymph node involvement is more common at these sites and imaging is not able to reliably exclude lymph node metastases. Sentinel lymph node biopsy (SLNB) is more accurate than random lymph node sampling. Pathologic confirmation should be obtained for patients with abnormal lymph nodes (>1 cm in diameter), or they should be treated as having pathologic lymphadenopathy.

Staging and Risk Stratification

Staging and risk stratification in RMS is complex but important, because treatment intensity follows a risk-adapted approach.[21] Patients are assigned to a pretreatment stage using the tumor, node, metastasis (TNM) classification (**Table 3**) and to a surgicopathologic group using the Intergroup Rhabdomyosarcoma (IRS) group classification (**Table 4**). The IRS group is a prechemotherapy staging system determined by the extent of the initial surgical resection and the presence of pathologic lymph nodes and distant metastases. Factors that determine prognosis include tumor biology, including PAX fusion status; favorable or unfavorable tumor site (**Table 5**); lymph node status; patient age; tumor size; metastases; and IRS group (see **Table 4**).

Risk-group assignment incorporates pretreatment stage (**Table 6**), IRS group, tumor biology, and patient age.[22]

TREATMENT OPTIONS

Treatment of patients with RMS is multimodal, always includes chemotherapy, and usually includes a combination of radiotherapy (RT) and surgery.

Table 3
Tumor, node, metastasis staging classification

T1	Tumor confined to tissue of origin
T2	Tumor extends beyond tissue of origin
A	≤5 cm in maximum diameter
B	>5 cm in maximum diameter
N0	No nodal involvement
N1	Nodal involvement
NX	Regional lymph nodes not examined; no information
M0	No distant metastases
M1	Distant metastases

Chemotherapy

The intensity and duration of chemotherapy are increased according to risk-group assignment (**Tables 7** and **8**). The Children's Oncology Group (COG) and European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) use chemotherapy backbone regimens that differ in that the alkylating agent is substituted, with cyclophosphamide used by COG and ifosfamide by EpSSG. Comparisons between these alkylating agents have shown no significant differences in outcome but each gives rise to different late effects: ifosfamide is more nephrotoxic and cyclophosphamide is more gonadotoxic.[23]

Adult patients are likely to benefit from entering clinical trials in common with pediatric patients and, when treated in line with pediatric treatment protocols, have had better outcomes.[24] However, pleiomorphic RMS is chemoresistant like other high-grade soft tissue sarcomas of adulthood, and the best combination chemotherapy is not defined for this subtype.[3]

Radiotherapy

In most patients (85%), RT is required to obtain local control at the primary site, and is always required for pathologically involved lymph nodes.[25] There are only a few selected groups of patients with low-risk disease where RT can be safely avoided without potentially compromising cure, such as completely resected paratesticular RMS or vaginal RMS with a complete chemotherapy response. Intensity-modulated RT (IMRT), brachytherapy, and proton beam RT may achieve adequate tumor control with reduced radiation to normal surrounding tissues.[26]

SURGICAL TREATMENT

Primary Resection

Primary resection is indicated if the tumor can be excised with R0 margins (resection should be attempted only if it is anticipated that all gross tumor can be excised,

Table 4
Intergroup Rhabdomyosarcoma Group surgical-pathologic (clinical) grouping classification

IRS-I	Tumor completely removed
IRS-II	a. Microscopic residual tumor b. Involved regional nodes c. Both
IRS-III	Gross residual tumor after incomplete resection or biopsy only
IRS-IV	Distant metastatic disease

Table 5
Favorable/unfavorable prognostic tumor sites

Favorable Primary Tumor Sites	Unfavorable Primary Tumor Sites
Head and neck	Parameningeal
Orbital	Extremities
Genitourinary (now also includes bladder/prostate in EpSSG)	Bladder/prostate (remains unfavorable site in COG)
Biliary	Trunk
	Chest wall
	Other sites

Abbreviations: COG, Children's Oncology Group; EpSSG, European Pediatric Soft Tissue Sarcoma Study Group.

because leaving gross residual disease behind has a similar outcome to biopsy alone). Complete resection should include a rim of surrounding tissue with a margin of at least 0.5 cm without significant morbidity.[27,28]

Pretreatment Reexcision

Pretreatment reexcision (PRE) is a wide, nonmutilating reexcision to achieve a complete resection (R0 margin) in patients with microscopic residual disease after a primary procedure, which could have been a biopsy or incomplete tumor excision.[29] PRE needs to be done before other adjuvant therapies begin and as soon as possible after the primary resection. If R0 margins are obtained at the PRE operation, the patient should then be classified as IRS group I with its associated improved survival and potential for a decreased intensity of therapy.[30] PRE should only be offered if the resection of the entire tumor bed can occur with a margin without loss of function or form.

Delayed Primary Excision

Delayed primary excision (DPE) occurs after induction chemotherapy if the tumor can be macroscopically removed without danger or mutilation; this is most often combined with postoperative RT. Debulking operations are not recommended and there is no evidence that this improves oncological outcome compared with biopsy alone.[31] A complete R0 resection should be targeted; however, a microscopic residual R1 resection may decrease the amount of adjuvant RT needed.[32]

Fertility Preservation

Fertility-preserving procedures, such as gonadal transposition, should be considered before RT or ovarian/testicular cryopreservation.[33] In pubertal patients, sperm or egg

Table 6
Pretreatment staging system

Stage	Site[b]	T Stage[a]	Size[a]	Node Stage[a]	Metastases[a]
1	Favorable	T1 or T2	Any size	N0 or N1 or Nx	M0
2	Unfavorable	T1 or T2	a, ≤5 cm	N0 or Nx	M0
3	Unfavorable	T1 or T2	a, ≤5 cm	N1	M0
			b, >5 cm	N0 or N1 or Nx	
4	Any site	T1 or T2	Any size	N0 or N1 or Nx	M1

[a] Refer to TNM classification.
[b] Refer to Table 5.

Table 7
Children's Oncology Group risk-group assignment

Risk Group	Fusion Status	Stage	Group
Low risk	Fusion negative	1	I, II, III (orbit only)
	Fusion negative	2	I, II
Intermediate risk	Fusion negative	1	III (nonorbit)
		2, 3	III
		3	I, II
		4	IV (age<10 y)
	Fusion positive	1, 2, 3	I, II, III
High risk	Fusion positive	4	IV
	Fusion negative	4	IV(age $\geq$ 10 y)

storage should be offered if it can be performed without undue treatment delay, otherwise gonadal cryopreservation should be considered.

In prepubertal patients, gonadal cryopreservation should be discussed with the parents.[34,35]

Site-Specific Surgical Treatment

Bladder/prostate rhabdomyosarcoma

The aim of local treatment of bladder/prostate RMS is oncologic control in conjunction with preservation of bladder and sexual function.[36]

To achieve optimal outcomes an experienced multispeciality team needs to offer the spectrum of local treatment modalities, including surgery and reconstruction, as well as RT, including brachytherapy and proton beam RT.[36–39]

Vaginal rhabdomyosarcoma

Tumors at this site are generally very chemosensitive. Patients with favorable histology and biopsy-proven complete response to chemotherapy do not require any local therapy.[40] For those with residual disease after chemotherapy, local control is necessary. Patients with unfavorable histology must receive RT. Intracavitary brachytherapy has generally replaced surgery for local control, combined with temporary ovarian transposition away from the radiation field.[33]

Resection should only be considered if an R0 resection can be achieved with preservation of function and fertility.

Table 8
European Pediatric Soft Tissue Sarcoma Study Group risk-group assignment

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low risk	A	Negative	I	Any	N0	Both Favorable
Standard risk	B	Negative	I	Any	N0	One or both Unfavorable
	C	Negative	II, III	Favorable	N0	Any
High risk	D	Negative	II, III	Unfavorable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very high risk	G	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Paratesticular rhabdomyosarcoma

Paratesticular RMS (PT-RMS) should be removed by radical orchidectomy through an inguinal approach.[41,42] The cord should be clamped at the internal ring before mobilization of the tumor. Care is taken not to breach the tunica vaginalis when the tumor, testis, and entire cord up to the internal ring are removed as a single specimen. When scrotal skin is fixed or invaded by tumor, it should be resected en bloc with the specimen, otherwise there is no indication for hemiscrotectomy.

PRE without formal hemiscrotectomy is required after incomplete resection to remove tumor-contaminated scrotal and/or cord tissue.[43]

Retroperitoneal lymph node assessment

Accurate staging of nodal metastases in PT-RMS is important because lymph node involvement is frequent (26% in IRS-I and IRS-II trials) and patients with positive nodes require intensified chemotherapy and RT.[44] All patients should have MRI/CT imaging of the retroperitoneal nodes, and those 10 years of age or older should also undergo surgical staging of the lymph nodes. A pooled analysis from North America and Europe of 319 patients 10 years of age or older with PT-RMS found that nodal involvement was present in approximately 30% and disease failures were most likely to occur in the nodes. Surgical evaluation of retroperitoneal lymph nodes was the only treatment variable that was associated with EFS.[45] There was a 30% lymph node relapse in patients 10 years of age or older who had nodal staging with imaging alone.[46–49]

Template retroperitoneal lymph node dissection (RPLND) has frequently been avoided because of concern about potential complications. Routh and colleagues[49] report that sampling between 7 and 12 lymph nodes taken from multiple areas in the ipsilateral retroperitoneum up to the renal vessels may be similarly efficacious to identify nodal involvement while minimizing the complications of template RPLND.

Extremity rhabdomyosarcoma

Several adverse prognostic factors are frequently associated with extremity RMS, including older age at presentation, PAX fusion–positive tumors, tumors that invade surrounding tissues, incomplete initial surgical resection, metastatic disease, and lymph node involvement.[18]

Aggressive surgical procedures resulting in loss of function are generally not indicated because the efficacy of chemotherapy and RT usually allows sparing of vital structures.[50] The primary goal of local tumor resection, which is usually a DPE, is limb-sparing complete (R0) resection. An incision is made along the major axis of the anatomic compartment containing the tumor and must include en bloc resection of previous biopsy and drain sites. An R1 (microscopically involved margins) resection with RT usually achieves oncological control while maintaining optimal functional outcome. Ablative procedures should only be performed after a second opinion from a specialized center.

Bile ducts and liver rhabdomyosarcoma

Patients with bile ducts and liver RMS usually present with jaundice, pruritus, and dilatation of the biliary tract. Ultrasonography and MRI with magnetic resonance cholangiopancreatography show the extent of the primary lesion and lymph node involvement, as well as ruling out other causes of biliary obstruction. Biopsy rather than primary excisional surgery is recommended because these tumors usually have a favorable subtype (fusion-negative/botryoid histopathology) that respond well to chemotherapy.[51]

Definitive local control is planned after induction chemotherapy.[51] Complete tumor resection can be considered, which may require partial hepatectomy; however, RT

has similar outcomes to DPE, but the long-term effects of RT to the hepatic pedicle are unknown in young patients.[52]

Treatment of metastases

Current standard of care recommends systematic RT of all metastatic sites that can feasibly be treated without disruption of bone marrow function; however, it is not clear whether this strategy improves outcome. Surgical resection of end-of-therapy residual masses does not show any survival advantage.[53]

Follow-up

Following completion of treatment, the frequency of follow-up assessments is conventionally every 3 to 4 months for the first 2 years. There is a need for risk-adapted follow-up strategies to improve the efficiency of follow-up after RMS treatment.[54] RMS rarely relapses later than 3 years from diagnosis. At 5 years from end of treatment, patients can be referred to the long-term follow-up clinic.

Relapse

The commonest pattern of relapse in localized RMS is relapse at the primary site (75%) with or without nodal and distant metastases. Relapsed RMS carries a poor prognosis, although 35% of those who relapse following treatment of localized disease remain curable. Relapse of primary metastatic disease is usually fatal.

Local relapse patients should only be treated in tertiary cancer centers. When treatment with curative intent is deemed feasible after interdisciplinary consultation, the general principle of complete resection should be pursued, and in rare situations may include radical ablative procedures.[55,56]

Biopsies should be taken at relapse, because genomic profiling should be performed, so patients can be considered for targeted therapies or early-phase trials.[5,57]

New developments

SLNB using indocyanine green has been reported to stage lymph nodes in paratesticular and extremity RMS, and is likely to become more widely adopted, as has happened with cervical cancers in adult patients, because it offers a less invasive operative approach (**Fig. 2**).[58–61] With advances in understanding the biology of RMS, ways need to be found to optimize translation of preclinical findings into clinical trials, using rational combinations of targeted agents, conventional chemotherapeutics, and/or immunotherapeutics. International, multidisciplinary research teams are increasingly being established to facilitate discovery, share learning, and pool data[5] (https://cri-app02.bsd.uchicago.edu/instruct).

There are now more than 2 dozen preclinical biological targets with promising corresponding novel therapies in development; some of these are highlighted. WEE1 is a tyrosine kinase that is activated in response to DNA damage and halts progression of cells through the mitotic cycle, allowing DNA repair before cell division. A WEE1 inhibitor (AZD1775) administered in the setting of chemotherapy-induced DNA damage could lead to death of mitotic RMS cells.[62]

Aberrant activation of the receptor tyrosine kinase–mediated RAS signaling cascade is the primary driver of PAX fusion–negative RMS. Oncolytic virus-mediated RAS targeting in RMS can significantly reduce tumor growth and suggests that targeted gene-editing cancer therapies have promising translational applications.[63,64]

However, single-agent therapies do not seem to achieve durable responses because of the acquisition of resistance to treatment. Monoclonal antibodies can directly target cancer cells through several mechanisms, including inhibition of

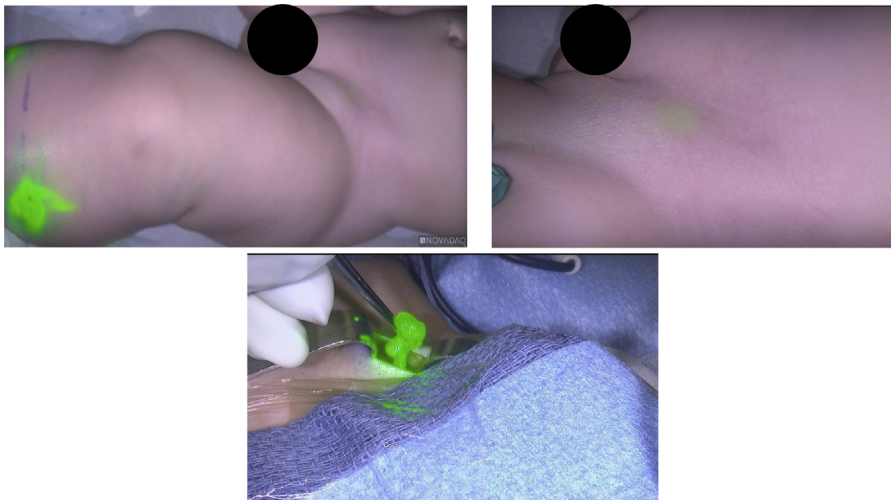

Fig. 2. SLNB using indocyanine green.

oncogenic signaling pathways, delivery of cytotoxic moieties to malignant cells, or induction of antibody-dependent cellular toxicity.[65] However, their role in treating RMS is not well established.

The clinical efficacy of CAR (chimeric antigen receptor) T-cell therapy to pediatric solid tumors has so far been limited, because of heterogeneous antigen expression; limited migration of T cells to tumor sites; and an immunosuppressive, hostile microenvironment.[66] RMS is a rare disease, so the incentives for pharmaceutical companies to develop specific therapeutic agents to directly target PAX-FOXO1 are neither strong nor imminent.

SUMMARY

Treatment of RMS involves a multimodality approach including chemotherapy, surgery, and RT while minimizing the long-term treatment-related morbidities. This article outlines the key points related to the diagnosis and management of RMS with a focus on current surgical management of RMS at specific tumor sites. There is a need for improved RT and surgical techniques as well as systemic therapy in RMS to reduce locoregional and metastatic relapse, reduce late sequelae of treatment, and improve functional outcomes. Better understanding of the biology of the RMS subtypes found in adult patients, with increased enrollment into cooperative group studies, is required.

CLINICS CARE POINTS

- The myriad clinical presentations of rhabdomyosarcoma are dependent on patient age, site of origin of the tumor and the pattern of tumor spread.
- Biopsy and appropriate staging should typically be completed before definitive local therapy, with paratesticular tumors being the only usual exception.
- Surgical lymph node assessment should be performed for certain named primary tumor sites where the risk for lymph node metastases and relapse are significant.
- Definitive locoregional treatment with multimodality approaches is integral, combined with chemotherapy, to control disease and minimize morbidity.

DISCLOSURE

The authors have nothing to disclose.

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