National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Testicular Cancer

V.2.2009

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NCCN Guidelines Panel Disclosures

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† Medical oncology
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§ Radiotherapy/Radiation oncology
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£ Supportive Care including Palliative, Pain Management, Pastoral care and Oncology social work
Þ Internal medicine
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Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2008.

Summary of the Guidelines updates

The Guidelines were updated to version 2.2009 to represent the addition of the discussion correspondent to the changes in the algorithm.

Summary of changes in the 1.2009 version of the Testicular Cancer Guidelines from the 1.2008 version include:

Testicular Cancer
TEST-1
- **Primary treatment: "radical" was added to "inguinal orchiectomy" for clarification.**

Seminoma
TEST-3:
Primary Treatment:
- **Stage IA, IB: "Surveillance" was changed from a category 2A designation to a category 1 designation.**
- **Single agent carboplatin was changed from a category 2B designation to a category 1 designation.**
- **Single agent carboplatin doses, "AUC=7 x 1 cycle or AUC=7 x 2 cycles" were added.**
- **Stage IA, IB: "RT" was changed from a category 2A designation to a category 1 designation.**
- **Stage 1S, primary treatment was clarified as "RT: Infradiaphragmatic (25-30 Gy) to include para-aortic ± ipsilateral iliac nodes"**

TEST-4
- **Residual mass (nodes > 3 cm on CT): "Surgery" was clarified as a category 2B.**

Nonseminoma
TEST-10
- **Poor risk, Stage IIIC: "VIP for 4 cycles for selected patients" was added as a postdiagnostic treatment option with corresponding footnote l, "Patients who may not tolerate bleomycin."**

TEST-A:
- **Footnote 1, "Markers used for risk classification are post-orchiectomy" is new to the page.**

TEST-B
- **Previously untreated, intermediate, or poor risk: "VIP"regimen was added.**

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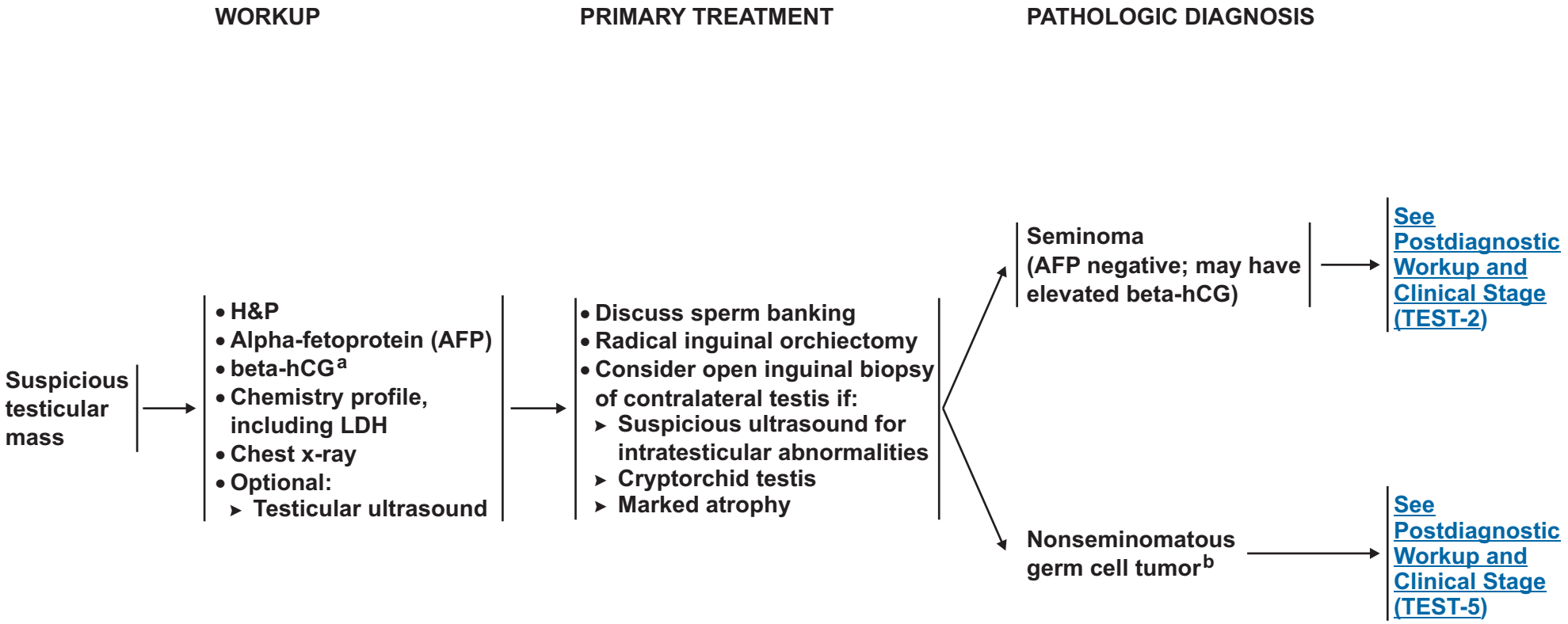
Testicular Cancer



[a] Quantitative analysis of beta subunit.
[b] This includes seminoma histology with elevated AFP.

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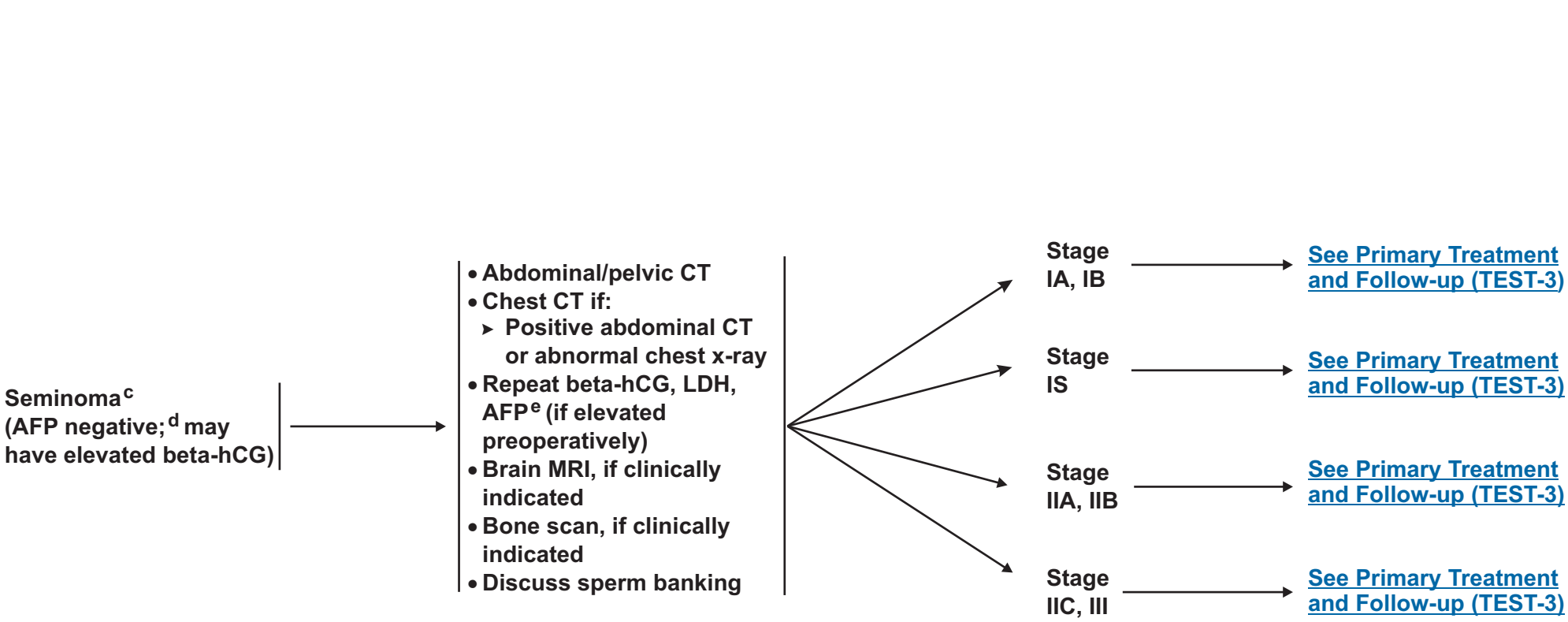

[c]Mediastinal seminoma should be treated as good risk nonseminomatous germ cell tumor with etoposide/cisplatin for 4 cycles or bleomycin/etoposide/cisplatin for 3 cycles.

[d]If positive, treat as nonseminoma.

[e]Elevated values should be followed with repeated determination to allow precise staging.

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CLINICAL STAGE	PRIMARY TREATMENT	FOLLOW-UP
Stage IA, IB	Surveillance if: (category 1) • Horseshoe or pelvic kidney • Inflammatory bowel disease • Prior RT Consider surveillance if: (category 2B) • T1 or T2 histology in selected patients committed to long-term follow-up or Single agent carboplatin (category 1) (AUC=7 x 1 cycle or AUC=7 x 2 cycles) or RT: Infradiaphragmatic (20-30 Gy) to include para-aortic ± ipsilateral iliac nodes (category 1)	H&P, AFP, beta-hCG, LDH: every 3-4 mo for years 1-3, every 6 mo for years 4-7, then annually Abdominal/pelvic CT at each visit, chest x-ray at alternative visits (up to 10 y) → Recurrence, treat according to extent of disease at relapse H&P + chest x-ray, AFP, beta-hCG, LDH: every 3-4 mo for year 1, every 6 mo for year 2, then annually Pelvic CT annually for 3 years (for patients status post only para-aortic RT) → Recurrence, treat according to extent of disease at relapse
Stage IS	RT: Infradiaphragmatic (25-30 Gy) to include para-aortic ± ipsilateral iliac nodes	
Stage IIA, IIB	RT: Infradiaphragmatic (35-40 Gy) to include para-aortic and ipsilateral iliac nodes or Consider EP x 4 cycles for selected stage IIB patients	H&P + chest x-ray, AFP, beta-hCG, LDH: every 3-4 mo for years 1-3, every 6 mo for year 4, then annually Abdominal CT at month 4 of year 1 → Recurrence, treat according to extent of disease at relapse See Additional Therapy and Follow-up on TEST-4
Stage IIC, III	Good risk[f] → EP for 4 cycles (category 1) or BEP for 3 cycles (category 1) Intermediate risk → BEP for 4 cycles (category 1)	See Additional Therapy and Follow-up on TEST-4

EP = Etoposide/cisplatin
BEP = Bleomycin/etoposide/cisplatin

[f] See Risk Classification (TEST-A).

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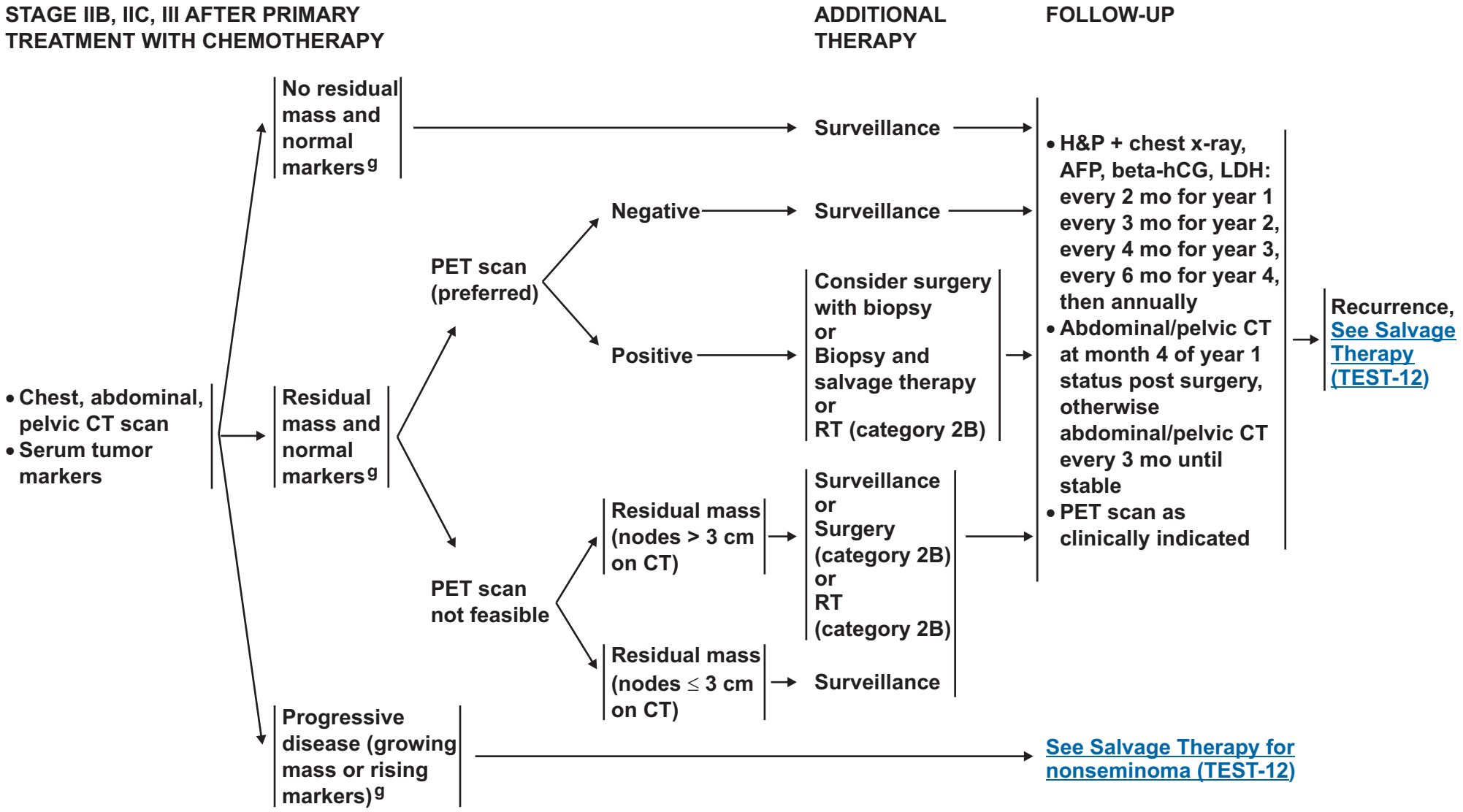

[g]For persistent elevated beta-hCG which is not rising, repeat serial markers, testosterone suppression test and consider a PET scan.

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PATHOLOGIC DIAGNOSIS | **POSTDIAGNOSTIC WORKUP** | **CLINICAL STAGE[h]**

Nonseminomatous germ cell tumor[b]

- **Abdominal/pelvic CT**
- **Chest CT if:**
  - **Abnormal abdominal CT**
  - **Abnormal chest x-ray**
- **Repeat beta-hCG, LDH, AFP[e]**
- **Brain MRI, if clinically indicated**
- **Bone scan, if clinically indicated**
- **Discuss sperm banking**

→ **Stage IA, IB, IS:** See Postdiagnostic Treatment (TEST-6)

→ **Stage IIA, IIB:** See Postdiagnostic Treatment (TEST-7)

→ **Stage IIC, IIIA, IIIB, IIIC, and brain metastasis:** See Postdiagnostic Treatment (TEST-10)

[b] This includes seminoma histology with elevated AFP.
[e] Elevated values should be followed with repeated determination to allow precise staging.
[h] Treatment may be initiated prior to histology for patients with rising markers and a deteriorating clinical situation.

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CLINICAL STAGE	POSTDIAGNOSTIC TREATMENT	
Stage IA	Surveillance (in compliant patients)	See Follow-up for Nonseminoma (TEST-11)
	or	
	Open nerve-sparing RPLND[i]	See Postsurgical Management (TEST-9)
Stage IB	Open nerve-sparing RPLND[i]	See Postsurgical Management (TEST-9)
	or	
	Chemotherapy: BEP for 2 cycles (category 2B)	See Postchemotherapy Management (TEST-8)
	or	
	Surveillance (only if T2, compliant patients [category 2B])	See Follow-up for Nonseminoma (TEST-11)
Stage IS	Persistent marker elevation → Chemotherapy: EP for 4 cycles or BEP for 3 cycles	See Postchemotherapy Management (TEST-8)

The EP and BEP chemotherapy regimens have shown survival advantage in randomized clinical trials and may be considered as category 1 compared with other chemotherapy regimens.

EP = Etoposide/cisplatin
BEP = Bleomycin/etoposide/cisplatin
RPLND = Retroperitoneal lymph node dissection

[i]Surgery is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).

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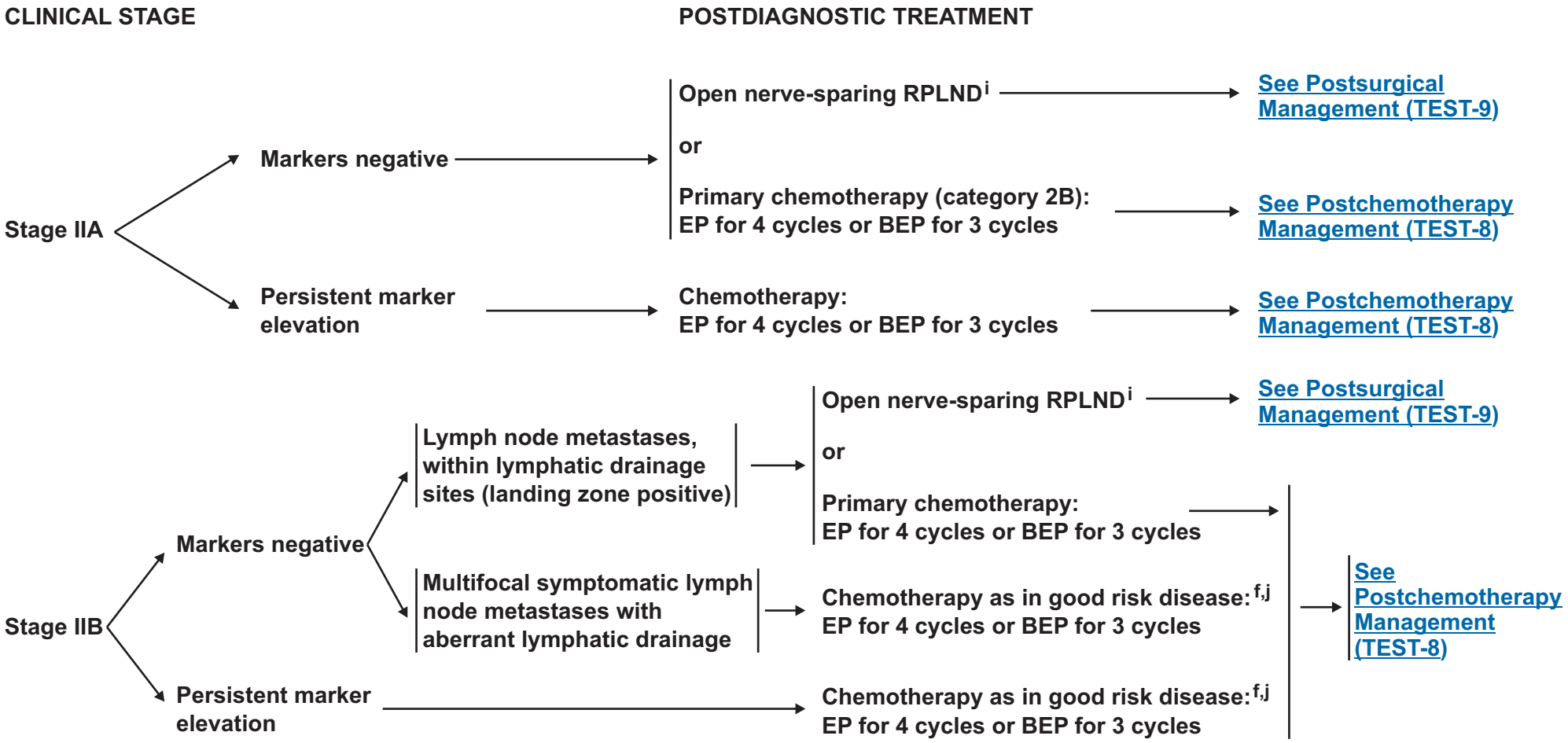

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RPLND = Retroperitoneal lymph node dissection

[f] See Risk Classification (TEST-A).
[i] Surgery is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
[j] See Primary Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-B).

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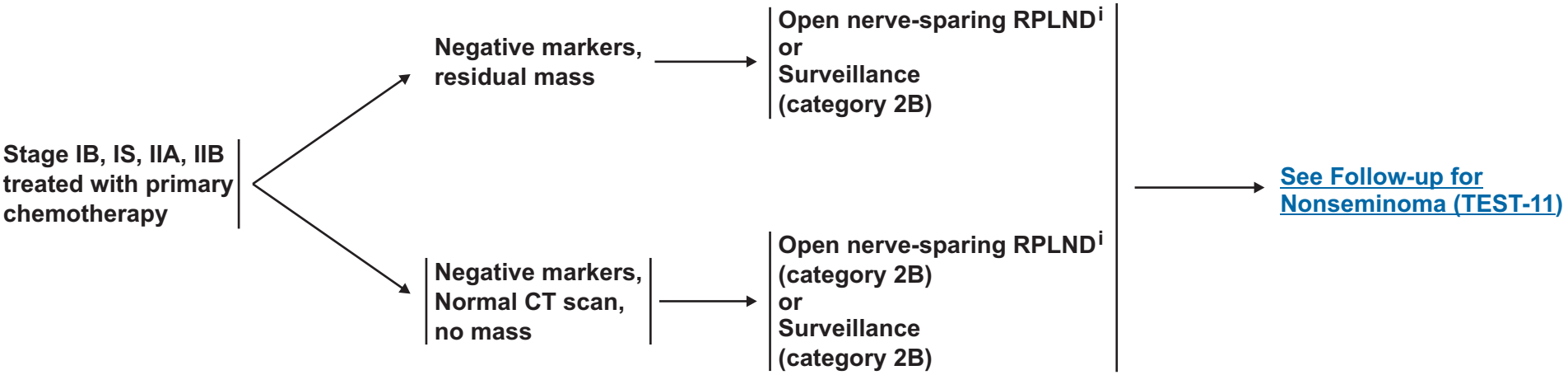
POSTCHEMOTHERAPY MANAGEMENT



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[i]Surgery is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).

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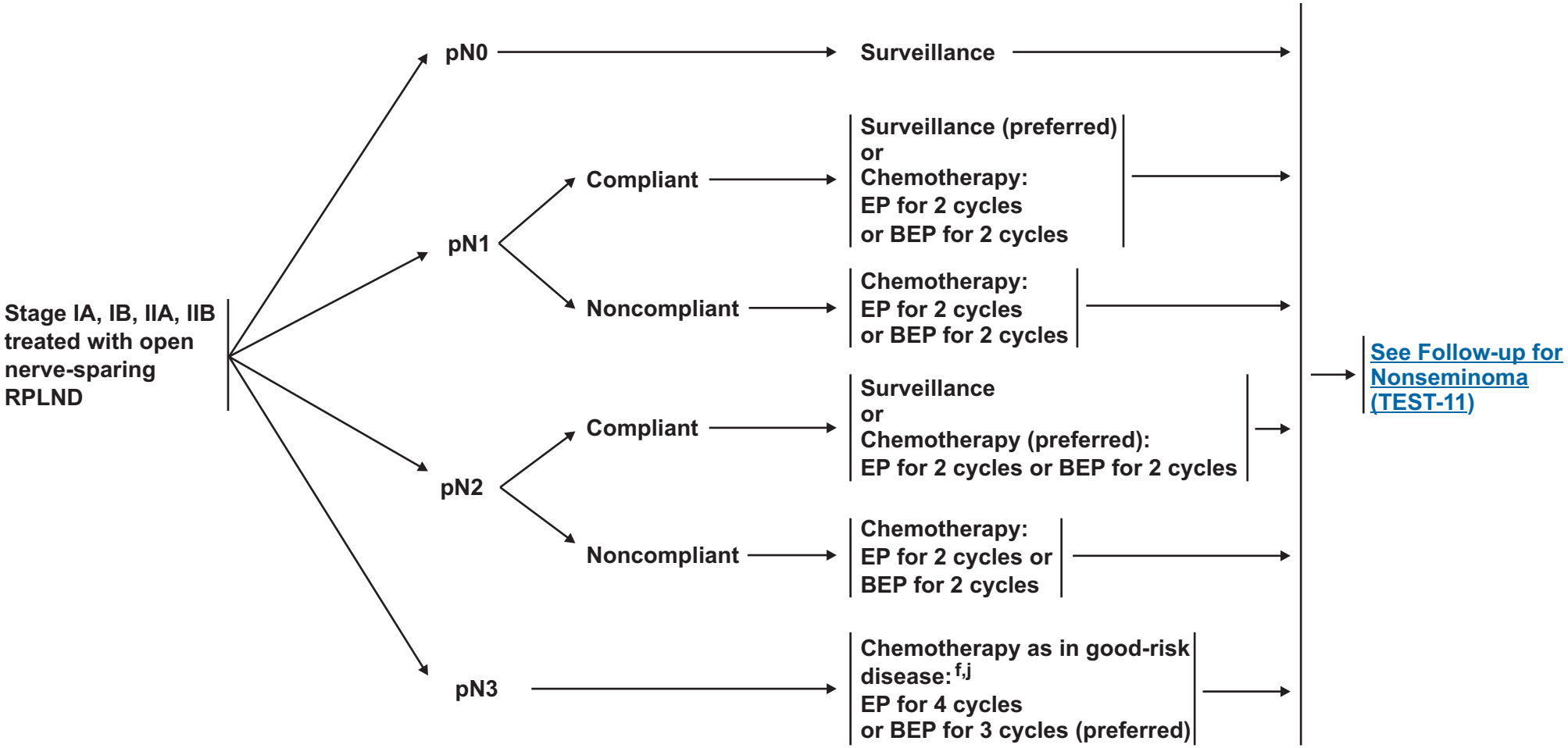
POSTSURGICAL MANAGEMENT



EP = Etoposide/cisplatin
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[f] See Risk Classification (TEST-A).
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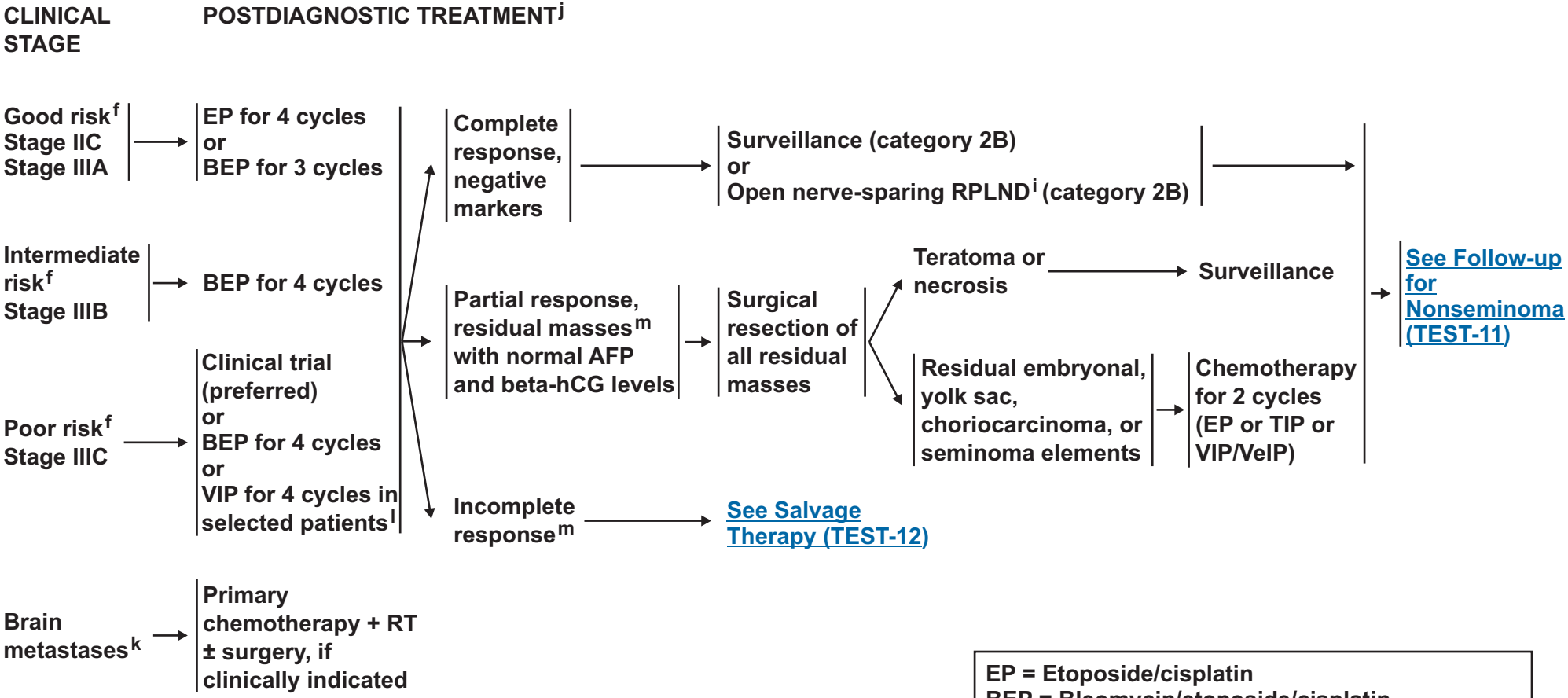

The EP and BEP chemotherapy regimens have shown survival advantage in randomized clinical trials and may be considered as category 1 compared with other chemotherapy regimens.

EP = Etoposide/cisplatin
BEP = Bleomycin/etoposide/cisplatin
TIP = Paclitaxel/ifosfamide/cisplatin
VeIP = Vinblastine/ifosfamide/cisplatin
VIP = Etoposide/ifosfamide/cisplatin
RPLND = Retroperitoneal lymph node dissection

[f] See Risk Classification (TEST-A).
[i] Surgery is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
[j] See Primary Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-B).
[k] Patients should receive adequate treatment for brain metastases, in addition to cisplatin-based chemotherapy.
[l] Patients who may not tolerate bleomycin.
[m] There is limited predictive value for PET scan for residual masses.

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FOLLOW-UP FOR NONSEMINOMA

Surveillance for Stage IA, IB Testicular Cancer

Year	Months between visits, markers, chest x-ray	Months between abdominal/pelvic CT
1	1-2	2-3
2	2	3-4
3	3	4
4	4	6
5	6	12
6+	12	12

Surveillance After Complete Response to Chemotherapy and/or RPLND

Year	Months between visits, markers, chest x-ray (category 2B for chest x-ray frequency)	Months between abdominal/pelvic CT[n]
1	2-3	6
2	2-3	6-12
3	4	12
4	4	12
5	6	12
6+	12	12-24

Recurrence, See Salvage Therapy (TEST-12)

[n]CT scans apply only to patients treated with chemotherapy. Patients status post RPLND, a postoperative baseline CT scan is recommended.

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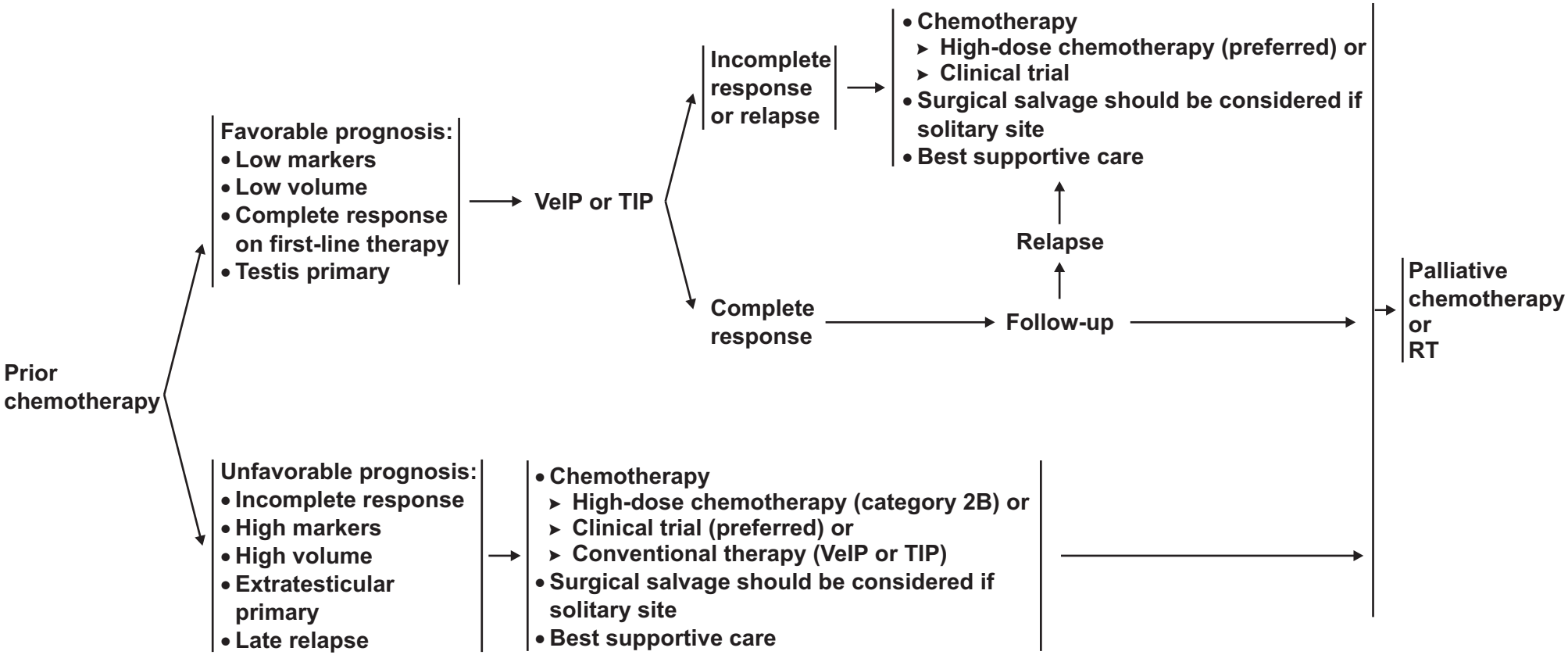
RECURRENCE

SALVAGE THERAPY[o]



No prior chemotherapy → Treat as per risk status on TEST-10

VeIP = Vinblastine/ifosfamide/cisplatin
TIP = Paclitaxel/ifosfamide/cisplatin

[o] See Salvage Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-C).

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RISK CLASSIFICATION[1]

Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Good markers- all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any HCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Intermediate markers- any of: AFP 1,000-10,000 ng/mL hCG 5,000-50,000 iu/L LDH 1.5-10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any HCG Any LDH
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Poor markers- any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

Source: Figure 4 from the International Germ Cell Cancer Collaborative Group: International Germ Cell Consensus Classification: A Prognostic Factor-Based Staging System for Metastatic Germ Cell Cancers. J Clin Oncol. 15(2);1997:594-603. Reprinted with permission of the American Society of Clinical Oncology.

[1] Markers used for risk classification are post-orchiectomy.

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PRIMARY CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

Tumor status	Regimen
Previously untreated, good risk	(EP) Etoposide, 100 mg/m^2 IV daily for 5 days, + cisplatin, 20 mg/m^2 IV daily for 5 days, for 4 cycles administered at 21-day intervals[1] or (BEP) Etoposide, 100 mg/m^2 IV daily for 5 days, cisplatin, 20 mg/m^2 IV daily for 5 days, + bleomycin, 30 units IV weekly on days 1, 8, 15* for 3 cycles administered at 21-day intervals[2]
Tumor status	**Regimen**
Previously untreated, intermediate, or poor risk	(BEP) Etoposide, 100 mg/m^2 IV daily for 5 days, cisplatin, 20 mg/m^2 IV daily for 5 days, + bleomycin, 30 units IV weekly on days 1, 8, 15* for 4 cycles administered at 21-day intervals[2] or (VIP) Etoposide 75 mg/m^2 daily for 5 days, ifosfamide 1200 mg/m^2 daily for 5 days, mesna 120 mg/m^2 slow IV push is given before ifosfamide on day 1, followed by 1200 mg/m^2 continuous infusion on days 1 through 5, cisplatin 20 mg/m^2 on days 1 through 5[3]

*Some NCCN Institutions administer bleomycin on a 2, 9, 16 schedule.

[1] Xiao H, Mazumdar M, Bajorin DF, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. J Clin Oncol 1997;15(7):2553-2558.

[2] Saxman SB, Finch D, Gonin R & Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: The Indiana University Experience. J Clin Oncol 1998;16(2):702-706.

[3] Nichols CR, Catalano PJ, Crawford ED et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 1998;16:1287-1293.

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SALVAGE CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

Tumor status	Regimen
Previously treated, salvage therapy	(VeIP) Vinblastine 0.11 mg/kg IV per day for 2 days, ifosfamide 1200 mg/m^2 IV daily for 5 days, mesna 400 mg/m^2 IV every 8 h x 5 days, and cisplatin 20 mg/m^2 IV daily for 5 days[1] or (TIP) Paclitaxel 250 mg/m^2 IV day 1, followed by ifosfamide 1500 mg/m^2 and cisplatin 25 mg/m^2 IV daily on days 2-5, mesna 500 mg/m^2 IV before, and then 4 and 8 h after each dose of ifosfamide[2]

Palliative, Second line salvage therapy	Regimen
	(GEMOX) Gemcitabine 1000 mg/m^2 IV on days 1 and 8, followed by oxaliplatin 130 mg/m^2 IV on day 1 administered every 3 weeks[3,4]
	(GEMOX) Gemcitabine 1250 mg/m^2 IV on days 1 and 8, followed by oxaliplatin 130 mg/m^2 IV on day 1 administered every 3 weeks[5]

[1] Loehrer PJ Sr, Lauer R, Roth BJ, et al. Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med 1988;109(7):540-546.
[2] Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;23(27):6549-6555.
[3] Pectasides D, Pectasides M, Farmakis D, et al. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumors: a phase II study. Ann Oncol 2004;15(3):493-497.
[4] Kollmannsberger C, Beyer J, Liersch R, et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: A study of the German Testicular Cancer Study Group. J Clin Oncol 2004; 22(1):108-114.
[5] De Giorgi U, Rosti G, Aieta M, et al. Phase II study of oxaliplatin and gemcitabine salvage chemotherapy in patients with cisplatin-refractory nonseminomatous germ cell tumor. Eur Urol 2006;50(5):893-894.

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Staging

Table 1

AJCC Staging of Testis Tumors

Primary Tumor (pT)

The extent of primary tumor is usually classified after radical orchiectomy, and for this reason, a *pathologic* stage is assigned.

*pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g. histologic scar in testis)
pTis	Intratubular germ-cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion

**Note*: Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Pathologic (pN)

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass, 2 cm or less in greatest dimension and less than or equal to 5 nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional nodal or pulmonary metastasis
M1b	Distant metastasis other than to non-regional lymph nodes and lungs

Continued...

Serum Tumor Markers (S)

SX	Marker studies not available or not performed
SO	Marker study levels within normal limits
S1	LDH < 1.5 x N AND
	hCG (mIu/mL) < 5000 AND
	AFP (ng/ml) < 1000
S2	LDH 1.5-10 x N OR
	hCG (mIu/mL) 5000-50,000 OR
	AFP (ng/ml) 1000-10,000
S3	LDH > 10 x N OR
	hCG (mIu/mL) > 50,000 OR
	AFP (ng/ml) > 10,000

*N indicates the upper limit of normal for the LDH assay.

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Stage Grouping

Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	PT3	N0	M0	S0
	PT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/Tx	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

An estimated 8,090 new cases of testicular cancer will be diagnosed in the United States in 2008.[1] Germ cell tumors (GCTs) comprise 95% of malignant tumors arising in the testes. These tumors also occur occasionally in extragonadal primary sites, but they are still managed the same as testicular GCTs. Although GCTs are relatively uncommon tumors that comprise only 2% of all human malignancies, they constitute the most common solid tumor in men between the ages of 15 and 34 years. In addition, the worldwide incidence of these tumors has more than doubled in the past 40 years.

Several risk factors for GCT development have been identified, including prior history of a GCT, positive family history, cryptorchidism, testicular dysgenesis, and Klinefelter's syndrome. GCTs are classified as seminoma or nonseminoma. Nonseminomatous tumors often include multiple cell types, including embryonal cell carcinoma, choriocarcinoma, yolk sac tumor, and teratoma. Teratomas are considered to be either mature or immature depending on whether adult-type differential cell types or partial somatic differentiation, similar to that present in the fetus, is found. Rarely, a teratoma histologically resembles a somatic cancer, such as sarcoma or adenocarcinoma, and is then referred to as a teratoma with malignant transformation.

The serum tumor markers alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), and human chorionic gonadotropin (hCG) are critical in diagnosing the presence of tumors, determining prognosis, and assessing treatment outcome. These should be determined before, during, and after treatment and throughout the follow-up period. AFP is a serum tumor marker produced by nonseminomatous cells (embryonal carcinoma, yolk-sac tumor) and may be seen at any stage. The approximate half-life of AFP is 5 to 7 days. A nonseminoma, therefore, is associated with elevated serum concentrations of AFP. An elevated serum concentration of hCG, which has a half-life of approximately 1–3 days, may also be present with seminomatous and nonseminomatous tumors. Seminomas are occasionally associated with an elevated serum concentration of hCG but not an elevated concentration of AFP.

Nonseminoma is the more clinically aggressive tumor. When both a seminoma and elements of a nonseminoma are present, management follows that for a nonseminoma. Therefore, the diagnosis of a seminoma is restricted to pure seminoma histology and a normal serum concentration of AFP.

More than 90% of patients diagnosed with GCTs are cured, including 70% to 80% of patients with advanced tumors who are treated with chemotherapy. A delay in diagnosis correlates with a higher stage at presentation. Standard therapy has been established at essentially all stages of management and must be closely followed to ensure the potential for cure.

Clinical Presentation

A painless solid testicular mass is pathognomonic for testicular tumor. More often, patients present with testicular discomfort or swelling suggestive of epididymitis or orchitis. A trial of antibiotics may be given in this circumstance, but persistent tenderness, swelling, or any palpable abnormality warrants further evaluation using testicular ultrasound. Although testicular ultrasound is optional if the diagnosis is obvious from the physical examination, it is performed in most instances to define the lesion (TEST-1).

If an intratesticular mass is identified, further evaluation includes measurement of the serum concentrations of alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), and beta-human chorionic gonadotropin (beta-hCG) and a chest radiograph. Elevated values of beta-hCG, LDH, or AFP should be followed up with repeated tests to allow precise staging. Inguinal orchiectomy is considered the primary treatment for most patients who present with a suspicious testicular mass.[2] If a GCT is found, an abdominopelvic computed tomographic (CT) scan is performed. Serum concentrations of hCG and LDH may be elevated in patients with seminoma. An elevated AFP level indicates nonseminoma, and the patient should be managed accordingly. A chest CT may be indicated if the abdominopelvic CT shows retroperitoneal adenopathy or the chest radiograph shows abnormal results. An open inguinal biopsy of the contralateral testis is not routinely performed, but can be considered when a cryptorchid testis or marked atrophy is present.[3] Biopsy may also be considered if a suspicious intratesticular abnormality, such as a hypoechoic mass or macrocalcifications, is identified on ultrasound. In contrast, if microcalcifications without any other abnormality can be observed, testicular biopsy is not necessary. These studies, and others as clinically indicated, determine the clinical stage and direct patient management. If clinical signs of metastases are present, magnetic resonance imaging (MRI) of the brain and bone scanning are indicated (TEST-2 and TEST-5).

Further management is dictated by histology, a diagnosis of seminoma or nonseminoma, and stage (ST-1). Patients should consider sperm banking before undergoing any therapeutic intervention that may compromise fertility, including radiation therapy, surgery, and chemotherapy.

Seminoma

The risk classification for seminoma is defined in TEST-A.

Stages IA and IB

Patients with disease in stages IA and IB are treated with radiation (20–30 Gy) to the infradiaphragmatic area, including para-aortic lymph nodes with or without radiation to the ipsilateral ileoinguinal nodes.[4] Prophylaxis to the mediastinum is not provided, because relapse rarely occurs at this site. A single dose of carboplatin has also been investigated as an alternative to radiation therapy. Oliver et al[5] reported on the results of a trial that randomized 1477 patients with stage 1 testicular cancer to undergo either radiotherapy or one injection of carboplatin. In the study, carboplatin was administered at a dose of AUC X 7 (AUC=area under the dose-time concentration curve). The doses were given intravenously and calculated by a formula based on the AUC estimate of drug disappearance from the body. The dose was calculated by the formula 7 X (glomerular filtration rate [GFR, mL/min] + 25) mg. With a median follow-up of 4 years, the relapse-free survivals for both groups were similar. Because late relapses and secondary germ cell tumors can occur beyond 5 and 10 years, the authors continued follow-up of these patients. The updated follow-up results of 1,148 patients were reported at the 2008 ASCO Annual Meeting.[6] In an intent-to-treat analysis, the relapse free rates at 5 years were 94.7% for the carboplatin arm and 96% for the radiotherapy arm (hazard ratio, 1.25; P = .37), There was a significant difference in the rate of new germ cell tumors (2 on carboplatin versus 15 on radiation therapy), giving a hazard ratio (HR) of 0.22 (95% CI 0.05, 0.95 p=0.03). The

authors conclude that a single dose of carboplatin is less toxic and just as effective in preventing disease recurrence as adjuvant radiotherapy in men with stage I seminoma after orchiectomy, The NCCN panel now recommends single dose of carboplatin (category 1) as an alternative to radiation therapy for patients with stages IA and IB disease. Between 15% and 20% of patients with seminoma, experience relapse during surveillance if they do not undergo adjuvant radiation therapy after orchiectomy.[7] The median time to relapse is approximately 12 months, but relapses can occur more than 5 years after orchiectomy.

Because both radiation and chemotherapy can potentially lead to late morbidity, surveillance for stage I seminoma is an option for management of stage I seminoma (category 1). In particular, observation may be offered to selected patients with T1 or T2 disease (category 2B) who are committed to long-term follow-up (TEST-3). Relapse occurring after observation essentially represents a prolongation in the lead time of treatment. Therefore, these patients are treated according to the stage at relapse. Patients for whom radiation therapy is generally not given include those with patients at higher risk for morbidity from radiation therapy. These patients include those with stages IA and IB with a horseshoe or pelvic kidney, with inflammatory bowel disease, and who underwent prior radiation therapy.

Follow up includes a history and physical, with measurement of serum tumor markers, performed every 3 to 4 months for the first year, and 6 months for the second year and annually thereafter. More intense follow-up is recommended for patients not undergoing radiation therapy - a history and physical, with measurement of serum tumor markers, should be performed every 3 to 4 months for the first 3 years, and 6 months for the next 3 years and annually thereafter. Annual pelvic CT is recommended for 3 years for patients who underwent para-aortic RT, whereas an abdominal/pelvic CT scan is recommended at each visit and chest x-ray at alternate visit for up to 10 years for those treated with a single dose of carboplatin or those under surveillance.

Stage 1S

Patients with stage IS are treated with radiation (25-30 Gy) to the infradiaphragmatic area, including para-aortic lymph nodes with or without radiation to the ipsilateral ileo inguinal nodes.[4] Follow-up recommendations are similar to that of patients with stages 1A and 1B. If advanced, disseminated disease is suspected, than full course chemotherapy is administered according to guidelines for good risk GCT.

Stages IIA and IIB

Stage IIA is defined as disease measuring less than 2 cm in diameter on CT scan, and stage IIB as disease measuring 2 to 5 cm in maximum diameter. For patients with stage IIA or IIB disease, 35 to 40 Gy is administered to the infradiaphragmatic area, including para-aortic and ipsilateral iliac lymph nodes. As in the management of stage I disease, prophylactic mediastinal radiation therapy is not indicated.[8] Surveillance is not an option for patients with stage IIA or IIB disease with relative contraindications for radiation. Instead, 4 courses of etoposide and cisplatin (EP) are recommended.

Follow-up for patients with stage IIA or IIB disease includes a history and physical, with measurement of serum tumor markers, should be performed every 3 to 4 months for the first 3 years, and 6 months for the fourth year and annually thereafter. Abdominal CT is recommended after 4 months during the first year (TEST-3).

Stages IIC and III

Patients with stage IIC or III disease are those considered at good or intermediate risk (TEST-3). All stage IIC and stage III disease is considered good risk except for stage III disease with non-pulmonary

visceral metastases, which is considered intermediate risk (TEST-A). Standard chemotherapy is used for both groups of patients, but for patients with good risk, either 4 cycles of EP are recommended or 3 cycles of bleomycin, etoposide, and cisplatin (BEP). In contrast, 4 cycles of BEP are recommended for those with intermediate risk disease. These options are all considered category 1 recommendations.[9-12]

After initial chemotherapy, patients with stage IIC and III are evaluated with serum tumor markers and a CT scan of the chest abdomen and pelvis (TEST-4). Patients are then classified according to the presence or absence of a residual mass and the status of serum tumor markers. Patients with no residual mass and normal markers need no further treatment and undergo surveillance. In patients with a residual mass with normal markers, a positron emission tomography (PET) scan is recommended to assess for residual viable tumor.[13] To reduce the incidence of false-positive results, the PET scan is typically performed no less then 6 weeks after completion of chemotherapy. Notably, granulomatous disease, such as sarcoid, is a frequent source of false-positive results. If the PET scan is negative, no further treatment is needed however, the patient should be observed closely for recurrence. If it is positive, then biopsy should be considered followed by surgical excision (category 2B), or salvage therapy. Alternatively, the patient can be treated with radiation therapy (category 2B).

For patients who cannot undergo a PET scan, post-chemotherapy management is based on CT scan findings. Controversy exists regarding optimal management when the residual mass is greater than 3 cm, because approximately 25% of these patients have a viable seminoma or previously unrecognized nonseminoma.[14] Options include surgery (category 2B), radiation therapy (category 2B), and observation.[8] If surgery is selected, the procedure consists of resection of the residual mass or multiple biopsies. A full bilateral or modified retroperitoneal lymph node dissection (RPLND) is not performed because of its technical difficulty in patients with seminoma and because of extensive fibrosis, which may be associated with severe morbidity.[15] If the residual mass is 3 cm or less, patients should undergo observation, which is detailed in TEST-4.

Recurrent disease is initially treated according to the stage at recurrence. Salvage therapy is recommended for patients with rising markers or a growing mass detected on CT scan (TEST-12). Salvage therapy for seminoma and nonseminoma is similar and is discussed further in section on nonseminomas.

Patients with seminoma arising from an extragonadal site, such as the mediastinum, are treated with standard chemotherapy regimens according to risk status.

Approximately 90% of patients with advanced seminoma are cured with cisplatin-containing chemotherapy.[16]

Nonseminoma

The risk classification for nonseminoma is defined in TEST-A. Stage-dependent treatment options after inguinal orchiectomy include observation, chemotherapy, and RPLND. Although the timing of the RPLND may vary, most patients with nonseminoma will undergo an RPLND for either diagnostic or therapeutic purposes at some point during treatment. The major morbidity associated with bilateral dissection is retrograde ejaculation, resulting in infertility. Nerve-dissection techniques preserve antegrade ejaculation in 90% of cases.[17] Template dissections, which avoid the contralateral sympathetic chain, postganglionic sympathetic fibers, and hypogastric plexus, preserve ejaculation in approximately 80% of patients. In general, an open nerve-sparing RPLND rather than a laparoscopic RPLND is recommended for therapeutic purposes. For example, a concern exists that a laparoscopic RPLND may result in false-negative

results caused by inadequate sampling, and no published reports focus on the therapeutic efficacy of a laparoscopic dissection. Because the recommended number of cycles of chemotherapy is based on the number of positive nodes identified, inadequate sampling may lead to partial treatment.[18]

Stage IA

Two management options exist for patients with stage IA disease after orchiectomy: (1) surveillance (in compliant patients) or (2) open nerve-sparing RPLND (TEST-6).

The cure rate with either approach exceeds 95%. However, the high cure rate associated with surveillance depends on adherence to periodic follow-up examinations and subsequent chemotherapy for the 20% to 30% of patients who experience relapse. The follow-up examinations in those electing surveillance include an abdominopelvic CT scan every 2 to 3 months for the first year and every 3 to 4 months during the second year. Serum marker determination and the chest radiograph should be performed every 1 to 2 months during the first year and every 2 months during the second year (TEST-11). Noncompliant patients are treated with open RPLND.

The open nerve sparing RPLND is typically performed within 4 weeks of a CT scan and within 7 to 10 days of repeat serum marker testing to ensure accurate presurgical staging. If the dissected lymph nodes are not involved with a tumor (pN0), no adjuvant chemotherapy is given after open nerve sparing RPLND. However, if the resected lymph nodes involve tumor, the decision whether to use adjuvant chemotherapy is based on the degree of nodal involvement and the ability of the patient to comply with surveillance (TEST-9). Chemotherapy is preferred over surveillance in patients with pN2 or pN3 disease. Recommended regimens include either EP or BEP; 2 cycles of either regimen are recommended for patients with pN1 or pN2 disease, with 4 cycles of EP and 3 cycles of BEP (preferred) for patients with pN3 disease.

Stage IB

Open nerve sparing RPLND is a treatment option in patients with stage IB disease and the subsequent adjuvant therapy options are similar to those for stage IA. Chemotherapy with 2 cycles of BEP (category 2B) followed by open nerve sparing RPLND or surveillance is another option (TEST-8). Finally, surveillance alone may be offered to compliant patients with T2 disease (category 2B) (TEST-6). Vascular invasion is a significant predictor of relapse when orchiectomy is followed by surveillance alone.[2] Surveillance is generally not recommended for T2 disease with vascular invasion because of the 50% chance of relapse. Exceptions are made according to individual circumstances in compliant patients. When surveillance is opted in selected patients with T2 disease, both the patient and the physician must be compliant with follow-up recommendations.

Stage IS

Patients with stage IS disease exhibit a persistent elevation of markers but no radiographic evidence of disease. These patients are treated with standard chemotherapy with either 4 cycles of EP or 3 cycles of BEP (TEST-6). Either regimen is preferable to initial open nerve sparing RPLND because these patients nearly always have disseminated disease.[19,20]

Stages IIA and IIB

Treatment for patients with stage IIA nonseminoma depends on serum tumor marker levels. When the levels of tumor markers are persistently elevated, patients are treated with chemotherapy with 4 cycles of EP or 3 cycles of BEP, followed by open nerve sparing RPLND or surveillance (TEST-7).

When the tumor marker levels are negative, 2 treatment options are available. Patients can undergo primary chemotherapy with 4 cycles of EP or 3 cycles of BEP (category 2B), followed by open nerve sparing RPLND or surveillance (TEST-7).[21] This treatment is considered particularly appropriate if the patient has multifocal disease. Alternatively, the patient can undergo open nerve sparing RPLND followed by adjuvant chemotherapy or surveillance, depending on the number of positive lymph nodes identified and patient compliance (TEST-9). For example, surveillance is preferred in compliant patients with pN1 disease, whereas chemotherapy is preferred for pN2 disease and surveillance is not recommended for pN3 disease. Recommended chemotherapy consists of 2 cycles of BEP or EP, resulting in a nearly 100% relapse-free survival rate.[22]

Treatment for patients with stage IIB disease depends on both tumor marker levels and radiographic findings (TEST-7). When tumor markers are negative, the CT findings determine the proper course of treatment. If abnormal radiographic findings are limited to sites within the lymphatic drainage (i.e., the landing zone), 2 management options are available. One option is to perform open nerve sparing RPLND and to consider adjuvant chemotherapy as described for patients with stage II A disease (TEST-9). The second option is to treat with primary chemotherapy with either 4 cycles of EP or 3 cycles of BEP, followed by open nerve sparing RPLND or surveillance (TEST-8). If metastatic disease (based on radiographic findings) is not confined to the lymphatic drainage (i.e., multifocal lymph node metastases outside the lymphatic drainage sites), similar primary chemotherapy is recommended and initial open RPLND is not.

Stages IIC and III

Patients with stage IIC and stage III disease are treated with primary chemotherapy regimens based on risk status (TEST-A). Also, patients with an extragonadal primary site, whether retroperitoneal or mediastinal, are treated with initial chemotherapy. Classifications of risk status emerged from chemotherapy research designed to decrease the toxicity of the regimens while maintaining maximal efficacy.

Initial chemotherapy combinations studied in the 1970s contained cisplatin, vinblastine, and bleomycin and achieved a complete response in 70% to 80% of patients with metastatic GCTs. These regimens were associated with serious adverse effects, including neuromuscular toxic effects, death from myelosuppression or bleomycin-induced pulmonary fibrosis, and Raynaud's phenomenon.

The high cure rate and toxicity associated with cisplatin, vinblastine, and bleomycin regimens resulted in efforts to stratify patients and tailor therapy according to risk. Extent of disease and serum tumor markers were identified as important prognostic features, and models were developed to stratify patients into good- and poor-risk categories.

The International Germ Cell Cancer Consensus Classification was developed and incorporated the risk groups into the American Joint Committee on Cancer staging for GCTs (ST-1). This classification categorized patients as good-, intermediate-, or poor-risk.[23]

Good-Risk (Stages IIC and IIIA) Nonseminoma

Treatment programs for good-risk GCTs were designed to decrease toxicity while maintaining maximal efficacy. Randomized clinical trials showed that this was achieved by substituting etoposide for vinblastine,[24,25] and either eliminating or reducing the dose of bleomycin.[25,26] Presently, 2 regimens are considered standard treatment programs in the United States for good-risk GCTs: 4 cycles of EP or 3 cycles of BEP (TEST-B). Either regimen is well tolerated and cures approximately 90% of patients with good risk.[27]

Intermediate- (Stage IIIB) and Poor-Risk (Stage IIIC) Nonseminoma

Between 20% and 30% of all patients with metastatic GCTs are not cured with conventional cisplatin therapy. Poor prognostic features at diagnosis that can be used to identify these patients include nonpulmonary visceral metastases and high serum tumor marker concentrations or mediastinal primary site in patients with nonseminoma.[28] In patients with these prognostic factors, clinical trials are directed at improving efficacy.

For patients with intermediate risk, the cure rate is approximately 70% for standard therapy with 4 cycles of BEP. In patients with poor-risk GCTs (stage IIIC), less than one half experience a durable complete response to 4 cycles of BEP, and therefore treatment in a clinical trial is preferred.[28] The panel recommends 4 cycles of etoposide, iphosphamide, and cisplatin (VIP regimen) for patients who may not tolerate bleomycin.[29]

Primary chemotherapy plus radiotherapy is indicated for patients in whom brain metastases are detected. If clinically indicated, surgery should also be performed.

Postchemotherapy Management for Stages IIC and IIIA–IIIC Nonseminoma

At the conclusion of induction chemotherapy, CT scans of the abdomen and pelvis are indicated, along with serum tumor marker assays. PET scans for residual disease have limited predictive value. If a complete response is found and the tumor markers are negative, 2 management options exist: surveillance (category 2B) or an open nerve sparing RPLND (category 2B).

If residual disease is found and the serum tumor markers have normalized, then all sites of residual disease are resected. If only necrotic debris or mature teratoma is encountered, no further therapy is necessary and standard observation is initiated. In the 15% of patients who have viable residual cancer, 2 cycles of chemotherapy (EP, VelP [paclitaxel/ifosfamide/cisplatin], or TIP [vinblastine/ifosfamide/cisplatin]) are administered.

After patients are rendered disease-free, standard observation is initiated (TEST-11). Patients who experience an incomplete response to first-line therapy or unresectable disease at surgery are treated with salvage therapy (TEST-12).

Salvage Therapy

Patients who do not experience a complete response to first-line therapy are divided into those with a favorable or unfavorable prognosis (TEST-12). Favorable prognostic factors include a testicular primary site, prior complete response to first-line therapy, low levels of serum markers, and low-volume disease.[30] Standard therapy for patients with these features is 4 cycles of cisplatin and ifosfamide combined with vinblastine or paclitaxel (TEST-C). Approximately 50% of patients treated with the vinblastine regimen experience a complete response, and 25% experience durable complete remission.[31,32] If the patient experiences an incomplete response or relapses after salvage chemotherapy, high-dose chemotherapy with autologous stem cell support is the preferred option. Surgical salvage should be considered if a single site of metastasis is present and resectable. Other options are participation in a clinical trial or best supportive.

Patients with unfavorable prognostic features for conventional-dose salvage therapy (e.g., an incomplete response to first-line therapy) and patients requiring third-line salvage therapy are considered for treatment with high-dose chemotherapy plus autologous stem cell support (category 2B), participation in a clinical trial (preferred), or best supportive care. Third-line therapy with 2 cycles of high-dose carboplatin plus etoposide, with or without cyclophosphamide (or

ifosfamide), results in a durable complete response in 15% to 20% of patients.[33]

For patients being considered for treatment with a high-dose program, prognostic factors are used in deciding treatment. Patients with a testicular primary site and rising markers during first-line therapy are considered for high-dose programs as second-line therapy. Predictors of poor outcome to high-dose carboplatin-containing chemotherapy include a high serum hCG concentration, mediastinal primary site, and insensitivity to cisplatin (absolute refractory disease).[34] Patients with these features are generally spared the morbidity of this therapy and are considered for investigational therapy or surgical resection—particularly patients with a mediastinal primary or single site of metastasis.

For patients who do not experience complete response to high-dose therapy, the disease is nearly always incurable; the only exception is the rare patient with elevated serum tumor markers and a solitary site of metastasis (usually retroperitoneal) that undergoes surgical resection.[35] All other patients should be considered for palliative outpatient chemotherapy or radiation therapy. A recommended palliative second line salvage therapy for patients with intensively pretreated, cisplatin-resistant, or refractory germ cell tumor is combination of gemcitabine with oxaliplatin (category 2A recommendation). This recommendation is based on data from phase II studies.[36-38] These studies investigated the efficacy and the toxicity of gemcitabine and oxaliplatin (GEMOX) in patients with relapsed or cisplatin-refractory GCTs. Toxicity was found to be primarily hematological and generally manageable. The results showed that oxaliplatin-gemcitabine combination is a safe for patients with cisplatin-refractory testicular GCTs and may offer a chance of long-term survival.[36-38]

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