National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Testicular Cancer

Version 1.2011

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011 Panel Members
Testicular Cancer

NCCN Guidelines Index
Testicular Cancer TOC
Discussion

* **Robert J. Motzer, MD/Chair † Þ**
Memorial Sloan-Kettering Cancer Center

Neeraj Agarwal, MD ‡
Huntsman Cancer Institute at the University of Utah

Clair Beard, MD §
Dana-Farber/Brigham and Women's Cancer Center

Sam Bhayani, MD ω
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Graeme B. Bolger, MD †
University of Alabama at Birmingham Comprehensive Cancer Center

Michael A. Carducci, MD † Þ
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Sam S. Chang, MD ω
Vanderbilt-Ingram Cancer Center

Toni K. Choueiri, MD † Þ
Dana-Farber/Brigham and Women's Cancer Center

Steven L. Hancock, MD § Þ
Stanford Comprehensive Cancer Center

Gary R. Hudes, MD † ‡
Fox Chase Cancer Center

Eric Jonasch, MD †
The University of Texas M. D. Anderson Cancer Center

David Josephson, MD ω
City of Hope Comprehensive Cancer Center

Ellis G. Levine, MD †
Roswell Park Cancer Institute

Daniel W. Lin, MD ω
University of Washington Medical Center/Seattle Cancer Care Alliance

Kim A. Margolin, MD † ‡
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

M. Dror Michaelson, MD, PhD †
Massachusetts General Hospital Cancer Center

Thomas Olencki, DO †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Roberto Pili, MD †
Roswell Park Cancer Institute

Thomas W. Ratliff, MD †
St. Jude Children's Research Hospital/University of Tennessee Cancer Institute

Bruce G. Redman, DO †
University of Michigan Comprehensive Cancer Center

Cary N. Robertson, MD ω
Duke Comprehensive Cancer Center

Charles J. Ryan, MD † ω
UCSF Helen Diller Family Comprehensive Cancer Center

Joel Sheinfeld, MD ω
Memorial Sloan-Kettering Cancer Center

Philippe E. Spiess, MD ω
H. Lee Moffitt Cancer Center & Research Institute

Jue Wang, MD †
UNMC Eppley Cancer Center at The Nebraska Medical Center

Richard B. Wilder, MD §
H. Lee Moffitt Cancer Center & Research Institute

† Medical oncology
‡ Hematology/hematology oncology
§ Radiotherapy/Radiation oncology
ϕ Diagnostic Radiology
£ Supportive Care including Palliative, Pain Management, Pastoral care and Oncology social work
Þ Internal medicine
ω Urology
* Writing committee member

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011 Table of Contents Testicular Cancer

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

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011 Updates Testicular Cancer

NCCN Guidelines Index
Testicular Cancer TOC
Discussion

Updates in Version 1.2011 of the NCCN Testicular Cancer Guidelines from Version 2.2010 include:

Testicular cancer

TEST-1

- Workup, "optional" was removed from testicular ultrasound.
- Pathologic diagnosis,
  - "Pure" was added to seminoma germ cell tumor.
  - "Includes mixed seminoma tumors and seminoma histology with elevated AFP" was added to nonseminoma.
- Footnote b, "Though rare, when a patient presents with rapidly increasing beta-hCG, symptoms related to disseminated disease and a testicular mass, chemotherapy can be initiated immediately without a biopsy diagnosis" was added to the page.

Seminoma

TEST-2

- Postdiagnostic workup, "if elevated preoperatively" was removed from "repeat beta-hCG, LDH, AFP".
- Footnote 'c' was modified, "Mediastinal *primary site* seminoma should be treated by *risk status used for gonadal seminomas* with...".
- Footnote 'e' was modified, "Elevated values should be followed *after orchiectomy* with repeated determination to allow precise staging." (Also for TEST-5)

TEST-3

- Stage IA, IB
  - Surveillance:
    - "for pT1 or pT2 tumors" and "preferred" were added.
    - "horseshoe or pelvic kidney, inflammatory bowel disease, and prior RT" were removed.
  - RT:
    - dose range was changed from 20-30 Gy to 20-25 Gy.
    - "preferred for pT3 tumors or tumors > 4 cm" was added.
    - "± ipsilateral iliac nodes" was removed.
  - Footnote h, "In special circumstances, RT to ipsilateral iliac nodes may be administered (category 3)" is new to the page.
  - Follow-up after surveillance or single dose carboplatin with abdominal/pelvic CT was changed from "at each visit" to "every 3-4 mo for years 1-3, every 6 mo for years 4-7, then annually at each visit up to 10 years" and chest x-ray was changed from "at alternate visits" to "as clinically indicated".
- Stage IS
  - RT dose range was changed from 25-30 Gy to 25 Gy.
  - Follow-up after RT, chest x-ray was changed to "as clinically indicated". Also for Stages IA, IB.
- Stage IIA, IIB
  - RT dose range was changed from 35-40 Gy to 30-35 Gy.
  - Chemotherapy, "BEP for 3 cycles" was added.

TEST-4

- Residual mass and normal markers
  - "> 3 cm" was added as a qualifier to residual mass.
  - PET scan not feasible was removed.
  - PET scan, "approximately 6 wks post chemotherapy" was added.
  - PET scan negative, "Consider RPLND, if technically feasible" replaced "surgery with biopsy".
- "or residual mass ≤ 3cm" was added to "no residual mass and normal markers".
- Follow-up, "abdominal/pelvic CT 4 mo post surgery then as clinically indicated" was changed to "Abdominal/pelvic CT, post RPLND: 3-6 mo, then as clinically indicated" and "after all other primary management as clinically indicated".

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011 Updates Testicular Cancer

NCCN Guidelines Index
Testicular Cancer TOC
Discussion

Updates in Version 1.2011 of the NCCN Testicular Cancer Guidelines from Version 2.2010 include:

Nonseminoma

TEST-5

- Post diagnostic workup, "Chest CT if abnormal abdominal CT or abnormal chest x-ray" was removed and "± chest imaging" was added to "abdominal/pelvic CT".
- Footnote j, "PET scan is not clinically indicated for nonseminoma" was added to the page.

TEST-6

- Stage IB, primary chemotherapy, "BEP for 1 cycle" was added with a category 2B designation.
- Stage IS with persistent elevated markers has been redirected to TEST-10.
- Statement in the box was modified, "The EP and BEP chemotherapy regimens *given at doses and schedules on TEST-B* may be considered as category 1 compared with other chemotherapy regimens". Also for TEST-7 and TEST-10.

TEST-7

- Stage IIA and IIB with persistent marker elevation have been redirected to TEST-10.

TEST-8

- For negative markers, "≥ 1 cm" was added to residual mass.
- Negative markers, normal CT scan, no mass, "or residual mass < 1 cm" was added.
- "Bilateral" was added to "nerve-sparing RPLND."

TEST-10

- Stage IS and Stage IIA,S1 and Stage IIB, S1 were added to the good risk category.
- Complete response, negative markers, "nerve-sparing RPLND" was changed to "bilateral RPLND ± nerve-sparing".

TEST-11

- Surveillance after Stage IA, IB testicular cancer:
  - "Months between abdominal/pelvic CT" was change to "Months between abdominal CT".
  - The intervals for each year were modified as follows:
    - Year 1 from 2-3 mo to 3-4 mo
    - Year 2 from 3-4 mo to 4-6 mo
    - Year 3 from 4 mo to 6-12 mo
    - Year 4 from 6 mo to 6-12 mo
    - Year 6+ from 12 mo to 12-24 mo
- Surveillance after complete response to chemotherapy and/or RPLND
  - The intervals for each year were modified as follows:
    - Year 3 from 4 mo to 3-6 mo
    - Year 4 from 4 mo to 6 mo
    - Year 5 from 6 mo to 6-12 mo

TEST-12

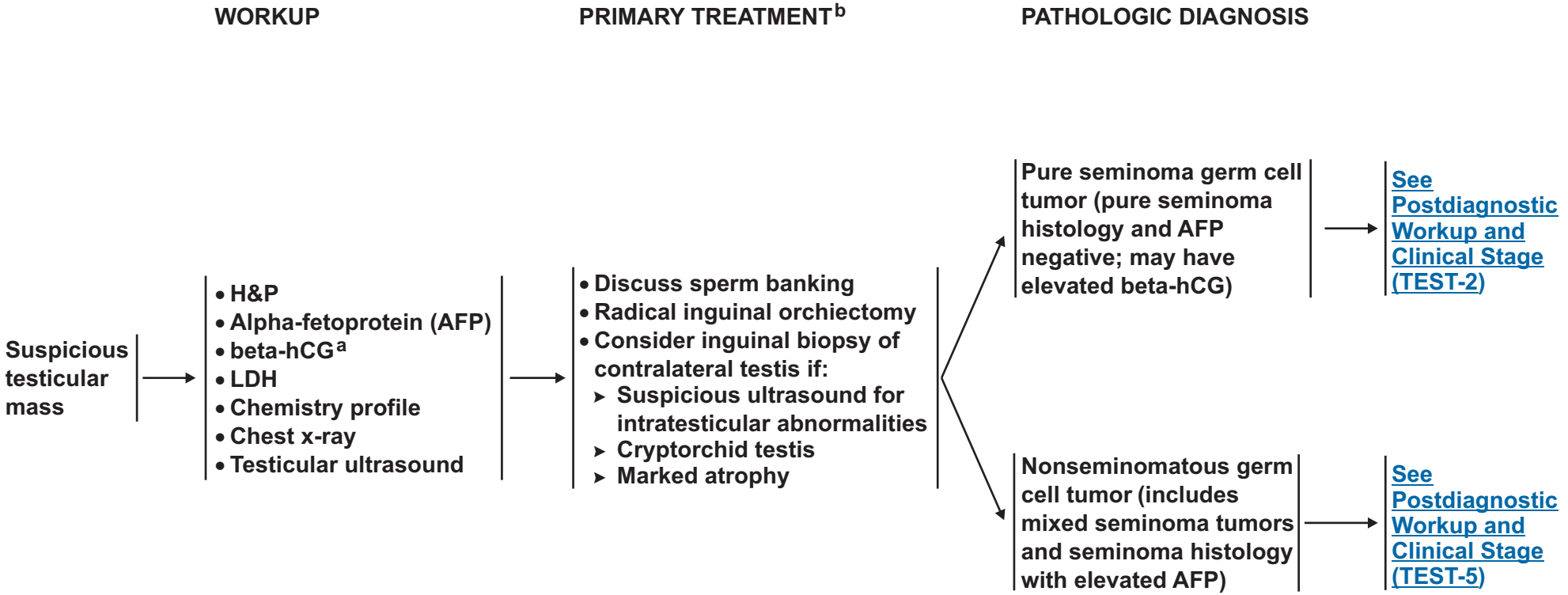
- Footnote p, "It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease" was added to the page.

TEST-A:

- "For advanced disease" was added to the title "risk classification".
- "Post-orchiectomy" was added under the title.

TEST-D

- Principles of Surgery is new to the guidelines.



[a] Quantitative analysis of beta subunit.

[b] Though rare, when a patient presents with rapidly increasing beta-hCG, symptoms related to disseminated disease and a testicular mass, chemotherapy can be initiated immediately without waiting for a biopsy diagnosis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PATHOLOGIC DIAGNOSIS | **POSTDIAGNOSTIC WORKUP** | **CLINICAL STAGE**

Pure seminoma germ cell tumor[c] (pure seminoma histology and AFP negative;[d] may have elevated beta-hCG)

- **Abdominal/pelvic CT**
- **Chest CT if:**
  - **Positive abdominal CT or 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 → **See Primary Treatment and Follow-up (TEST-3)**

Stage IS → **See Primary Treatment and Follow-up (TEST-3)**

Stage IIA, IIB → **See Primary Treatment and Follow-up (TEST-3)**

Stage IIC, III → **See Primary Treatment and Follow-up (TEST-3)**

[c] Mediastinal primary site seminoma should be treated by risk status used for gonadal seminomas with etoposide/cisplatin for 4 cycles or bleomycin/etoposide/cisplatin for 3 cycles.

[d] If AFP positive, treat as nonseminoma.

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
Testicular Cancer - Pure Seminoma

NCCN Guidelines Index
Testicular Cancer TOC
Discussion

CLINICAL STAGE	PRIMARY TREATMENT	FOLLOW-UP
Stage IA, IB	Surveillance for pT1 or pT2 tumors (category 1) (preferred) or Single agent carboplatin (category 1) (AUC=7 x 1 cycle or AUC=7 x 2 cycles) or RT: Infradiaphragmatic (20-25 Gy) to include para-aortic nodes[h] (category 1) (preferred for pT3 tumors or tumors > 4 cm)	• 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 every 3-4 mo for years 1-3, every 6 mo for years 4-7, then annually at each visit up to 10 years; chest x-ray as clinically indicated • H&P + 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) chest x-ray as clinically indicated
Stage IS	RT: Infradiaphragmatic (25 Gy) to include para-aortic ± ipsilateral iliac nodes	• 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
Stage IIA, IIB	RT: Infradiaphragmatic (30-35 Gy) to include para-aortic and ipsilateral iliac nodes or Consider primary chemotherapy for selected stage IIB patients:[g] EP for 4 cycles or BEP for 3 cycles	See Post Chemotherapy Management and Follow-up (TEST-4)
Stage IIC, III — Good risk[f]	Primary chemotherapy:[g] EP for 4 cycles (category 1) or BEP for 3 cycles (category 1)	See Post Chemotherapy Management and Follow-up (TEST-4)
Stage IIC, III — Intermediate risk[f]	Primary chemotherapy:[g] BEP for 4 cycles (category 1)	See Post Chemotherapy Management and Follow-up (TEST-4)

Recurrence, treat according to extent of disease at relapse

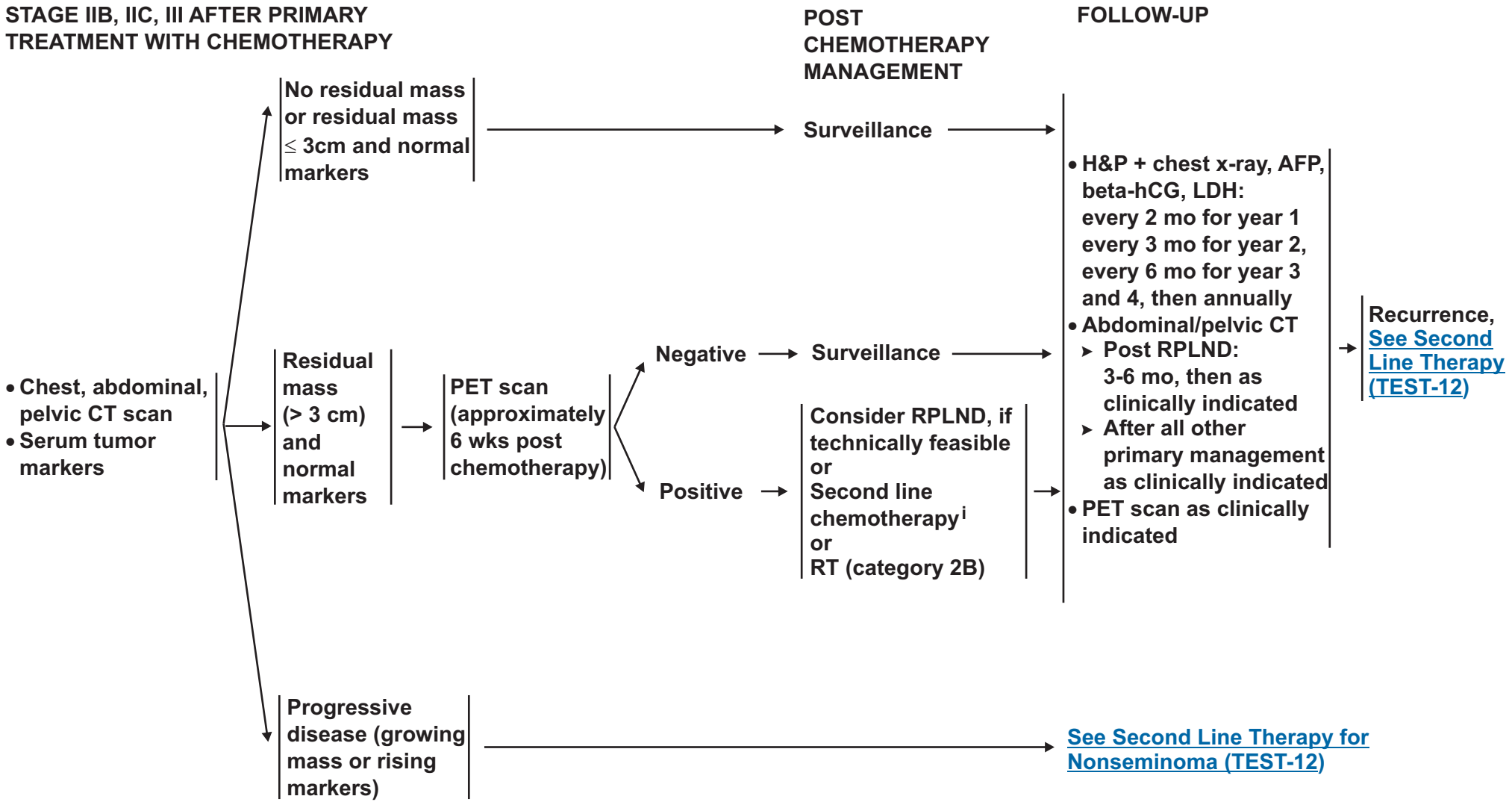
EP = Etoposide/cisplatin
BEP = Bleomycin/etoposide/cisplatin

[f] See Risk Classification (TEST-A).
[g] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-B).
[h] In special circumstances, RT to ipsilateral iliac nodes may be administered (category 3).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines™ Version 1.2011
Testicular Cancer - Pure Seminoma

NCCN Guidelines Index
Testicular Cancer TOC
Discussion



RPLND = retroperitoneal lymph node dissection

[i] See Second Line or Subsequent Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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

Nonseminomatous germ cell tumor (includes mixed seminoma tumors and seminoma histology with elevated AFP)

- **Abdominal/pelvic CT ± chest imaging**
- **Repeat beta-hCG, LDH, AFP[e]**
- **Brain MRI, if clinically indicated**
- **Bone scan, if clinically indicated**
- **Discuss sperm banking**

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

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

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

[e]Elevated values should be followed after orchiectomy with repeated determination to allow precise staging.
[j]PET scan is not clinically indicated for nonseminoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL STAGE	PRIMARY TREATMENT	
Stage IA	Surveillance (in compliant patients)	See Follow-up for Nonseminoma (TEST-11)
	or	
	Nerve-sparing RPLND[k,l]	See Postsurgical Management (TEST-9)
Stage IB	Nerve-sparing RPLND[k,l]	See Postsurgical Management (TEST-9)
	or	
	Primary chemotherapy:[g] BEP for 2 cycles or BEP for 1 cycle (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	See Primary Treatment (TEST-10)

The EP and BEP chemotherapy regimens given at doses and schedules on TEST-B may be considered as category 1 compared with other chemotherapy regimens.

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

[g] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-B).
[k] Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
[l] See Principles of Surgery (TEST-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL STAGE | **PRIMARY TREATMENT**

Stage IIA

- **Markers negative** →
  - **Nerve-sparing RPLND[k,l]** → See Postsurgical Management (TEST-9)
  - **or**
  - **Primary chemotherapy[g] (category 2B): EP for 4 cycles or BEP for 3 cycles** → See Postchemotherapy Management (TEST-8)
- **Persistent marker elevation** → See Primary Treatment (TEST-10)

Stage IIB

- **Markers negative**
  - **Lymph node metastases, within lymphatic drainage sites (landing zone positive)** →
    - **Nerve-sparing RPLND[j,k]** → See Postsurgical Management (TEST-9)
    - **or**
    - **Primary chemotherapy:[g] EP for 4 cycles or BEP for 3 cycles** → See Postchemotherapy Management (TEST-8)
  - **Multifocal, symptomatic, or lymph node metastases with aberrant lymphatic drainage** →
    - **Primary chemotherapy:[g] EP for 4 cycles or BEP for 3 cycles** → See Postchemotherapy Management (TEST-8)
- **Persistent marker elevation** → See Primary Treatment (TEST-10)

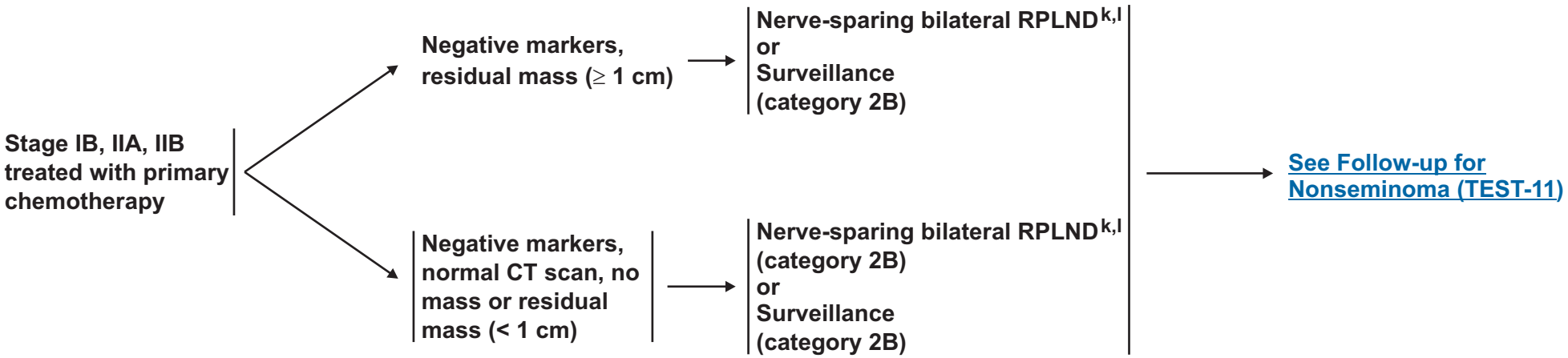
The EP and BEP chemotherapy regimens given at doses and schedules on TEST-B may be considered as category 1 compared with other chemotherapy regimens.

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

[g] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-B).
[k] Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
[l] See Principles of Surgery (TEST-D).

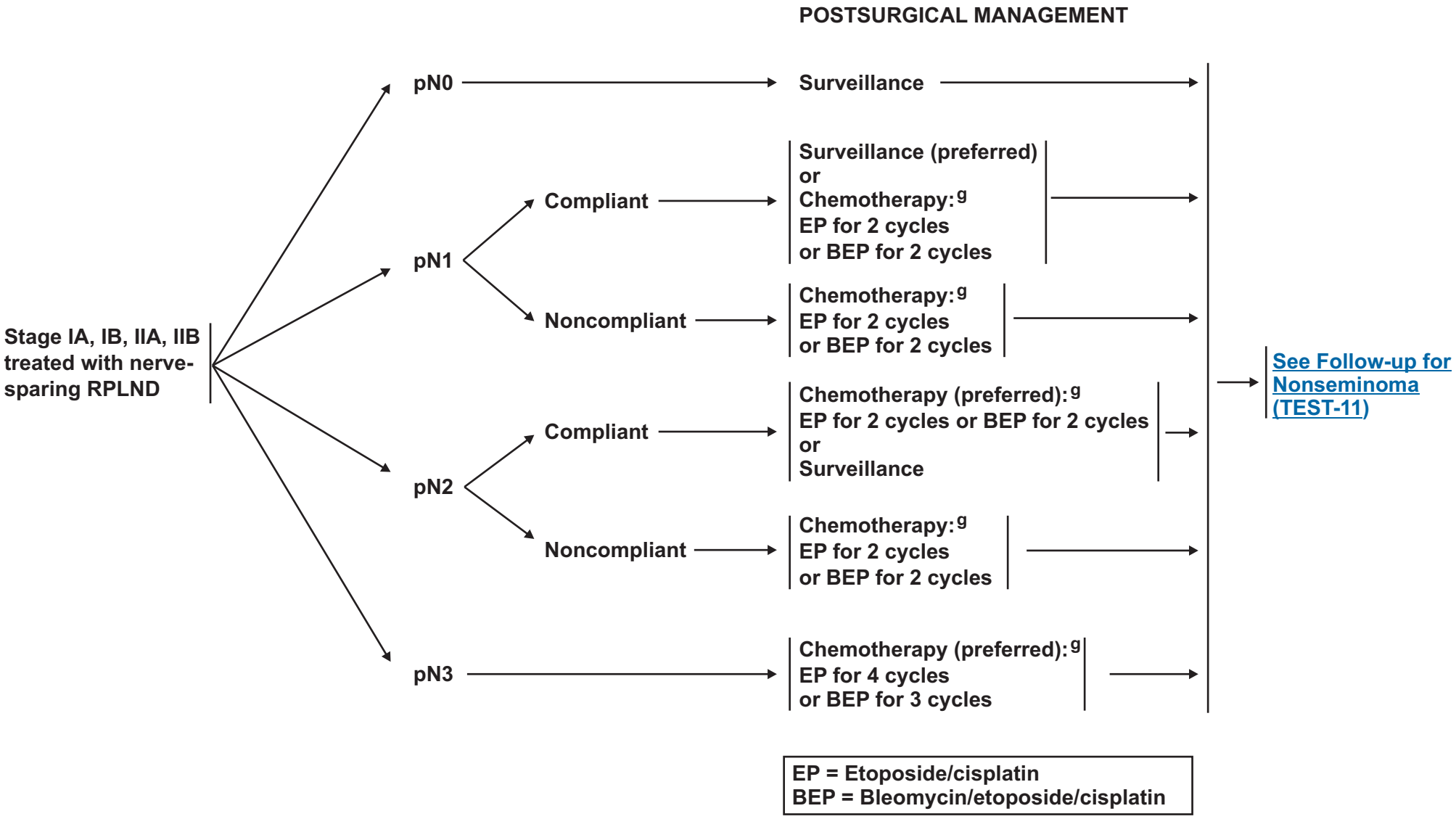
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

POSTCHEMOTHERAPY MANAGEMENT



[k] Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
[l] See Principles of Surgery (TEST-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

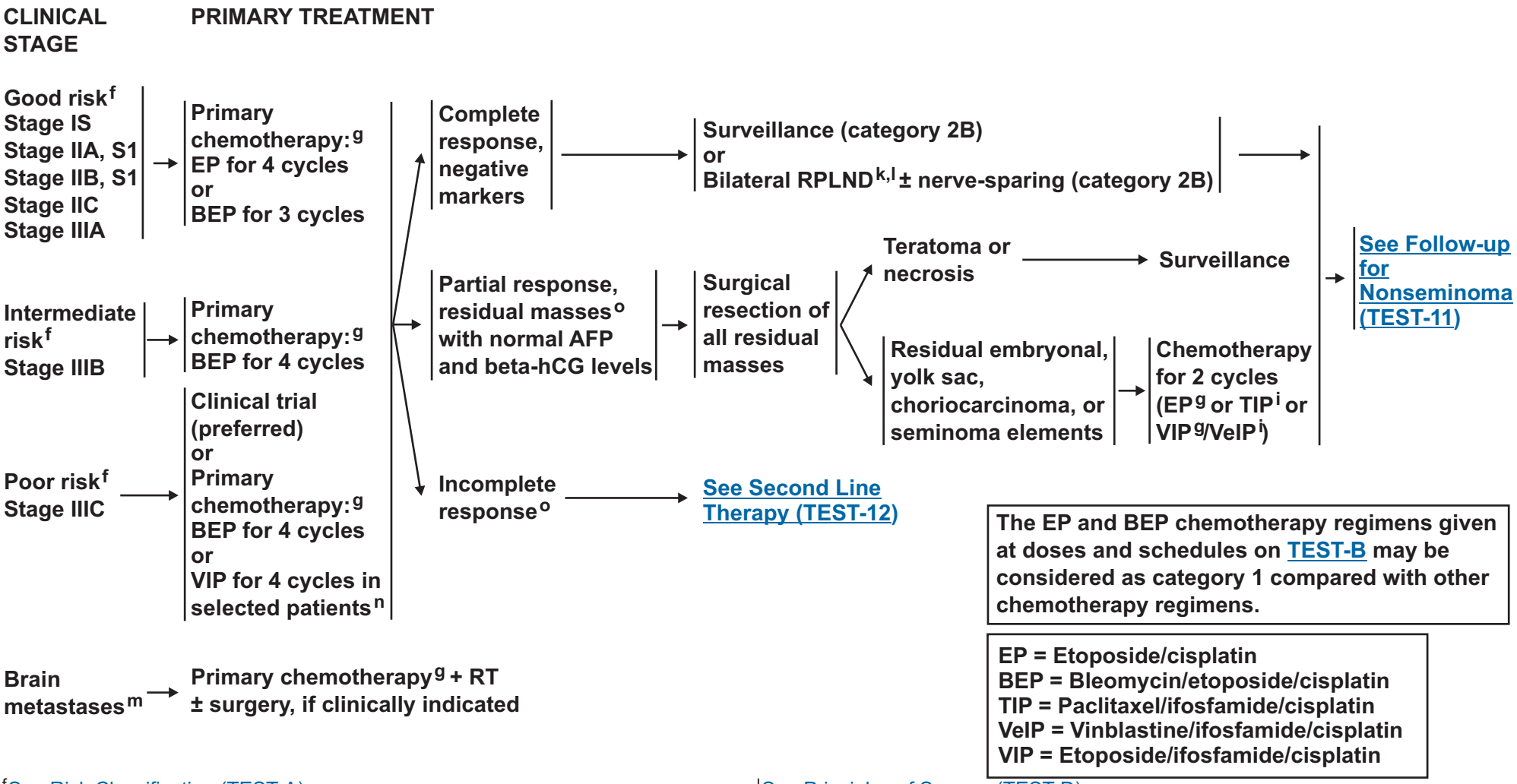


g See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines™ Version 1.2011
Testicular Cancer - Nonseminoma

NCCN Guidelines Index
Testicular Cancer TOC
Discussion



The EP and BEP chemotherapy regimens given at doses and schedules on TEST-B 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

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLLOW-UP FOR NONSEMINOMA

Surveillance for Stage IA, IB Testicular Cancer

Year	Months between visits, markers, chest x-ray	Months between abdominal CT
1	1-2	3-4
2	2	4-6
3	3	6-12
4	4	6-12
5	6	12
6+	12	12-24

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*
1	2-3	6
2	2-3	6-12
3	3-6	12
4	6	12
5	6-12	12
6+	12	As clinically indicated

*CT scans apply only to patients treated with chemotherapy alone. For patients who are post RPLND, a postoperative baseline CT scan is recommended and additional CT scans as clinically indicated.

Recurrence, See Salvage Therapy (TEST-12)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RECURRENCE[p]

SECOND LINE THERAPY

Prior chemotherapy

Favorable prognosis:
- Low markers
- Low volume
- Complete response on first-line therapy
- Testis primary

→ **Chemotherapy[i]**
- Conventional dose therapy (VeIP or TIP) or
- High-dose chemotherapy

Incomplete response or relapse →
- **Chemotherapy[i]**
  - High-dose chemotherapy (preferred if not previously given) or
  - Clinical trial
- **Surgical salvage should be considered if solitary site**
- **Best supportive care**

Complete response → **Follow-up** → **Relapse** (↑ Follow-up)

→ **Palliative chemotherapy[i] or RT**

Unfavorable prognosis:
- Incomplete response
- High markers
- High volume
- Extratesticular primary
- Late relapse

→ **Chemotherapy[i]**
- Clinical trial (preferred) or
- Conventional dose therapy (VeIP or TIP) or
- High-dose chemotherapy (category 2B)

Surgical salvage should be considered if solitary site

Best supportive care

→

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

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

[i] See Second Line or Subsequent Chemotherapy Regimens for Germ Cell Tumors (TEST-C).

[p] It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RISK CLASSIFICATION FOR ADVANCED DISEASE (post orchiectomy)[1]

Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy 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 Post-orchiectomy 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 Post-orchiectomy 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 1997;15(2):594-603. Reprinted with permission of the American Society of Clinical Oncology.

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRIMARY CHEMOTHERAPY REGIMENS FOR GERM CELL TUMORS

EP
Etoposide 100 mg/m^2 IV on Days 1 - 5
Cisplatin 20 mg/m^2 IV on Days 1 - 5
Repeat every 21 days[1]

BEP
Etoposide 100 mg/m^2 IV on Days 1 - 5
Cisplatin 20 mg/m^2 IV on Days 1 - 5
Bleomycin 30 units IV weekly on Days 1, 8, and 15*
Repeat every 21 days[2]

VIP
Etoposide 75 mg/m^2 IV on Days 1-5
Mesna 120 mg/m^2 slow IV push before ifosfamide on Day 1, then
Mesna 1200 mg/m^2 IV continuous infusion on Days 1-5
Ifosfamide 1200 mg/m^2 on Days 1-5
Cisplatin 20 mg/m^2 IV on Days 1-5
Repeat every 21 days[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;15:2553-2558.

[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;16:702-706.

[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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SECOND LINE OR SUBSEQUENT CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

Conventional dose chemotherapy regimens

VeIP
Vinblastine 0.11 mg/kg IV Push on Days 1 - 2
Mesna 400 mg/m^2 IV every 8 hours on Days 1 - 5
Ifosfamide 1200 mg/m^2 IV on Days 1 - 5
Cisplatin 20 mg/m^2 IV on Days 1 - 5
Repeat every 21 days[1]

TIP
Paclitaxel 250 mg/m^2 IV on Day 1
Ifosfamide 1500 mg/m^2 IV on Days 2 - 5
Mesna 500 mg/m^2 IV before ifosfamide, and then 4 and 8 hours after each ifosfamide dose on Days 2 - 5
Cisplatin 25 mg/m^2 IV on Days 2 - 5
Repeat every 21 days[2]

Palliative chemotherapy regimen

GEMOX
Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 followed by
Oxaliplatin 130 mg/m^2 IV on Day 1
Repeat every 21 days[3,4]

or

Gemcitabine 1250 mg/m^2 IV on Days 1 and 8 followed by
Oxaliplatin 130 mg/m^2 IV on Day 1
Repeat every 21 days[5]

High-dose chemotherapy regimens

Carboplatin 700 mg/m^2 (Body Surface Area) IV
Etoposide 750 mg/m^2 IV
Administer 5, 4, and 3 days before peripheral blood stem cell infusion for 2 cycles[6]

Paclitaxel 200 mg/m^2 IV over 24 hours
Ifosfamide 2000 mg/m^2 over 4 hours with mesna protection
Repeat every 14 days for 2 cycles followed by
Carboplatin AUC 7 - 8 IV over 60 minutes Days 1 - 3
Etoposide 400 mg/m^2 IV Days 1 - 3
Administer with peripheral blood stem cell support at 14 - 21 day intervals for 3 cycles[7]

See Chemotherapy References (TEST-C 2 of 2)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SECOND LINE OR SUBSEQUENT CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

CHEMOTHERAPY REFERENCES

[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;109:540-546.

[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;23:6549-6555.

[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;15:493-497.

[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;50:893-894.

[6] Einhorn LH, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 2007;357:340-348.

[7] Kondagunta GV, Bacik J, Sheinfeld J, et al. Paclitaxel plus Ifosfamide followed by high-dose carboplatin plus etoposide in previously treated germ cell tumors. J Clin Oncol 2007;25:85-90.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SURGERY

- **RPLND is the standard approach to the surgical management of nonseminoma germ cell tumor (NSGCT) in both primary and post-chemotherapy setting.**
- **A template dissection or a nerve-sparing approach to minimize the risk of ejaculatory disorders should be considered in patients undergoing primary RPLND for stage I nonseminoma.**
- **The "split and roll" technique in which lumbar vessels are identified and sequentially ligated allows resection of all lymphatic tissue around and behind the great vessels (aorta, IVC) and minimizes the risk of an in-field recurrence.**

Post-chemotherapy setting

- **Referral to high volume centers should be considered for surgical resection of masses post-chemotherapy.**
- **Completeness of resection is an independent and consistent predictive variable of clinical outcome. In post-chemotherapy RPLND, surgical margins should not be compromised in an attempt to preserve ejaculation. Additional procedures and resection of adjacent structures may be required.**
- **Post-chemotherapy RPLND is indicated in metastatic NSGCT patients with a residual retroperitoneal mass following systemic chemotherapy and normalized post-chemotherapy serum tumor markers.**
- **A full bilateral template RPLND should be performed in all patients undergoing RPLND in the post-chemotherapy setting, with the boundaries of dissection being the renal hilar vessels (superiorly), ureters (laterally), and the common iliac arteries (inferiorly).**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Testis Cancer (7th ed., 2010)

Primary Tumor (T)*

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.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Regional Lymph Nodes (N)

Clinical

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 five 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 five 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)

M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lung

Table 1 (continued)

American Joint Committee on Cancer (AJCC)
TNM Staging System for Testis Cancer (7th ed., 2010)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Group	T	N	M	S (Serum Tumor Markers)
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

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) < 5,000 *and* AFP (ng/ml) < 1,000
S2	LDH 1.5-10 x N *or* hCG (mIu/mL) 5,000-50,000 *or* AFP (ng/ml) 1,000-10,000
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.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/26/10

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 8,400 new cases of testicular cancer will be diagnosed in the United States in 2009.[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.

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. 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. If a GCT is found, an abdominopelvic computed tomographic (CT) scan is performed. A chest CT may be indicated if the abdominopelvic CT shows retroperitoneal adenopathy or the chest radiograph shows abnormal results. Inguinal orchiectomy is considered the primary treatment for most patients who present with a suspicious testicular mass.[2] 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.

Further management is dictated by histology, a diagnosis of seminoma or nonseminoma, and stage. Consideration of sperm banking must be discussed with the patients before undergoing any therapeutic intervention that may compromise fertility, including radiation therapy, surgery, and chemotherapy.

Seminoma

In 1997, the International Germ Cell Cancer Consensus Group (IGCCCG) defined a prognostic factor-based classification system based on identification of some clinically independent prognostic features such as extent of disease and levels of serum tumor markers post orchidectomy. The risk groups have been incorporated into the American Joint Committee on Cancer staging for GCTs. This classification categorized patients with seminoma and non-seminoma GCT into good-, intermediate-, or poor-risk groups.[4]

Seminoma Stages IA and IB

For patients with disease in stages IA and IB, the category 1 options include radiotherapy or chemotherapy with single dose carboplatin (discussed further in the subsequent paragraphs). However these two options can potentially lead to late morbidity. Therefore, surveillance is also an option for these patients. The NCCN panel recommends surveillance (category 1) for patients who have undergone previous radiotherapy, who have a horseshoe kidney, or who have inflammatory

bowel disease and also for selected patients with T1 or T2 disease (category 2B) who are committed to long-term follow-up. Between 15% and 20% of patients with seminoma, experience relapse during surveillance if they do not undergo adjuvant radiation therapy after orchiectomy.[5] The median time to relapse is approximately 12 months, but relapses can occur more than 5 years after orchiectomy. Relapse occurring after surveillance essentially represents a prolongation in the lead time of treatment. Therefore, these patients are treated according to the stage at relapse.

Radiation (category 1) (20–30 Gy) is given to the infradiaphragmatic area, including para-aortic lymph nodes and may include the ipsilateral ileoinguinal nodes.[6] Prophylaxis to the mediastinum is not provided, because relapse rarely occurs at this site. 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 have undergone prior radiation therapy.

A single dose of carboplatin is as an alternative to radiation therapy (category 1) for patients with stages IA and IB disease. Oliver et al[7] 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.[8] 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.

Follow up for patients treated with radiotherapy includes a history and physical, with measurement of post orchiectomy serum tumor markers, performed every 3 to 4 months for the first year, and 6 months for the second year and annually thereafter. Annual pelvic CT is recommended for 3 years for patients who underwent para-aortic RT. More intense follow-up is recommended for patients not undergoing radiation therapy - a history and physical, with measurement of post orchiectomy 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. 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.

Seminoma 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.[6] Follow-up recommendations are similar to that of patients with stages 1A and 1B. If advanced, disseminated disease is suspected, a full course of chemotherapy is administered according to guidelines for good risk GCT.

Seminoma 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.[9] Surveillance is not an option for patients with stage IIA or IIB disease with relative contraindications for radiation. In stage IIB chemotherapy with 4 courses of etoposide and cisplatin (EP) is an alternative recommendation.

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.

Seminoma Stages IIC and III

Patients with stage IIC or III disease are those considered at good or intermediate risk. 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. Standard chemotherapy is used for both groups of patients, but for patients with good risk, either 4 cycles of EP [10,11] are recommended or 3 cycles of bleomycin, etoposide, and cisplatin (BEP).[12-14] In contrast, 4 cycles of BEP are recommended for those with intermediate risk disease.[15] All these options are category 1 recommendations.

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. 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.[16] 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 second line chemotherapy. Alternatively, the patient can be treated with radiation therapy (category 2B). Cisplatin-based combination chemotherapy is used for second line treatment. The recommended regimens are four cycles of TIP (paclitaxel, ifosfamide, cisplatin) [17] or four cycles of VeIP (vinblastine, ifosfamide, cisplatin).[18,19]

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.[20] Options include surgery (category 2B), radiation therapy (category 2B), and observation. 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.[21] 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. Second line chemotherapy therapy is recommended for patients with rising serum tumor markers or a growing mass detected on CT scan. Second line therapy for seminoma and nonseminoma is similar and is discussed further in the section on nonseminoma. Approximately 90% of patients with advanced seminoma are cured with cisplatin-containing chemotherapy.[22]

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

Nonseminoma

The risk classification for nonseminoma into good-, intermediate- and poor-risk groups by the IGCCCG [4] is defined in TEST-A.
Stage-dependent treatment options after inguinal orchiectomy include surveillance, 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.[23] 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.[24]

Nonseminoma Stage IA

Two management options exist for patients with stage IA disease after orchiectomy: (1) surveillance (in compliant patients) [25-27] or (2) open nerve-sparing RPLND.

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.

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. 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. [28-34] For patients with pN3 disease, longer courses of chemotherapy with 4 cycles of EP or 3 cycles of BEP (preferred) is recommended.

The follow-up examinations in those electing surveillance in the current NCCN guidelines 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.

Nonseminoma Stage IB

After orchidectomy, either open nerve sparing RPLND or chemotherapy with 2 cycles of BEP (category 2B) are adjuvant treatment options to reduce the risk of relapse in patients with stage IB disease.[31,35].

A trial by Albers et al randomized stage I patients after orchiectomy, to undergo RPLND (n = 191) or one adjuvant course of BEP.(n = 191) [36] After a median follow-up of 4.7 years two relapses were reported in the group of patients treated with one course of adjuvant BEP and 13 patients with relapse in the arm treated with RPLND (*P* = 0.0011). This study indicates that one course of BEP is active in patients and could be an option in patients unable to tolerate the toxicity of treatment. The results of this study are promising and merits further investigation. The current standard of care practiced by most NCCN institutions is two courses of BEP.

The subsequent management following primary open nerve sparing RPLND for patients with IB is similar to that described for stage IA in the section above. Subsequent management following primary chemotherapy may be open nerve sparing RPLND or surveillance (if the patient is compliant).

Surveillance alone may be offered to compliant patients with T2 disease (category 2B). 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.

Nonseminoma Stage IS

Patients with stage IS disease exhibit a persistent elevation of serum tumor markers post orchiectomy but no radiographic evidence of disease. These patients are treated with standard chemotherapy with either 4 cycles of EP or 3 cycles of BEP. Either regimen is preferable to initial open nerve sparing RPLND because these patients nearly always have disseminated disease.[37,38] Primary chemotherapy may be followed by open nerve sparing RPLND or surveillance.

Nonseminoma Stages IIA and IIB

Treatment for patients with stage IIA nonseminoma depends on post orchiectomy 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.

For patients with stage IIA disease, when the tumor marker levels are normal, 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 [39] or surveillance. This treatment is considered particularly appropriate if the patient has multifocal disease. Alternatively, the patient can undergo primary nerve-sparing RPLND with adjuvant chemotherapy (two cycles of EP or BEP).

Treatment for patients with stage IIB disease depends on both post orchiectomy tumor marker levels and radiographic findings. 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 in the retroperitoneum (i.e., the

landing zone), two management options are available. One option is to perform open nerve sparing RPLND and to consider adjuvant chemotherapy as described for patients with stage IIA disease. 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.

Both options, of primary chemotherapy or primary RPLND are comparable options in terms of outcome but side-effects and toxicity are different.[40] The reported relapse free survival with either approach is close to 98%.[41-47]

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), or if there is persistent marker elevation, similar primary chemotherapy (4 cycles of EP or 3 cycles of BEP) is recommended. Initial open RPLND is not recommended in this situation.

Subsequent management of Stage IIA and IIB
Following primary chemotherapy, either surveillance or an open nerve sparing RPLND is recommended depending on the presence of a residual mass.

Following primary open nerve sparing RPLND, surveillance may be opted for depending on the number of positive lymph nodes identified and patient compliance. For example, surveillance is opted in pN0 patients and 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 for pN1 and pN2 consists of 2 cycles of BEP or EP, resulting in a nearly 100% relapse-free survival rate.[45] For pN3, the guidelines recommend 4 cycles of EP or 3 cycles of BEP.

Nonseminoma Stages IIC and III
Patients with stage IIC and stage III disease are treated with primary chemotherapy regimens based on risk status. 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 levels of post orchiectomy serum tumor markers were identified as important prognostic features, and models were developed to stratify patients. The International Germ Cell Cancer Consensus Classification was developed and incorporated the risk groups into the American Joint Committee on Cancer staging for GCTs. This classification categorized patients as good-, intermediate-, or poor-risk.[4]

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,[48,49] and either eliminating or reducing the dose of bleomycin.[48,50] 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. Either regimen is well tolerated and cures approximately 90% of patients with good risk.[51]

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.[52] In patients with these prognostic factors, clinical trials are directed at improving efficacy.

For patients with intermediate risk, the cure rate is approximately 70% with standard therapy using 4 cycles of BEP.[53,54]

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.[51] The panel recommends 4 cycles of etoposide, ifosfamide, and cisplatin (VIP regimen) for patients who may not tolerate bleomycin.[55] Due to the less than favorable prognosis of patients in the poor-risk group, treating them in the context of a clinical trial is the preferred recommendation by the NCCN Testicular Cancer panel.

Primary chemotherapy using cisplatin-based regimen plus radiotherapy is indicated for patients in whom brain metastases are detected. If clinically indicated, surgery should also be performed. Surgery can be performed if clinically indicated such as in the case of a solitary metastasis, depending on the systemic state of the disease, the histology of the primary tumor and the location of the metastasis.

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 (AFP and beta-HCG) 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 patients must be put under surveillance. In the 15% of patients who have viable residual cancer, 2 cycles of conventionally dosed chemotherapy (EP, VelP [paclitaxel/ifosfamide/cisplatin], or TIP [vinblastine/ifosfamide/cisplatin]) are administered.

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

Second Line Therapy for Metastatic Germ Cell Tumors

Patients who do not experience a durable complete response to first-line therapy can be divided into those with a favorable or unfavorable prognosis based on prognostic factors.

Standard second line therapy includes conventional dose chemotherapy or high dose chemotherapy. Prognostic factors can be used in deciding whether a patient is a candidate for conventional dose therapy or high-dose therapy with stem cell support as a second line option. Favorable prognostic factors to conventional dose second-line chemotherapy include a testicular primary site, prior complete response to first-line therapy, low levels of post orchiectomy serum tumor markers, and low-volume disease.[56] The conventional dose regimen include cisplatin and ifosfamide combined with either vinblastine or paclitaxel.[57] If the patient experiences an incomplete response or relapses after second-line conventional dose chemotherapy, the preferred third-line option would be high-dose chemotherapy with autologous stem cell support.

Unfavorable prognostic features include incomplete response to first-line treatment, high levels of serum markers, high volume disease and presence of extratesticular primary tumor. Patients with a testicular primary site and rising post orchiectomy serum tumor markers during first-line therapy are usually considered for high-dose programs. Chemotherapy options for patients with poor prognostic features include chemotherapy in the context of a clinical trial (preferred); conventional-dose second line therapy; high-dose chemotherapy plus autologous stem cell support (category 2B). Alternatively, the patients may be put on best supportive care or salvage surgery if feasible.

The high dose regimens include high-dose carboplatin plus etoposide followed by autologous stem cell transplant [58,59] or paclitaxel, ifosfamide followed by high dose carboplatin plus etoposide with stem cell support.[60] For patients who do not experience complete response to second line 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.[61] Other options are participation in a clinical trial or best supportive care.

Subsequent Therapy for Patients with Persistent or Recurrent Metastatic Germ Cell Tumors

The more advanced the disease, the higher the likelihood of recurrence. All patients with either persistent or recurrent disease should be considered for palliative chemotherapy or radiation therapy. A recommended palliative chemotherapy 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.[62-64] These studies investigated the efficacy and the toxicity of gemcitabine and oxaliplatin (GEMOX) in patients with relapsed or cisplatin-refractory GCTs. 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.[62-64] Toxicity of GEMOX was found to be primarily hematological and generally manageable.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59:225-249.

2. Jones RH, Vasey PA. Part I: testicular cancer--management of early disease. Lancet Oncol. 2003;4:730-737.

3. Fossa SD, Chen J, Schonfeld SJ, et al. Risk of contralateral testicular cancer: a population-based study of 29,515 U.S. men. J Natl Cancer Inst. 2005;97:1056-1066.

4. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol. 1997;15:594-603.

5. Alomary I, Samant R, Gallant V. Treatment of stage I seminoma: a 15-year review. Urol Oncol. 2006;24:180-183.

6. Jones WG, Fossa SD, Mead GM, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol. 2005;23:1200-1208.

7. Oliver RT, Mason MD, Mead GM, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. Lancet. 2005;366:293-300.

8. Oliver RT, Mead GM, Fogarty PJ, Stenning SP, TE19 M, EORTC 30982 trial collaborators. Radiotherapy versus carboplatin for stage I seminoma: Updated analysis of the MRC/EORTC randomized trial (ISRCTN27163214). ASCO Meeting Abstracts. 2008;26:Abstract 1.

9. Gospodarwicz MK, Sturgeon JF, Jewett MA. Early stage and advanced seminoma: role of radiation therapy, surgery, and chemotherapy. Semin Oncol. 1998;25:160-173.

10. Bajorin DF, Sarosdy MF, Pfister DG, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol. 1993;11:598-606.

11. Kondagunta GV, Bacik J, Bajorin D, et al. Etoposide and cisplatin chemotherapy for metastatic good-risk germ cell tumors. J Clin Oncol. 2005;23:9290-9294.

12. de Wit R, Roberts JT, Wilkinson PM, et al. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol. 2001;19:1629-1640.

13. Loehrer PJ, Sr., Johnson D, Elson P, Einhorn LH, Trump D. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. J Clin Oncol. 1995;13:470-476.

14. 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 Indian University experience. J Clin Oncol. 1998;16:702-706.

15. de Wit R, Louwerens M, de Mulder PH, Verweij J, Rodenhuis S, Schornagel J. Management of intermediate-prognosis germ-cell cancer: results of a phase I/II study of Taxol-BEP. Int J Cancer. 1999;83:831-833.

16. Becherer A, De Santis M, Karanikas G, et al. FDG PET is superior to CT in the prediction of viable tumour in post-chemotherapy seminoma residuals. Eur J Radiol. 2005;54:284-288.

17. Kondagunta GV, Bacik J, Sheinfeld J, et al. Paclitaxel plus Ifosfamide followed by high-dose carboplatin plus etoposide in previously treated germ cell tumors. J Clin Oncol. 2007;25:85-90.

18. Miller KD, Loehrer PJ, Gonin R, Einhorn LH. Salvage chemotherapy with vinblastine, ifosfamide, and cisplatin in recurrent seminoma. J Clin Oncol. 1997;15:1427-1431.

19. Loehrer PJ, Sr., Lauer R, Roth BJ, Williams SD, Kalasinski LA, Einhorn LH. Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med. 1988;109:540-546.

20. Warde P, Gospodarowicz MK, Panzarella T, et al. Stage I testicular seminoma: results of adjuvant irradiation and surveillance. J Clin Oncol. 1995;13:2255-2262.

21. Puc HS, Heelan R, Mazumdar M, et al. Management of residual mass in advanced seminoma: results and recommendations from the Memorial Sloan-Kettering Cancer Center. J Clin Oncol. 1996;14:454-460.

22. Mencel PJ, Motzer RJ, Mazumdar M, Vlamis V, Bajorin DF, Bosl GJ. Advanced seminoma: treatment results, survival, and prognostic factors in 142 patients. J Clin Oncol. 1994;12:120-126.

23. Sheinfeld J, Herr HW. Role of surgery in management of germ cell tumor. Semin Oncol. 1998;25:203-209.

24. Carver BS, Sheinfeld J. The current status of laparoscopic retroperitoneal lymph node dissection for non-seminomatous germ-cell tumors. Nat Clin Pract Urol. 2005;2:330-335.

25. Colls BM, Harvey VJ, Skelton L, et al. Late results of surveillance of clinical stage I nonseminoma germ cell testicular tumours: 17 years' experience in a national study in New Zealand. BJU Int. 1999;83:76-82.

26. Read G, Stenning SP, Cullen MH, et al. Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. J Clin Oncol. 1992;10:1762-1768.

27. Kakiashvili D, Anson-Cartwright, L, Sturgeon, JF, Warde, PR, Chung, P, Moore, M, Wang, L, Azuero, J, Jewett, MA. Non risk-adapted surveillance management for clinical stage I nonseminomatous testis tumors. . J Urol 2007;177:278 (abstract 835).

28. Bohlen D, Borner M, Sonntag RW, Fey MF, Studer UE. Long-term results following adjuvant chemotherapy in patients with clinical stage I testicular nonseminomatous malignant germ cell tumors with high risk factors. J Urol. 1999;161:1148-1152.

29. Bohlen D, Burkhard FC, Mills R, Sonntag RW, Studer UE. Fertility and sexual function following orchiectomy and 2 cycles of chemotherapy for stage I high risk nonseminomatous germ cell cancer. J Urol. 2001;165:441-444.

30. Chevreau C, Mazerolles C, Soulie M, et al. Long-term efficacy of two cycles of BEP regimen in high-risk stage I nonseminomatous testicular germ cell tumors with embryonal carcinoma and/or vascular invasion. Eur Urol. 2004;46:209-214.

31. Cullen MH, Stenning SP, Parkinson MC, et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol. 1996;14:1106-1113.

32. Oliver RT, Raja MA, Ong J, Gallagher CJ. Pilot study to evaluate impact of a policy of adjuvant chemotherapy for high risk stage 1 malignant teratoma on overall relapse rate of stage 1 cancer patients. J Urol. 1992;148:1453-1455.

33. Pont J, Albrecht W, Postner G, Sellner F, Angel K, Holtl W. Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. J Clin Oncol. 1996;14:441-448.

34. Studer UE, Fey MF, Calderoni A, Kraft R, Mazzucchelli L, Sonntag RW. Adjuvant chemotherapy after orchiectomy in high-risk patients with

clinical stage I non-seminomatous testicular cancer. Eur Urol. 1993;23:444-449.

35. Sharir S, Foster RS, Donohue JP, Jewett MA. What is the appropriate follow-up after treatment? Semin Urol Oncol. 1996;14:45-53.

36. Albers P, Siener R, Krege S, et al. Randomized Phase III Trial Comparing Retroperitoneal Lymph Node Dissection With One Course of Bleomycin and Etoposide Plus Cisplatin Chemotherapy in the Adjuvant Treatment of Clinical Stage I Nonseminomatous Testicular Germ Cell Tumors: AUO Trial AH 01/94 by the German Testicular Cancer Study Group. J Clin Oncol. 2008;26:2966-2972.

37. Culine S, Theodore C, Terrier-Lacombe MJ, Droz JP. Primary chemotherapy in patients with nonseminomatous germ cell tumors of the testis and biological disease only after orchiectomy. J Urol. 1996;155:1296-1298.

38. Davis BE, Herr HW, Fair WR, Bosl GJ. The management of patients with nonseminomatous germ cell tumors of the testis with serologic disease only after orchiectomy. J Urol. 1994;152:111-113; discussion 114.

39. Foster R, Bihrle R. Current status of retroperitoneal lymph node dissection and testicular cancer: when to operate. Cancer Control. 2002;9:277-283.

40. Weissbach L, Bussar-Maatz R, Flechtner H, Pichlmeier U, Hartmann M, Keller L. RPLND or primary chemotherapy in clinical stage IIA/B nonseminomatous germ cell tumors? Results of a prospective multicenter trial including quality of life assessment. Eur Urol. 2000;37:582-594.

41. Donohue JP, Thornhill JA, Foster RS, Bihrle R, Rowland RG, Einhorn LH. The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University experience (1965 to 1989). J Urol. 1995;153:85-89.

42. Hartlapp JH, Weissbach L, Bussar-Maatz R. Adjuvant chemotherapy in nonseminomatous testicular tumour stage II. Int J Androl. 1987;10:277-284.

43. Horwich A, Norman A, Fisher C, Hendry WF, Nicholls J, Dearnaley DP. Primary chemotherapy for stage II nonseminomatous germ cell tumors of the testis. J Urol. 1994;151:72-77.

44. Logothetis CJ, Swanson DA, Dexeus F, et al. Primary chemotherapy for clinical stage II nonseminomatous germ cell tumors of the testis: a follow-up of 50 patients. J Clin Oncol. 1987;5:906-911.

45. Motzer RJ, Sheinfeld J, Mazumdar M, et al. Etoposide and cisplatin adjuvant therapy for patients with pathologic stage II germ cell tumors. J Clin Oncol. 1995;13:2700-2704.

46. Sternberg CN. Role of primary chemotherapy in stage I and low-volume stage II nonseminomatous germ-cell testis tumors. Urol Clin North Am. 1993;20:93-9109.

47. Williams SD, Stablein DM, Einhorn LH, et al. Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. N Engl J Med. 1987;317:1433-1438.

48. Bosl GJ, Geller NL, Bajorin D, et al. A randomized trial of etoposide + cisplatin versus vinblastine + bleomycin + cisplatin + cyclophosphamide + dactinomycin in patients with good-prognosis germ cell tumors. J Clin Oncol. 1988;6:1231-1238.

49. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med. 1987;316:1435-1440.

50. Einhorn LH, Williams SD, Loehrer PJ, et al. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ

cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol. 1989;7:387-391.

51. Jones RH, Vasey PA. Part II: testicular cancer--management of advanced disease. Lancet Oncol. 2003;4:738-747.

52. Toner GC, Motzer RJ. Poor prognosis germ cell tumors: current status and future directions. Semin Oncol. 1998;25:194-202.

53. de Wit R, Stoter G, Sleijfer DT, et al. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. Br J Cancer. 1998;78:828-832.

54. Frohlich MW, Small EJ. Stage II nonseminomatous testis cancer: the roles of primary and adjuvant chemotherapy. Urol Clin North Am. 1998;25:451-459.

55. Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. 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.

56. Motzer RJ, Geller NL, Tan CC, et al. Salvage chemotherapy for patients with germ cell tumors. The Memorial Sloan-Kettering Cancer Center experience (1979-1989). Cancer. 1991;67:1305-1310.

57. Loehrer PJ, Sr., Gonin R, Nichols CR, Weathers T, Einhorn LH. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. J Clin Oncol. 1998;16:2500-2504.

58. Motzer RJ, Bosl GJ. High-dose chemotherapy for resistant germ cell tumors: recent advances and future directions. J Natl Cancer Inst. 1992;84:1703-1709.

59. Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med. 2007;357:340-348.

60. Feldman DR, Sheinfeld J, Bajorin DF, et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. J Clin Oncol. 2010;28:1706-1713.

61. Wood DP, Jr., Herr HW, Motzer RJ, et al. Surgical resection of solitary metastases after chemotherapy in patients with nonseminomatous germ cell tumors and elevated serum tumor markers. Cancer. 1992;70:2354-2357.

62. 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;50:1032-1038; discussion 1038-1039.

63. 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;22:108-114.

64. 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;15:493-497.