Overview

An estimated 8590 new cases of testicular cancer will be diagnosed in the United States in 2012. Germ cell tumors (GCTs) constitute 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 uncommon tumors that constitute only 2% of all human malignancies, they are the most common solid tumor in men between 15 and 34 years of age. 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 history of a GCT, positive family history, cryptorchidism, testicular dysgenesis, alpha-fetoprotein, lactate dehydrogenase, human chorionic gonadotropin, cisplatin, seminoma, and nonseminoma.

Key Words

NCCN Categories of Evidence and Consensus
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines<sup>®</sup> 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<sup>®</sup> (NCCN<sup>®</sup>) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

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and Klinefelter 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 β-human chorionic gonadotropin (β-HCG) are critical in diagnosing GCTs, determining prognosis, and assessing treatment outcome. These should be determined before, during, and after treatment and throughout the follow-up period. Serum tumor markers are useful for monitoring all stages of nonseminomas. They are also useful in monitoring metastatic seminomas, because elevated marker levels is the early sign of relapse.

LDH is a less-specific marker than AFP and β-HCG. 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. When patients with a histologically “pure” testicular seminoma have an elevated level of AFP, it is generally assumed that an undetected focus of nonseminoma is present.2,3

Text continues on p. 521
Testicular Cancer Version 1:2012

WORKUP

Suspicious testicular mass

- H&P
- Alpha-fetoprotein (AFP)
- beta-hCG
- LDH
- Chemistry profile
- Chest x-ray
- Testicular ultrasound

Primary Treatment

- Discuss sperm banking
- Radical inguinal orchectomy
- Consider inguinal biopsy of contralateral testis if:
  - Suspicious ultrasound for intratesticular abnormalities
  - Cryptorchid testis
  - Marked atrophy

Pathologic Diagnosis

Pure seminoma germ cell tumor (pure seminoma histology and AFP negative, may have elevated beta-HCG)

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

Notes:

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.

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.
**Testicular Cancer Version 1:2012**

**PURE SEMINOMA**

**POSTDIAGNOSTIC WORKUP***

- Abdominal/pelvic CT
- Chest CT if:
  - Positive abdominal CT or abnormal chest x-ray
- Repeat beta-HCG, LDH, AFP¹
- Brain MRI, if clinically indicated
- Bone scan, if clinically indicated
- Discuss sperm banking

**CLINICAL STAGE**

<table>
<thead>
<tr>
<th>Stage</th>
<th>See Primary Treatment and Follow-Up (page 506)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA, IB</td>
<td></td>
</tr>
<tr>
<td>Stage IS</td>
<td></td>
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<tr>
<td>Stage IIA, IIB</td>
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<tr>
<td>Stage IIC, III</td>
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<tr>
<td>Stage IA, IB, IS</td>
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</tr>
<tr>
<td>Stage IIA, IIB</td>
<td></td>
</tr>
<tr>
<td>Stage IIC, IIIA, IIIB, IIIC, and brain metastasis</td>
<td>See Primary Treatment (page 510)</td>
</tr>
</tbody>
</table>

*PET scan is not clinically indicated for nonseminoma.

¹Elevated values should be followed after orchiectomy with repeated determination to allow precise staging.
**Testicular Cancer Version 1:2012**

### Clinical Trials

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

### 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 (category 1)

### Stage IS

- RT to include para-aortic and ipsilateral iliac lymph nodes to a dose of 30 to 36 Gy
  - or
  - Consider primary chemotherapy for selected stage IIB patients:
    - EP for 4 cycles or BEP for 3 cycles

### Stage IIA, IIB

- RT with para-aortic and ipsilateral iliac lymph nodes to a dose of 30 to 36 Gy
  - or
  - Consider primary chemotherapy for selected stage IIB patients:
    - EP for 4 cycles or BEP for 3 cycles

### Stage IIC, III

- Good risk
  - Primary chemotherapy:
    - EP for 4 cycles (category 1) or
    - BEP for 3 cycles (category 1)

- Intermediate risk
  - Primary chemotherapy:
    - BEP for 4 cycles (category 1)

---

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

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°See Principles of Radiotherapy for Pure Testicular Seminoma (pages 513-516).
°See Discussion for further information on the management of stage IS.
°See Risk Classification for Advanced Disease (page 517).
°See Primary Chemotherapy Regimens for Germ Cell Tumors (page 518).
# Testicular Cancer Version 1:2012

## PURE SEMINOMA

### STAGE IIB, IIC, III AFTER PRIMARY TREATMENT WITH CHEMOTHERAPY

- Chest, abdominal, pelvic CT scan
- Serum tumor markers

### FOLLOW-UP

#### POST-CHEMOTHERAPY MANAGEMENT

- **Surveillance**
  - H&P + chest x-ray, AFP, beta-HCG, LDH: every 2 mo for year 1, every 3 mo for year 2, every 6 mo for years 3 and 4, then annually
  - Abdominal/pelvic CT: Post RPLND: 3-6 mo, then as clinically indicated
  - After all other primary management as clinically indicated
  - PET scan as clinically indicated

#### FOLLOw-UP

- **Recurrence**, see Second-Line Therapy (page 512)

### FLOWCHART:

- **No residual mass or residual mass ≤ 3 cm and normal markers** → **Surveillance**
  - Progression, see Second-Line Therapy for Nonseminoma (page 512)

- **Residual mass (> 3 cm) and normal markers**
  - PET scan (approximately 6 wk post-chemotherapy)
  - **Negative** → **Surveillance**
  - **Positive** → **Consider RPLND, if technically feasible**
    - or **Second-line chemotherapy**
    - or **RT (category 2B)**

- **Progressive disease** (growing mass or rising markers) → **See Second-Line Therapy for Nonseminoma (page 512)**

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### Notes:

- gSee Principles of Radiotherapy for Pure Testicular Seminoma (pages 513-516).
- hIf viable seminoma found by retroperitoneal lymph node dissection (RPLND), see page 510 (residual embryonal, yolk sac, choriocarcinoma, or seminoma elements).
- iSee Second-Line or Subsequent Chemotherapy Regimens for Metastatic Germ Cell Tumors (page 519).
CLINICAL STAGE

Stage IA
- Surveillance or Nerve-sparing RPLND<sup>m,n</sup>

Stage IB
- Nerve-sparing RPLND<sup>m,n</sup> or Primary chemotherapy:<sup>i</sup> BEP for 2 cycles or BEP for 1 cycle (category 2B) or Surveillance for T2 only (category 2B)

Stage IS
- Persistent marker elevation

Stage IIA
- Markers negative or Persistent marker elevation

Stage IIB
- Markers negative or Multifocal, symptomatic, or lymph node metastases with aberrant lymphatic drainage

PRIMARY TREATMENT

See Follow-Up for Nonseminoma (page 511)
See Postsurgical Management (page 509)
See Postchemotherapy Management (page 509)
See Postsurgical Management (page 509)
See Primary Treatment (page 510)
See Postsurgical Management (page 509)
See Postchemotherapy Management (page 509)
See Primary Treatment (page 510)
See Postsurgical Management (page 509)
See Postchemotherapy Management (page 509)
See Primary Treatment (page 510)

Postchemotherapy Management

Stage IB, IIA, IIB treated with primary chemotherapy
See Follow-Up for Nonseminoma (page 511)
See Primary Chemotherapy Regimens for Germ Cell Tumors (page 518)
Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers.

Postoperative Management

pN0
- Surveillance (preferred) or Chemotherapy: EP for 2 cycles or BEP for 2 cycles

pN1
- Surveillance

pN2
- Chemotherapy (preferred): EP for 2 cycles or BEP for 2 cycles or Surveillance

pN3
- Chemotherapy: EP for 4 cycles or BEP for 3 cycles

Note:
- See Follow-Up for Nonseminoma (page 511)
- EP = Etoposide/cisplatin
- BEP = Bleomycin/etoposide/cisplatin

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

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**TESTICULAR CANCER Version 1:2012**

**NONSEMINOMA**

### CLINICAL STAGE

**Stage IA**
- Surveillance
- Nerve-sparing RPLND\(^{m,n}\)

**Stage IB**
- Nerve-sparing RPLND
- Primary chemotherapy:
  - BEP for 2 cycles
  - BEP for 1 cycle (category 2B)
- Surveillance for T2 (category 2B)

**Stage IIS**
- Persistent marker elevation
- See Postchemotherapy Management (page 509)
- See Postsurgical Management (page 509)

**Stage IIA**
- Markers negative
- Persistent marker elevation
- Nerve-sparing RPLND
- Primary chemotherapy (category 2B):
  - EP for 4 cycles
  - BEP for 3 cycles
- See Primary Chemotherapy Regimens for Germ Cell Tumors (page 518).

**Stage IIB**
- Markers negative
- Persistent marker elevation
- Lymph node metastases, within lymphatic drainage sites (landing zone positive)
- Multifocal, symptomatic, or lymph node metastases with aberrant lymphatic drainage
- Primary chemotherapy:
  - EP for 4 cycles
  - BEP for 3 cycles
- Nerve-sparing RPLND
- See Postchemotherapy Management (page 509)
- See Postsurgical Management (page 509)

**Stage IIB**
- Markers negative
- Nerve-sparing bilateral RPLND
- Surveillance (category 2B)

**Stage IIB**
- Negative markers, residual mass (≥ 1 cm) on CT scan
- Nerve-sparing bilateral RPLND\(^{m,n}\)
- Surveillance (category 2B)

**Stage IIB**
- Negative markers, no mass or residual mass (< 1 cm) on CT scan
- Nerve-sparing bilateral RPLND\(^{m,n}\)
- Surveillance (category 2B)

### POSTCHEMOTHERAPY MANAGEMENT

**Stage IB, IIA, IIB treated with primary chemotherapy**
- See Follow-Up for Nonseminoma (page 511)

### POSTSURGICAL MANAGEMENT

**pN0**
- Surveillance

**pN1**
- Surveillance (preferred)
- Chemotherapy:
  - EP for 2 cycles
  - BEP for 2 cycles
- See Follow-Up for Nonseminoma (page 511)

**pN2**
- Chemotherapy (preferred):
  - EP for 2 cycles
  - BEP for 2 cycles
  - Surveillance
- See Follow-Up for Nonseminoma (page 511)

**pN3**
- Chemotherapy (preferred):
  - EP for 4 cycles
  - BEP for 3 cycles

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

\(^{1}\) See Primary Chemotherapy Regimens for Germ Cell Tumors (page 518).
\(^{m}\) Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers.
\(^{n}\) See Principles of Surgery (page 520).
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

### CLINICAL STAGE

<table>
<thead>
<tr>
<th>Good risk</th>
<th>Intermediate risk</th>
<th>Poor risk</th>
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<tbody>
<tr>
<td>Stage IS</td>
<td>Stage IIA, S1</td>
<td>Stage IIC</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Stage IIB, S1</td>
<td>Stage III</td>
</tr>
<tr>
<td>Stage IIB</td>
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</tr>
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<td></td>
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<tr>
<td>Stage IIIC</td>
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### PRIMARY TREATMENT

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<tr>
<td>Primary chemotherapy:</td>
<td>Primary chemotherapy:</td>
<td>Primary chemotherapy:</td>
</tr>
<tr>
<td>EP for 4 cycles</td>
<td>BEP for 4 cycles</td>
<td>BEP for 4 cycles</td>
</tr>
<tr>
<td>or BEP for 3 cycles</td>
<td>or VIP for 4 cycles in selected patients</td>
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</tbody>
</table>

### POST CHEMOTHERAPY MANAGEMENT

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<th>Good risk</th>
<th>Intermediate risk</th>
<th>Poor risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, negative markers</td>
<td>Partial response, residual masses(q) with normal AFP and beta-HCG levels</td>
<td>Incomplete response(q)</td>
</tr>
</tbody>
</table>

#### Post Chemotherapy Management - Nonseminoma

<table>
<thead>
<tr>
<th>Year</th>
<th>Months between H&amp;P, markers, chest x-ray</th>
<th>Months between abdominal CT</th>
<th>Months between abdominal/pelvic CT</th>
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<tr>
<td>1</td>
<td>2-3</td>
<td>6</td>
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<td>As indicated</td>
</tr>
<tr>
<td>3</td>
<td>3-6</td>
<td>6</td>
<td>As indicated</td>
</tr>
<tr>
<td>4</td>
<td>6-12</td>
<td>12</td>
<td>As indicated</td>
</tr>
<tr>
<td>5</td>
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<td>12</td>
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</tr>
<tr>
<td>6+</td>
<td>12-24</td>
<td>As indicated</td>
<td>As indicated</td>
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#### Post Chemotherapy Management - Seminoma

<table>
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<th>Year</th>
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<tr>
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<td>6-12</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>6-12</td>
<td>12</td>
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</table>

### Post Chemotherapy Management - Bilateral RPLND

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<th>Months between H&amp;P, markers, chest x-ray</th>
<th>Months between abdominal/pelvic CT</th>
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<tr>
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<td>2-3</td>
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<tr>
<td>2</td>
<td>2-3</td>
<td>As indicated</td>
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<tr>
<td>3</td>
<td>3-6</td>
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<tr>
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<td>As indicated</td>
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<tr>
<td>6+</td>
<td>12-24</td>
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### Post Chemotherapy Management - Surveillance

<table>
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<th>Year</th>
<th>Months between H&amp;P, markers, chest x-ray</th>
<th>Months between abdominal/pelvic CT</th>
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<td>2-3</td>
<td>As indicated</td>
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<tr>
<td>2</td>
<td>2-3</td>
<td>As indicated</td>
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<td>3</td>
<td>3-6</td>
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<tr>
<td>4</td>
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<td>6-12</td>
<td>As indicated</td>
</tr>
<tr>
<td>6+</td>
<td>12-24</td>
<td>As indicated</td>
</tr>
</tbody>
</table>

### Teratoma or necrosis

- Surveillance

### Residual embryonal, yolk sac, choriocarcinoma, or seminoma elements

- Chemotherapy for 2 cycles (EP or TIP or VPI or VeIP)

### Other Treatment Options

- Surgical resection of all residual masses
- Chemotherapy for 2 cycles (EP or TIP or VPI or VeIP)

### Follow-Up for Nonseminoma

- Surveillance (category 2B)
- Bilateral RPLND (category 2B)
- Nerve-sparing

### Second-Line Therapy

- See Second-Line Therapy (page 512)

### Follow-Up for Nonseminoma

- Surveillance (category 2B)

### Follow-Up for Seminoma

- Surveillance (category 2B)

### Principles of Surgery

- Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
- Patients who may not tolerate bleomycin.
- There is limited predictive value for PET scan for residual masses.

---

\(i\) See Risk Classification for Advanced Disease (page 517).
\(j\) See Primary Chemotherapy Regimens for Germ Cell Tumors (page 518).
\(k\) See Second-Line or Subsequent Chemotherapy Regimens for Metastatic Germ Cell Tumors (page 519).
\(m\) Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
\(n\) See Principles of Surgery (page 520).
\(o\) Patients should receive adequate treatment for brain metastases, in addition to cisplatin-based chemotherapy.
\(p\) Patients who may not tolerate bleomycin.
\(q\) There is limited predictive value for PET scan for residual masses.

---

**Legend**

- EP = Etoposide/cisplatin
- BEP = Bleomycin/etoposide/cisplatin
- TIP = Paclitaxel/ifosfamide/cisplatin
- VeIP = Vinblastine/ifosfamide/cisplatin
- VIP = Etoposide/ifosfamide/cisplatin
### FOLLOW-UP FOR NONSEMINOMA

#### Table 1  Follow-Up for Stage IA, IB on Surveillance Only

<table>
<thead>
<tr>
<th>Year</th>
<th>Months between H&amp;P, markers, chest x-ray</th>
<th>Months between abdominal CT</th>
</tr>
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<tbody>
<tr>
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<td>5</td>
<td>6</td>
<td>12</td>
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<td>6+</td>
<td>12</td>
<td>12-24</td>
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</table>

#### Table 2  Follow-Up After Complete Response to Chemotherapy and RPLND

<table>
<thead>
<tr>
<th>Year</th>
<th>Months between H&amp;P, markers, chest x-ray (category 2B for chest x-ray frequency)</th>
<th>Months between abdominal/pelvic CT</th>
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<tr>
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<td>5</td>
<td>6-12</td>
<td>12</td>
</tr>
<tr>
<td>6+</td>
<td>12</td>
<td>As clinically indicated</td>
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#### Table 3  Follow-Up After RPLND Only

<table>
<thead>
<tr>
<th>Year</th>
<th>Months between H&amp;P, markers, chest x-ray (category 2B for chest x-ray frequency)</th>
<th>Months between abdominal/pelvic CT</th>
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<td>5</td>
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</tr>
<tr>
<td>6+</td>
<td>12</td>
<td>As indicated</td>
</tr>
</tbody>
</table>

Recurrence, See Second-Line Therapy (page 512)
Examples of systems used to estimate prognosis are:


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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

General Principles
- Modern radiotherapy involves smaller fields and lower doses than were used in the past. References are provided to support current recommended management.
- Risk-adapted management using tumor size > 4 cm and rete testis invasion for stage I seminoma is discouraged. This is based on a validation study in 2010, which revealed that tumor size > 4 cm and rete testis invasion were not predictors of relapse.1,2
- Linear accelerators with > 6 MV photons should be used when possible.
- The mean dose (Dmean) and dose delivered to 50% of the volume (D50%) of the kidneys, liver, and bowel are lower with CT-based anteroposterior-posteroanterior (AP-PA) 3-dimensional conformal radiation therapy (3D-CRT) than intensity-modulated radiation therapy (IMRT).3 As a result, the risk of second cancers arising in the kidneys, liver, or bowel may be lower with 3D-CRT than IMRT, and IMRT is not recommended.4
- Timing of radiotherapy:
  - Radiotherapy should start within 7 weeks after orchiectomy.
  - Patients should be treated 5 days per week.
  - Patients who miss a fraction should be treated to the same total dose and with the same fraction size, extending the overall treatment time slightly.
  - Antiemetic medication significantly improves nausea. See NCCN Clinical Practice Guidelines (NCCN Guidelines) in Oncology for Antiemesis (available in this issue and online at www.NCCN.org). Antiemetic prophylaxis is encouraged at least 2 hours before each treatment, and some cases may require more frequent dosing.

Preparation for Radiotherapy
- A discussion of semen analysis and sperm banking before orchiectomy is recommended in patients who wish to preserve fertility.5,6 If sperm banking is desired, it should be performed before imaging and the delivery of adjuvant therapy.

Treatment Planning Principles
- A noncontrast CT simulation should be performed with the patient supine, arms at his sides, in the treatment position.
  - Immobilization with a cast may be used to improve the reproducibility of patient setup.
  - All patients, with the exception of those who have undergone bilateral orchiectomy, should be treated with a scrotal shield. The legs should be separated by a rolled towel of approximately the same diameter as the scrotal shield and its stand.
PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Stage I

- **Dose:** For stages IA, IB, and IS, a total dose of 20.0 Gy (midplane) in 10 daily 2.0-Gy fractions is recommended for the minority of patients who prefer adjuvant treatment realizing that there is a high likelihood of salvage should a relapse occur during surveillance.\(^9\)
- **Para-aortic (PA) strip fields**\(^10\) - field arrangement:
  - In patients with no history of pelvic or scrotal surgery, para-aortic strip irradiation may be delivered with opposed AP-PA fields. The weights of the fields may be equal.
  - Recent nodal mapping studies suggest that fields should target the retroperitoneal lymph nodes but not necessarily the ipsilateral renal hilar nodes (see lateral borders).\(^11,12\)
  - **Superior and inferior borders:** borders may be determined by bony anatomy.
    - The superior border should be placed at the bottom of vertebral body T11.\(^13\)
    - The inferior border should be placed at the inferior border of vertebral body L5.\(^10,14\)
  - **Lateral borders:**
    - Conventionally, PA strip fields are approximately 10 cm wide, encompassing the tips of the transverse processes of the para-aortic vertebrae.
    - The location of the kidneys within the PA strip fields varies from patient to patient.
      - For patients whose kidneys are relatively medial, small renal blocks may be added at the level of T12. The right and left kidney D50% should be ≤ 8 Gy (i.e., no more than 50% of each kidney can receive 8 Gy or higher).\(^3\)
      - If only one kidney is present, the kidney D15% should be ≤ 20 Gy (i.e., no more than 15% of the volume of the kidney can receive 20 Gy or higher).\(^3\)
      - An alternative 3D-CRT planning technique is to base the lateral borders on vascular structures on a treatment planning CT scan without contrast. The aorta and inferior vena cava may be contoured on the CT scan; one should allow a 1.2- to 1.9-cm margin on the aorta and inferior vena cava to include the para-aortic, paracaval, interaortocaval, and preaortic nodes in the clinical target volume.\(^11,15\) The planning target volume is then established by uniformly expanding the clinical target volume by 0.5 cm in all directions to account for treatment setup errors.\(^16\) A uniform 0.7-cm margin should be provided on the planning target volume to the block edge to take beam penumbra into account (Figure 1, see page 516).\(^3\)

Special Considerations

- **Ipsilateral pelvic surgery** (e.g., inguinal herniorrhaphy or orchiopexy) may alter the lymphatic drainage of the testis. As a result, irradiation of the ipsilateral iliac and inguinal lymph nodes, including the surgical scar from prior surgery, has been advocated even in stage I patients.\(^12,17\) Given the large volume of tissue that would be irradiated and the resulting increased risks of late effects, other management approaches are recommended for these patients.
PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Stage IIA-B

* For clinical stage IIA-B patients, treatment is delivered in 2 consecutive AP-PA phases (modified dog-leg fields and cone down). There is no break between the 2 phases.

* Modified dog-leg fields:
  - Dose: the initial phase consists of treatment of modified dog-leg fields to 20.0 Gy (midplane) in 10 daily 2.0-Gy fractions or 25.5 Gy in 15 daily 1.7-Gy fractions.
  - Target: the fields should include the retroperitoneal and proximal ipsilateral iliac lymph nodes.

* Cone Down:
  - Dose: the second phase (cone down) of the radiotherapy consists of daily 2-Gy fractions to a cumulative total dose of approximately 30 Gy for stage IIA and 36 Gy for stage IIB.
  - Target: the nodal mass (gross tumor volume) must be contoured. A uniform, 2-cm margin from the gross tumor volume to block edge should be provided for the AP-PA cone down fields (Figure 3, see page 516).
PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Figure 1

Figure 2

Figure 3

References

## Testicular Cancer Version 1:2012

### RISK CLASSIFICATION FOR ADVANCED DISEASE
(postorchietomy)\(^1\)

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Nonseminoma</th>
<th>Seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good Risk</strong></td>
<td>Testicular or retroperitoneal primary tumor and</td>
<td>Any primary site and</td>
</tr>
<tr>
<td></td>
<td>No nonpulmonary visceral metastases and</td>
<td>No nonpulmonary visceral metastases and</td>
</tr>
<tr>
<td></td>
<td>Postorchietomy markers - all of:</td>
<td>Normal AFP and</td>
</tr>
<tr>
<td></td>
<td>AFP &lt; 1,000 ng/mL</td>
<td>Any HCG</td>
</tr>
<tr>
<td></td>
<td>HCG &lt; 5,000 IU/L</td>
<td>Any LDH</td>
</tr>
<tr>
<td></td>
<td>LDH &lt; 1.5 x upper limit of normal</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate Risk</strong></td>
<td>Testicular or retroperitoneal primary tumor and</td>
<td>Any primary site and</td>
</tr>
<tr>
<td></td>
<td>No nonpulmonary visceral metastases and</td>
<td>No nonpulmonary visceral metastases and</td>
</tr>
<tr>
<td></td>
<td>Postorchietomy markers - any of:</td>
<td>Normal AFP and</td>
</tr>
<tr>
<td></td>
<td>AFP 1,000-10,000 ng/mL</td>
<td>Any HCG</td>
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<tr>
<td></td>
<td>HCG 5,000-50,000 IU/L</td>
<td>Any LDH</td>
</tr>
<tr>
<td></td>
<td>LDH 1.5-10 x upper limit of normal</td>
<td></td>
</tr>
<tr>
<td><strong>Poor Risk</strong></td>
<td>Mediastinal primary tumor or</td>
<td>No patients classified as poor prognosis</td>
</tr>
<tr>
<td></td>
<td>Nonpulmonary visceral metastases or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postorchietomy markers - any of :</td>
<td></td>
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<tr>
<td></td>
<td>AFP &gt; 10,000 ng/mL</td>
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<tr>
<td></td>
<td>LDH &gt; 10 x upper limit of normal</td>
<td></td>
</tr>
</tbody>
</table>


\(^1\)Markers used for risk classification are postorchietomy.
PRIMARY CHEMOTHERAPY REGIMENS FOR GERM CELL TUMORS

EP
Etoposide, 100 mg/m² IV on days 1-5
Cisplatin, 20 mg/m² IV on days 1-5
Repeat every 21 days¹

BEP
Etoposide, 100 mg/m² IV on days 1-5
Cisplatin, 20 mg/m² IV on days 1-5
Bleomycin, 30 units IV weekly on days 1, 8, and 15 or days 2, 9, 16
Repeat every 21 days²

VIP
Etoposide, 75 mg/m² IV on days 1-5
Mesna, 1200 mg/m² IV continuous infusion on days 1-5
Ifosfamide, 1200 mg/m² on days 1-5
Cisplatin, 20 mg/m² IV on days 1-5
Repeat every 21 days³

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/m² IV every 8 h on days 1-5
Ifosfamide, 1200 mg/m² IV on days 1-5
Cisplatin, 20 mg/m² IV on days 1-5

Repeat every 21 days¹

TIP
Paclitaxel, 250 mg/m² IV on day 1
Ifosfamide, 1500 mg/m² IV on days 2-5
Mesna, 500 mg/m² IV before ifosfamide, and then 4 and 8 h after each ifosfamide dose on days 2-5
Cisplatin, 25 mg/m² IV on days 2-5

Repeat every 21 days²

High-dose chemotherapy regimens

VeIP
Carboplatin, 700 mg/m² (body surface area) IV
Etoposide, 750 mg/m² IV
Administer 5, 4, and 3 days before peripheral blood stem cell infusion for 2 cycles³

Paclitaxel, 200 mg/m² IV over 24 h on day 1
Ifosfamide, 2000 mg/m² over 4 h with mesna protection on days 2-4
Repeat every 14 days for 2 cycles followed by
Carboplatin, AUC 7-8 IV over 60 min days 1-3
Etoposide, 400 mg/m² IV days 1-3
Administer with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles⁴

Palliative chemotherapy regimens*

Gemcitabine/oxaliplatin
Gemcitabine/paclitaxel
Gemcitabine/paclitaxel/oxaliplatin

*Please see references below for dosing.

GemOx
Paclitaxel/gemcitabine
Gemcitabine/oxaliplatin/paclitaxel

PRINCIPLES OF SURGERY

• RPLND is the standard approach to the surgical management of nonseminoma germ cell tumor (NSGCT) in both primary and postchemotherapy 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.

Postchemotherapy setting

• Referral to high-volume centers should be considered for surgical resection of masses postchemotherapy.

• Completeness of resection is an independent and consistent predictive variable of clinical outcome. In postchemotherapy RPLND, surgical margins should not be compromised in an attempt to preserve ejaculation. Additional procedures and resection of adjacent structures may be required.

• Postchemotherapy RPLND is indicated in patients with metastatic NSGCT with a residual retroperitoneal mass after systemic chemotherapy and normalized postchemotherapy serum tumor markers.

• A full bilateral template RPLND should be performed in all patients undergoing RPLND in the postchemotherapy setting, with the boundaries of dissection being the renal hilar vessels (superiorly), ureters (laterally), and the common iliac arteries (inferiorly).
An elevated serum concentration of \( \beta \)-HCG, which has a half-life of approximately 1 to 3 days, may also be present with seminomatous and nonseminomatous tumors. The elevations of \( \beta \)-HCG must be interpreted with caution, because hypogonadism and marijuana use may cause benign serum elevations of \( \beta \)-HCG.

Nonseminoma is the more clinically aggressive tumor. When both 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% 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.

**Diagnosis and Workup**

If an intratesticular mass is identified, complete blood count, creatinine, electrolytes, and liver enzymes should be obtained. Further evaluation includes measurement of serum tumor markers and a chest radiograph. Testicular ultrasound serves to confirm the presence of a testicular mass and to explore the contralateral testis; it is sensitive and has an important role in determining whether a mass is intra- or extratesticular.

Serum tumor markers are critical in assignment of prognosis and also management during treatment. Serum tumor markers are prognostic factors and contribute to diagnosis and staging. Markers are assessed before orchiectomy and repeated after orchiectomy. Elevated values of \( \beta \)-HCG, LDH, or AFP should be followed up with repeated tests to allow precise staging.

**Risk Classification for Advanced Disease**

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 postorchiectomy. Postorchiectomy markers are used to classify the patient according to the IGCCCG risk classification. This classification categorizes patients with pure seminoma and nonseminoma GCT into good-, intermediate-, or poor-risk groups.

Stage and risk classification are assigned according to the American Joint Committee on Cancer (AJCC) and IGCCCG classification.
Pure Seminoma

If a GCT is found, an abdominopelvic CT scan is performed. Abdominopelvic CT scanning is used to assess the retroperitoneal nodes. A chest CT is indicated if the abdominopelvic CT shows retroperitoneal adenopathy or the chest radiograph shows abnormal results. A chest CT scan is a sensitive way to evaluate the thorax and mediastinal nodes.

The panel members recommend a brain MRI or bone scan only if metastases to these organs is suspected.

Elevated values of β-HCG, LDH, or AFP should be followed up with repeated tests. Serum concentrations of β-HCG and LDH may be elevated in patients with seminoma. An elevated AFP level indicates nonseminoma, and patients should be managed accordingly. Initial management of pure seminoma involves a radical inguinal orchiectomy. Orchiectomy is both diagnostic and therapeutic. Patients with seminoma arising from an extragonadal site, such as the mediastinum, are treated with standard chemotherapy regimens according to risk status.

Pure Seminoma Stages IA and IB

Primary Treatment for Pure Seminoma Stages IA and IB: For patients with stages IA and IB pure seminoma, the standard treatment options after initial orchiectomy include surveillance, radiotherapy, or chemotherapy with 1 or 2 cycles of carboplatin. The disease-specific survival for stage I disease is 99%, irrespective of the management strategy used. Several prospective nonrandomized studies of surveillance have been conducted. The relapse rate seen in these studies is 15% to 20% at 5 years, and most of the relapses are first detected in infradiaphragmatic lymph nodes. Some studies report tumor size greater than 4 cm and rete testis invasion as risk factors for relapse. However, a validation study by Chung et al. showed that tumor size greater than 4 cm and rete testis invasion were not predictors of relapse. Therefore, the panel members discourage risk-adapted management based on tumor size greater than 4 cm and rete testis invasion for stage I pure seminoma. Surveillance is listed as the preferred option (category 1) for patients with pT1 and pT2 disease.

If surveillance is not applicable, alternatives are either adjuvant carboplatin or adjuvant radiotherapy, as described later. Each approach has distinct advantages and disadvantages. The physicians should discuss these with the patients and their families and pick the best approach on a case-by-case basis.

Oliver et al. reported on the results of a trial that randomized 1477 patients with stage I testicular cancer to undergo either radiotherapy or one injection of carboplatin. In the study, carboplatin (area under the curve [AUC] = 7) was administered intravenously. The dose was calculated by the formula 7 × (glomerular filtration rate [GFR, mL/min] + 25 mg). With a median follow-up of 4 years, the relapse-free survival rates were similar for both groups. Late relapses and secondary GCTs can occur beyond 5 and 10 years. Therefore, the investigators continued to follow these patients. The updated results reported noninferiority of single-dose carboplatin versus radiation therapy. 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). Two cases of contralateral GCTs were seen in the carboplatin arm versus 15 in the radiation therapy arm, with hazard ratio of 0.22; the contralateral GCT-free rates at 5 years are 99.8% and 98.8%, respectively. The authors concluded that a single dose of carboplatin is less toxic and as effective in preventing disease recurrence as adjuvant radiotherapy in men with stage I pure seminoma after orchiectomy. Two courses of adjuvant carboplatin have also been reported to reduce the relapse rate. The panel recommends either 1 or 2 cycles of carboplatin AUC × 7 as a category 1 recommendation for patients with stages IA and IB pure seminoma.

If radiation therapy is delivered, the panel recommends a total dose of 20 Gy (midplane) in 10 daily 2.0-Gy fractions, given to an infradiaphragmatic area, including para-aortic lymph nodes; in special circumstances, this area may include the ipsilateral ilioinguinal nodes. Patients for whom radiation therapy is generally not given include those at higher risk for morbidity from radiation therapy, such as those with a history of pelvic surgery. Prophylaxis to the mediastinum is not provided, because relapse rarely occurs at this site. For patients with stages IA and IB pure seminoma, adjuvant radiation therapy to include the para-aortic nodes is also a category 1 recommendation, although active surveillance is preferred (see Principles of Radiotherapy for Pure Testicular Seminoma, pages 513–516).
Follow-Up After Primary Treatment for Pure Seminoma Stages IA and IB: For follow-up, the different risk of recurrence associated with each treatment modality is important to distinguish (surveillance vs. adjuvant therapy). An analysis of more than 5000 patients with stage 1 seminoma from various trials showed that, independent of the treatment modality, the risk of recurrence is highest in the first 2 years and decreases after that.33

Follow-up during surveillance includes a history and physical, with measurement of postorchiectomy serum tumor markers (AFP, β-HCG, and LDH), performed every 3 to 4 months for 1 to 2 years, every 6 to 12 months for years 3 to 4, and annually thereafter.34,35 Controversy exists regarding how many imaging studies must be performed in patients on active surveillance. The panel recommends abdominal/pelvic CT every 6 months for years 1 to 2, every 6 to 12 months for year 3, and then annually for years 4 to 5. The most common site of relapse in patients managed with surveillance or adjuvant chemotherapy is the retroperitoneal nodes. Chest radiographs may be obtained as clinically indicated for years 1 to 5. The clinical trial TRISST (MRC TE24/Trial of Imaging and Schedule in Seminoma Testis) in the United Kingdom is currently studying whether a reduced CT schedule or MRI could be used as a safe and effective alternative to standard CT-based surveillance in the management of stage I seminoma.16

The risk of recurrence 5 years after adjuvant treatment is less than 0.3% annually.13 Follow-up of patients treated with carboplatin includes a history and physical, with measurement of postorchietomy serum tumor markers (AFP, β-HCG, and LDH) performed every 3 months the first year, every 4 months the second year, every 6 months the third year, and annually thereafter.

The panel recommends abdominal/pelvic CT annually for the first 3 years after radiotherapy or carboplatin. In a recently published meta-analysis of 2466 patients, Mead et al.16 reported that recurrence rarely occurred after more than 3 years from treatment with either radiotherapy or carboplatin. Relapse occurred after 3 years only in 4 of the 2466 patients (0.2%).16 They recommend that CT scans of the pelvis and chest can be omitted in these patients as part of routine follow-up. The panel recommends that chest radiographs be obtained only as clinically indicated.

Follow-up of patients treated with radiotherapy includes a history and physical, with measurement of postorchiectomy serum tumor markers (AFP, β-HCG, and LDH). Follow-up should be performed every 4 months for 1 to 2 years, and then annually for 3 to 10 years.33 Para-aortic radiation therapy is recommended when patients with stage I seminoma are irradiated (see pages 513–516). Patients treated with para-aortic radiation therapy have a slightly higher rate of pelvic relapse than those treated with “dog-leg” radiograph.30,31,37,38 Some NCCN Member Institutions obtain a CT scan of the pelvis only every 6 months for 3 years after para-aortic radiotherapy. Others obtain CT scans of the pelvis and abdomen annually for 3 years.30 The panel’s consensus recommendation is for abdominal and pelvic CT scans annually for 3 years in patients treated with para-aortic radiotherapy. Chest radiographs should be obtained only when clinically indicated. Recurrences are treated according to the stage at relapse.16

Pure Seminoma Stage IS
Primary Treatment for Pure Seminoma Stage IS: According to the AJCC definition, stage IS requires persistent elevation of serum tumor markers (LDH, AFP, and β-HCG) after orchiectomy. Stage IS is uncommon and patients are generally treated with radiation to an infradiaphragmatic area, including para-aortic lymph nodes with or without radiation to the ipsilateral ilioinguinal nodes.30–32

Follow-Up After Primary Radiation Treatment for Pure Seminoma Stage IS: Follow-up recommendations by the panel for patients with stage IS treated with adjuvant radiation therapy are similar to those for patients with stages IA and IB treated with adjuvant radiation therapy. Recurrences are treated according to the stage at relapse.

Pure Seminoma Stages IIA and IIB
Primary Treatment for Pure Seminoma Stages IIA and IIB: Stage IIA is defined as metastatic disease to lymph nodes, with a lymph node mass measuring less than 2 cm in diameter in greatest dimension on CT scan, whereas stage IIB is disease measuring 2 to 5 cm in maximum diameter.

Radiotherapy has been the mainstay of treatment in patients with stage IIA and IIB seminoma.39–41 The standard radiation field compared with stage I is extended from the para-aortic region to
include an ipsilateral iliac field. The relapse rates are moderate (5%–6% for stage IIA) and overall survival is almost 100%.39,41,42

For patients with stage IIA or IIB seminoma, the panel recommends radiation therapy to an infradiaphragmatic area, including para-aortic and ipsilateral iliac lymph nodes in 2 anteroposterior–posteroanterior phases. The initial phase consists of radiation to modified dog-leg fields at a dose of 20 Gy (midplane) in 10 daily 2.0-Gy fractions39 or 25.5 Gy in 15 daily 1.7-Gy fractions.43 The panel prefers modified ‘dog-leg’ fields as described by Classen et al.39 For details on field arrangement, see pages 513–516. The second phase (cone down) of radiotherapy consists of daily 2.0-Gy fractions to a cumulative total dose of approximately 30 Gy for stage IIA and 36 Gy for stage IIB.39 As with the management of stage I disease, prophylactic mediastinal radiation therapy is not indicated for stage II disease.44

For selected patients with stage IIB seminoma, such as those with adenopathy measuring more than 3 cm,45 chemotherapy with 4 courses of etoposide and cisplatin (EP) or 3 cycles of bleomycin, etoposide, and cisplatin (BEP) is an alternative to radiotherapy.42,46

**Follow-Up for Stages IIA and IIB Pure Seminoma After Primary Treatment:** The recommended follow-up schedules for patients with stage IIA/B seminoma after radiation therapy include a history and physical, with measurement of postorchiectomy serum tumor markers (AFP, β-HCG, and LDH) performed every 3 months for year 1, every 6 months for years 2 to 5, and then annually for years 6 to 10.

Chest radiograph is recommended every 6 months for the first 2 years. An abdominal CT scan is recommended every 6 months in years 1 to 2 and annually in year 3 after radiotherapy. In patients who have undergone retroperitoneal lymph node dissection (RPLND), it is recommended between 3 to 6 months postsurgery and then as clinically indicated.39

The follow-up of patients with stage IIB seminoma after chemotherapy is similar to follow-up after chemotherapy for patients with stages IIC and III seminoma, as discussed in Follow-Up for Pure Seminoma Stages IIB, IIC, and III After Chemotherapy on page 525.

**Pure Seminoma Stages IIC and III**

**Primary Treatment for Pure Seminoma Stages IIC and III:** Patients with stage IIC or III disease are those considered at either good or intermediate risk. All stage IIC and stage III seminoma is considered good-risk disease, except for stage III disease with nonpulmonary visceral metastases (e.g., bone, liver, brain), which is considered intermediate-risk. Standard chemotherapy is used for both groups of patients. However, for patients with good risk, 3 cycles of BEP47–49 or 4 cycles of EP50–52 are recommended. In contrast, more intensive chemotherapy (i.e., 4 cycles of BEP) is recommended for those with intermediate-risk disease.53,54 All of these chemotherapy options are category 1 recommendations according to the panel.

**Postchemotherapy Management of Pure Seminoma Stages IIB, IIC, and III:** After initial chemotherapy, patients with stage IIB, IIC, and III disease 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 normal markers and either no residual mass or residual mass of 3 cm or less need no further treatment. They should undergo surveillance, as discussed in Follow-Up for Pure Seminoma Stages IIB, IIC, and III After Chemotherapy, on page 525.

In cases of residual tumor larger than 3 cm and marker levels that are normal, a PET scan is recommended to assess whether residual viable tumor is present.53 A PET scan has high positive and negative predictive values with regard to the question of remaining disease in patients with residual masses after chemotherapy.56 To reduce the incidence of false-positive results, the PET scan is typically performed at least 6 weeks after completion of chemotherapy. Notably, granulomatous disease, such as sarcoid, is a source of false-positive results. The panel recommends a PET scan in patients with seminoma, a residual mass larger than 3 cm, and normal levels of markers, approximately 6 weeks after chemotherapy to determine whether to continue with surveillance or resume treatment.55,57–61

If the PET scan is negative, no further treatment is needed; however, the patient should undergo follow-up,62,63 as discussed in the next section on Follow-Up for Pure Seminoma Stages IIB, IIC, and III After Chemotherapy.

Because a positive PET scan is a strong indicator of residual active tumor, resection should be considered. Therefore, if technically feasible, RPLND may be considered (category 2A). The other option, if re-
section is not feasible, is second-line chemotherapy (category 2A). Cisplatin-based combination chemotherapy is used for second-line treatment. The regimens are 4 cycles of TIP (paclitaxel, ifosfamide, cisplatin) or 4 cycles of VelP (vinblastine, ifosfamide, cisplatin).

According to these NCCN Guidelines, second-line therapy for seminoma and nonseminoma is similar. This is discussed in Second-Line Therapy for Metastatic GCTs, on page 528. The follow-up of these patients is also described later.

**Follow-Up for Pure Seminoma Stages IIB, IIC, and III After Chemotherapy:** Recommended follow-up schedules include a history and physical with chest radiograph and measurement of postorchiectomy serum tumor markers every 2 months for the first year, every 3 months for the second year, every 6 months for the third and fourth years, and annually thereafter through the tenth year. An abdominal/pelvic CT scan is recommended as clinically indicated in all patients, except those who have undergone RPLND, in whom it is recommended between 3 and 6 months postsurgery and then as clinically indicated. A PET scan may be performed as clinically indicated.

### Nonseminoma

Similar to the workup for seminoma, if nonseminoma is found, CT of the abdomen and pelvis should be performed with chest imaging if needed. MRI of the brain and a bone scan should be conducted in the case of clinical indicators (symptoms) of involvement. PET scanning does not contribute and routine use is not recommended for patients with nonseminoma.

Elevated values of β-HCG, LDH, or AFP should be followed up with repeated tests. Nonseminoma includes mixed seminoma tumors and seminoma histology with elevated AFP. Postorchiectomy serum markers are important for classifying patients with nonseminoma into good-, intermediate- and poor-risk groups according to the IGCCCG risk classification.

In patients of reproductive age, sperm banking must be discussed before any therapeutic intervention is performed that may compromise fertility, including surgery, radiation therapy, or chemotherapy. If sperm banking is desired, it may be performed either before or after orchiectomy, but certainly before adjuvant therapy.

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.

### Nonseminoma Stage IA

**Primary Treatment of Nonseminoma Stage IA:** According to the panel, 2 management options exist for patients with stage IA disease after orchiectomy: surveillance and nerve-sparing RPLND. The cure rate with either approach exceeds 95%, although with surveillance, this depends on adherence to periodic follow-up examinations and subsequent chemotherapy for the 20% to 30% of patients who experience relapse. Patients who choose surveillance should agree to be compliant with follow-up. RPLND should be performed using a nerve-sparing technique. According to these guidelines, the nerve-sparing RPLND is recommended within 4 weeks of a CT scan and within 7 to 10 days of repeat serum marker testing to ensure accurate presurgical staging.

**Management of Nonseminoma Stage IA After RPLND:** After RPLND, if the dissected lymph nodes are not involved with a tumor (pN0), no adjuvant chemotherapy is given and the patients should undergo surveillance. However, if the resected lymph nodes involve tumor, the decision whether to use adjuvant chemotherapy is based on the degree of nodal involvement. Surveillance is preferred over chemotherapy for patients with pN1 disease. Chemotherapy is preferred in patients with pN2 or pN3 disease. Surveillance is an option for patients with pN2 but not those with pN3 disease. Recommended chemotherapy regimens include either EP or BEP. Two cycles of either regimen (EP or BEP) are recommended for patients with pN1 or pN2 disease. For patients with pN3 disease, longer courses of chemotherapy with 4 cycles of EP or 3 cycles of BEP is recommended.

**Follow-Up for Nonseminoma Stage IA:** In the current guidelines, the long-term follow-up tests for patients with stage IA disease electing primary surveillance or who have undergone RPLND or chemotherapy include serum marker assessment, chest ra-
diograph, and an abdominal CT scan. The frequency of these tests is outlined in Follow-Up for Nonseminoma, page 511.

**Nonseminoma Stage IB**

**Primary Treatment of Nonseminoma Stage IB:** After orchiectomy, either nerve-sparing RPLND or adjuvant chemotherapy is an option to reduce the risk of relapse in patients with stage IB disease.

Several studies using 2 cycles of BEP as primary treatment for patients with stage I nonseminoma have reported relapse-free survival in more than 95% of patients, leading the panel to consider this approach a category 2A recommendation. Late consequences of cisplatin-based chemotherapy have been reported based on long-term follow-up of patients. A trial by Albers et al. randomized patients with stage I disease after orchiectomy to undergo unilateral RPLND (n = 191) or one adjuvant course of BEP (n = 191). After a median follow-up of 4.7 years, 2 relapses were reported in the group of patients treated with one course of adjuvant BEP and in 13 patients with relapse in the arm treated with RPLND (P = .0011). This study indicates that one course of BEP is active, and could be an option in patients unable to tolerate the toxicity of treatment. The comparator arm in this trial (unilateral RPLND) is not the standard treatment approach. Therefore, although the results of this study are promising, this approach merits further investigation comparing 1 cycle of BEP versus 2 cycles with longer follow-up. The panel considers 1 cycle of BEP a category 2B option as primary therapy.

Surveillance alone may be offered to selected patients with T2 disease (category 2B). Vascular invasion is a significant predictor of relapse when orchiectomy is followed by surveillance alone. 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. When surveillance is opted in selected patients with T2 disease, both the patient and physician must be compliant with follow-up recommendations.

**Management of Nonseminoma Stage IB After Primary Treatment:** The adjuvant treatment after primary nerve-sparing RPLND for patients with IB disease is similar to that described for stage IA in Management of Nonseminoma Stage IA After RPLND, page 525.

Management of primary chemotherapy in patients with normal values of serum tumor markers may be nerve-sparing RPLND or surveillance. The panel considers nerve-sparing bilateral RPLND a category 2A recommendation for patients with residual mass of 1 cm or greater and a category 2B recommendation if the residual mass is smaller than 1 cm. Surveillance is category 2B for both populations. In the current guidelines, the long-term follow-up tests for patients electing surveillance include serum marker assessment, chest radiograph, and abdominal CT scan. The frequency of these tests is outlined in Follow-Up for Nonseminoma, on page 511.

**Nonseminoma Stage IS**

Patients with stage IS disease exhibit a persistent elevation of serum tumor markers postorchiectomy but no radiographic evidence of disease. The elevated levels of AFP and β-HCG after orchiectomy must be interpreted with caution, because these may be from causes other than disseminated nonseminoma, such as hepatobiliary disease, marijuana use, and hypogonadism.

**Primary Treatment of Nonseminoma Stage IS:** The panel consensus recommendation is that these patients be treated with standard chemotherapy with either 4 cycles of EP or 3 cycles of BEP. Either regimen is preferable to initial RPLND, because these patients nearly always have disseminated disease.

**Management of Stage IS Nonseminoma Postprimary Treatment:** The management of patients with stage IS nonseminoma after primary treatment with chemotherapy is similar to the management schema outlined for patients with good-risk nonseminoma, including stages IIB, IIC, and IIIA, described in the following sections.

**Nonseminoma Stage IIA**

**Primary Treatment of Nonseminoma Stage IIA:** Treatment for patients with stage IIA nonseminoma depends on postorchiectomy serum tumor marker levels.

For patients with stage IIA disease and normal postorchiectomy levels of AFP and β-HCG, the panel considers either primary RPLND (category 2A) or chemotherapy (category 2B) as treatment options. The chemotherapy regimens include 4 cycles of EP or 3 cycles of BEP. Chemotherapy is considered particularly appropriate if the patient has multifocal disease.
For patients with persistently elevated AFP or β-HCG levels, the panel recommends induction chemotherapy, based on data from 2 retrospective studies of patients with low-stage nonseminoma treated with RPLND.\textsuperscript{105,106} The presence of elevated postorchietomy AFP or β-HCG levels was associated with a high risk of relapse.\textsuperscript{105,106}

Management after primary chemotherapy and RPLND is discussed in the following sections.

**Management After Primary Treatment of Nonseminoma Stage IIA:** After primary chemotherapy, subsequent management depends on marker levels and the residual mass on CT scan. Therefore, patients must undergo a CT scan before treatment is decided. Lesions smaller than 1 cm on CT scan may represent false-positives and must be interpreted with caution. The options listed by the panel for managing patients with stage IIA disease after primary chemotherapy include nerve-sparing bilateral RPLND or surveillance.

The panel considers nerve-sparing bilateral RPLND a category 2A recommendation for patients with a residual mass of 1 cm or greater, and a category 2B recommendation if the residual mass is less than 1 cm. A bilateral RPLND involves removal of lymphatic tissue between both ureters, spanning from the diaphragmatic crus to the bifurcation of the common iliac arteries. The rationale for this extended region of dissection is the greater likelihood of bilateral disease with greater tumor burden.\textsuperscript{107} Referral to high-volume centers must be considered for RPLND postchemotherapy. Surveillance, however, is a category 2B recommendation for both populations.

After primary nerve-sparing RPLND, treatment options include either surveillance or chemotherapy. The treatment choice depends on the number of positive lymph nodes identified. For example, because RPLND is likely a curative procedure in patients with pathologic stage N0 (pN0), surveillance is the only option listed for this group. Surveillance and chemotherapy are options for patients with pN1 and pN2 disease. RPLND is a curative procedure in 60% to 90% of patients with pN1 disease,\textsuperscript{106,108,109} and therefore the panel prefers surveillance over chemotherapy for these patients. The risk of relapse in patients with pN2 through pN3 disease is greater than 50%.\textsuperscript{106,108,110} With 2 cycles of adjuvant cisplatin-based chemotherapy, the risk of relapse after RPLND is generally less than 1%\textsuperscript{106,111,112} The panel prefers 2 cycles of adjuvant chemotherapy for pN2 disease, and full-course chemotherapy (not surveillance) is recommended for pN3 disease. Recommended adjuvant chemotherapy regimens for pN1 and pN2 disease consists of 2 cycles of either BEP or EP,\textsuperscript{111} resulting in a relapse-free survival rate of nearly 100%. For pN3, the panel recommends a longer chemotherapy course consisting of either 4 cycles of EP or 3 cycles of BEP.

If patients with stage IIB disease have persistent marker elevation (i.e., stage IIA, S1), the primary treatment is chemotherapy as described later for good-risk nonseminoma.

**Nonseminoma Stage IIB**

**Primary Treatment of Nonseminoma Stage IIB:** Treatment for patients with stage IIB nonseminoma depends also on both postorchietomy 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), 2 management options are available. One option is to perform nerve-sparing RPLND and consider adjuvant treatment as described for patients with stage IIA disease. The second option is to treat with primary chemotherapy involving either 4 cycles of EP or 3 cycles of BEP, followed by 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.\textsuperscript{101} The reported relapse-free survival with either approach is close to 98%.\textsuperscript{108,111–118}

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), chemotherapy is recommended with either 4 cycles of EP or 3 cycles of BEP, followed by nerve-sparing RPLND or surveillance.

For patients with stage IIB disease with persistent marker elevation (stage IIB, S1), the primary treatment is chemotherapy as described for good-risk nonseminoma, including stages IS, IIC, and IIIA in later sections. Initial RPLND is not recommended in this situation.

**Management After Primary Treatment of Nonseminoma Stage IIB:** The management of patients with stage IIB nonseminoma after primary treatment with
either nerve-sparing bilateral RPLND or chemotherapy is similar to the management scheme outlined earlier for patients with stage IIA nonseminoma after primary treatment.

**Advanced Metastatic Nonseminoma**

The preferred primary chemotherapy regimens for patients with advanced disease depends on the IGCCCG risk classification. This classification categorizes patients as good-, intermediate-, or poor-risk. Also, patients with an extragonadal primary site, whether retroperitoneal or mediastinal, are treated with initial chemotherapy.

**Primary Treatment of Good-Risk Nonseminoma:**

Based on the IGCCCG good-risk classification, this group includes patients with stages IS; IIA and IIB (with persistent marker elevation); IIC; and IIA disease. Treatment for good-risk GCTs was designed to decrease toxicity while maintaining maximal efficacy. Randomized clinical trials showed that this can be achieved through either substituting etoposide for bleomycin, or eliminating or reducing the dose of bleomycin. Currently, 2 regimens are recommended by the panel: 4 cycles of EP or 3 cycles of BEP (both category 2A). Either regimen is well tolerated and cures approximately 90% of patients with good risk.

**Primary Treatment of Intermediate-Risk (Stage IIB) Nonseminoma:**

For patients with intermediate risk (stage IIB), the cure rate is approximately 70% with standard therapy using 4 cycles of BEP, and this is a category 2A recommendation by the panel.

**Primary Treatment of Poor-Risk (Stage IICC) Nonseminoma:**

Between 20% and 30% of all patients with poor-risk, (stage IICC) metastatic GCTs are not cured with conventional cisplatin therapy, and fewer than one-half experience a durable complete response with 4 cycles of BEP, and therefore the panel lists treatment in a clinical trial as the preferred option.

The standard chemotherapy regimen for poor-risk patients is 4 cycles of BEP. The regimen containing etoposide, ifosfamide, and cisplatin (VIP) was compared with BEP and found to be more toxic than BEP but equally as effective. Therefore, 4 cycles of VIP may be used for patients who may not tolerate bleomycin.

**Postchemotherapy Management for Good-, Intermediate-, and Poor-Risk 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. The frequency of these tests is outlined in Follow-Up for Nonseminoma, on page 511.

If a complete response to chemotherapy is found through radiographic imaging and the tumor markers are negative, the panel lists 2 management options: surveillance (category 2B) or bilateral RPLND using nerve-sparing technique, if possible (category 2B). If only necrotic debris or mature teratoma is encountered, no further therapy is necessary and patients must be put under surveillance. If embryonal, yolk sac, choriocarcinoma, or seminoma elements are found in the residual mass, 2 cycles of conventionally dosed chemotherapy (EP, VelP, or TIP) are administered.

After patients are rendered disease-free, standard surveillance is initiated. The frequency of these follow-up tests is outlined in Follow-Up for Nonseminoma, on page 511.

Patients who experience an incomplete response to first-line therapy are treated with second-line therapy (see following section). The panel prefers that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.

**Second-Line Therapy for Metastatic GCTs**

Patients who do not experience a durable complete response to first-line therapy or those who experience a recurrence can be divided into those with a favorable or unfavorable prognosis based on prognostic factors. 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. To determine the prognosis at initial diagnosis, the IGCCCG classification is used. However, for patients with progressive or relapsed disease after first-line treatment, several prognostic models have been reported.

Favorable prognostic factors for conventional-dose second-line chemotherapy include a testicular primary site, prior complete response to first-line therapy, low levels of postorchiectomy serum tumor markers, and low-volume disease. Standard second-line therapy includes conventional-dose
chemotherapy or high-dose chemotherapy. The conventional-dose regimen includes cisplatin and ifosfamide combined with either vinblastine or paclitaxel. In patients who experience an incomplete response or disease relapse after second-line conventional-dose chemotherapy, the preferred third-line option would be high-dose chemotherapy or chemotherapy in the context of a clinical trial.

Unfavorable prognostic features include incomplete response to first-line treatment, high levels of serum markers, high-volume disease, and presence of an extratesticular primary tumor. Patients with a testicular primary site and rising postorchectomy 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, conventional-dose second-line therapy (with VelP or TIP), or high-dose chemotherapy (category 2B). Alternatively, patients may undergo best supportive care or salvage surgery if feasible.

The high-dose regimens include high-dose carboplatin plus etoposide followed by autologous stem cell transplant or paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide with stem cell support (see Second-Line or Subsequent Chemotherapy Regimens for Metastatic Germ Cell Tumors, page 519).

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. Other options are participation in a clinical trial or best supportive care.

**Palliative Therapy**

All patients with either persistent or recurrent disease should be considered for palliative chemotherapy or radiation therapy.

Palliative chemotherapy options for patients with intensively pretreated, cisplatin-resistant, or refractory GCTs are combinations of gemcitabine and paclitaxel and/or oxaliplatin.

The recommendation for gemcitabine and oxaliplatin is based on data from phase II studies that investigated the efficacy and toxicity of gemcitabine and oxaliplatin in patients with relapsed or cisplatin-refractory GCTs. The results showed that the oxaliplatin and gemcitabine combination is safe for patients with cisplatin-refractory testicular GCTs, and may offer a chance of long-term survival.

Gemcitabine and paclitaxel is another option that has shown promising results in a phase II study, and long-term follow-up results with this combination show long disease-free survival in rare patients who experienced progression after high-dose chemotherapy and had not received prior paclitaxel or gemcitabine.

Furthermore, a phase II study of patients with treatment-refractory GCTs found the combination of gemcitabine, oxaliplatin, and paclitaxel to be effective, with acceptable toxicity.

Therefore, for palliative therapy, the panel recommends gemcitabine with oxaliplatin; gemcitabine with paclitaxel, or gemcitabine with oxaliplatin and paclitaxel (all are category 2A recommendations).

**Treatment of Brain Metastases**

The prognosis of patients with brain metastasis is poor. Primary chemotherapy (using a cisplatin-based regimen) with radiotherapy is indicated for patients in whom brain metastases are detected. If clinically indicated and feasible, surgical resection of the metastasis should also be performed.

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Testicular Cancer


Testicular Cancer

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<tr>
<td>Neeraj Agarwal, MD</td>
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<td>Claire Beard, MD</td>
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<td>Sam Bhayani, MD</td>
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<td>Graeme B. Bolger, MD</td>
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<td>Novartis AG; AVEO Pharmaceuticals, Inc.; and Pfizer Inc.</td>
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<td>2/6/12</td>
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<tr>
<td>Mark K. Buyyounouski, MD, MS</td>
<td>None</td>
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<td>8/4/11</td>
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<td>Sam S. Chang, MD</td>
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<tr>
<td>Toni K. Choueiri, MD</td>
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<td>GlaxoSmithKline plc; Novartis AG; AVEO Pharmaceuticals, Inc.; and Pfizer Inc.</td>
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<tr>
<td>Steven L. Hancock, MD</td>
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<tr>
<td>Gary R. Hudes, MD</td>
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<td>Boehringer Ingelheim GmbH; Genentech, Inc.; GlaxoSmithKline plc and AVEO Pharmaceuticals, Inc.</td>
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<td>Eric Jonasch, MD</td>
<td>GlaxoSmithKline plc; and Pfizer Inc.</td>
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<td>Daniel W. Lin, MD</td>
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<td>Kim A. Margolin, MD</td>
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<td>M. Dror Michaelson, MD, PhD</td>
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<td>Joel Sheinfeld, MD</td>
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