NCCN Testicular Cancer Panel Members

* 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

Barry Boston, MD †£
  St. Jude Children’s Research
  Hospital/University of Tennessee Cancer
  Institute

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

Robert A. Figlin, MD †
  City of Hope Comprehensive Cancer Center

Mayer Fishman, MD, PhD †‡þ
  H. Lee Moffitt Cancer Center & Research
  Institute

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

Timothy M. Kuzel, MD ‡
  Robert H. Lurie Comprehensive Cancer Center
  of Northwestern University

Paul H. Lange, MD ω
  Fred Hutchinson Cancer Research
  Center/Seattle Cancer Care Alliance

Ellis G. Levine, MD †
  Roswell Park Cancer Institute

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

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

Lawrence H. Schwartz, MD φ
  Memorial Sloan-Kettering Cancer Center

Joel Sheinfeld, MD ω
  Memorial Sloan-Kettering Cancer Center

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

† 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

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Summary of the Guidelines updates

The 2.2010 version of the Bladder Cancer guidelines represents the addition of the updated Discussion and the addition of the 2010 American Joint Committee on Cancer (AJCC) TNM Staging System for Testis Cancer (ST-1).

Summary of changes in the 1.2010 version of the Testicular Cancer Guidelines from the 2.2009 version include:

**Seminoma**

**TEST-4**
- Residual mass, positive PET scan, “salvage therapy’ was clarified as “second line chemotherapy”.
- Follow-up abdominal/pelvic CT interval was clarified as “4 mo post surgery, then as indicated”.

**Nonseminoma**

**TEST-11**
- Surveillance after complete response to chemotherapy and/or RPLND and months between abdominal/pelvic CT:
  - For 6 + years, the interval between CT scans was changed from “12- 24 mo” to “as clinically indicated”.
  - Previous footnote was modified as, “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” and moved under surveillance for clarification.

**TEST-12**
- Second line therapy for favorable prognosis, “high-dose chemotherapy” was added as a treatment option.
- Second line therapy, incomplete response or relapse, “high-dose chemotherapy” was modified by adding “if not previously given” to preferred.

**TEST-A:**
- Nonseminoma, “post-orchiectomy” was added to markers for clarification for each risk status

**TEST-C**
- High-dose chemotherapy regimens were added to the page.

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.
### Testicular Cancer

#### WORKUP

| Suspicious testicular mass | • H&P  
| | • Alpha-fetoprotein (AFP)  
| | • beta-hCG\(^a\)  
| | • LDH  
| | • Chemistry profile  
| | • Chest x-ray  
| | • Optional:  
| | ▶ Testicular ultrasound  

#### PRIMARY TREATMENT

| • Discuss sperm banking  
| | • Radical inguinal orchietomy  
| | • Consider open inguinal biopsy of contralateral testis if:  
| | ▶ Suspicious ultrasound for intratesticular abnormalities  
| | ▶ Cryptorchid testis  
| | ▶ Marked atrophy  

#### PATHOLOGIC DIAGNOSIS

| Seminoma  
| (AFP negative; may have elevated beta-hCG)  
| | Nonseminomatous germ cell tumor\(^b\)  

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\(^a\)Quantitative analysis of beta subunit.  
\(^b\)This includes seminoma histology with elevated AFP.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Mediastinal seminoma should be treated as good risk nonseminomatous germ cell tumor with etoposide/cisplatin for 4 cycles or bleomycin/etoposide/cisplatin for 3 cycles.

If positive, treat as nonseminoma.

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

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**CLINICAL STAGE**

- **Stage IA, IB**
  - Surveillance if: (category 1)
    - Horseshoe or pelvic kidney
    - Inflammatory bowel disease
    - Prior RT
    - Consider surveillance if: (category 2B)
    - T1 or T2 histology in selected patients committed to long-term follow-up
  - Single agent carboplatin (category 1) (AUC=7 x 1 cycle or AUC=7 x 2 cycles)
  - RT: Infradiaphragmatic (20-30 Gy) to include para-aortic ± ipsilateral iliac nodes (category 1)

- **Stage IS**
  - RT: Infradiaphragmatic (25-30 Gy) to include para-aortic ± ipsilateral iliac nodes

- **Stage IIA, IIB**
  - Consider primary chemotherapy:
    - EP for 4 cycles for selected stage IIB patients
    - EP = Etoposide/cisplatin
    - BEP = Bleomycin/etoposide/cisplatin
  - Good risk:
    - Primary chemotherapy:
      - EP for 4 cycles (category 1)
      - BEP for 3 cycles (category 1)
  - Intermediate risk:
    - Primary chemotherapy:
      - EP for 4 cycles (category 1)
      - BEP for 4 cycles (category 1)

**PRIMARY TREATMENT**

- **Stage IIA, IIB**
  - Consider pEP for 4 cycles for selected stage IIB patients
  - EP = Etoposide/cisplatin

**FOLLOW-UP**

- **H&P, AFP, beta-hCG, LDH:**
  - every 3-4 mo for years 1-3,
  - every 6 mo for years 4-7, then annually
  - Abdominal/pelvic CT at each visit, chest x-ray at alternative visits (up to 10 y)

- **H&P + chest x-ray, AFP, beta-hCG, LDH:**
  - every 3-4 mo for year 1,
  - every 6 mo for year 2, then annually
  - Pelvic CT annually for 3 years (for patients status post only para-aortic RT)

- **H&P + chest x-ray, AFP, beta-hCG, LDH:**
  - every 3-4 mo for years 1-3,
  - every 6 mo for years 4-7, then annually
  - Abdominal/pelvic CT at each visit, chest x-ray at alternative visits (up to 10 y)

- **H&P + chest x-ray, AFP, beta-hCG, LDH:**
  - every 3-4 mo for years 1-3,
  - every 6 mo for year 4, then annually
  - Abdominal CT at month 4 of year 1

**Recurrence, treat according to extent of disease at relapse**

**See Post Chemotherapy Management and Follow-up (TEST-4)**

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**See Risk Classification (TEST-A).**

**See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-B).**
STAGE IIB, IIC, III AFTER PRIMARY TREATMENT WITH CHEMOTHERAPY

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

No residual mass and normal markers

PET scan (preferred)

Positive

Negative

PET scan not feasible

Residual mass (nodes > 3 cm on CT)

Residual mass (nodes ≤ 3 cm on CT)

Progressive disease (growing mass or rising markers)

FOLLOW-UP

STAGE IIB, IIC, III AFTER PRIMARY TREATMENT WITH CHEMOTHERAPY

POST CHEMOTHERAPY MANAGEMENT

Surveillance

Consider surgery with biopsy or biopsy and second line chemotherapy or RT (category 2B)

Surveillance or Surgery (category 2B) or RT (category 2B)

Surveillance

See Second line Therapy for nonseminoma (TEST-12)

Recurrence, See Second line Therapy (TEST-12)

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Nonseminomatous germ cell tumor

**PATHOLOGIC DIAGNOSIS**

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

**POSTDIAGNOSTIC WORKUP**

**CLINICAL STAGE**

- 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)

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**CLINICAL STAGE**

**Stage IA**
- Surveillance (in compliant patients)
- Open nerve-sparing RPLND\(^k\)

**Stage IB**
- Open nerve-sparing RPLND\(^k\)
- Primary chemotherapy: \(^g\) BEP for 2 cycles (category 2B)
- Surveillance (only if T2, compliant patients [category 2B])

**Stage IS**
- Persistent marker elevation
- Primary chemotherapy: \(^g\) EP for 4 cycles or BEP for 3 cycles

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**Primary Treatment**

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

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

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\(^g\) 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).

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**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

Stage IIA
- Markers negative
- Persistent marker elevation

Stage IIB
- Markers negative
- Persistent marker elevation

PRIMARY TREATMENT

**Stage IIA**
- Markers negative
  - Open nerve-sparing RPLND
  - Primary chemotherapy: EP for 4 cycles or BEP for 3 cycles

- Persistent marker elevation
  - Open nerve-sparing RPLND
  - Primary chemotherapy: EP for 4 cycles or BEP for 3 cycles

**Stage IIB**
- Markers negative
  - Lymph node metastases, within lymphatic drainage sites (landing zone positive)
  - Open nerve-sparing RPLND
  - Primary chemotherapy: EP for 4 cycles or BEP for 3 cycles

- Persistent marker elevation
  - Multifocal symptomatic lymph node metastases with aberrant lymphatic drainage
  - Primary chemotherapy: EP for 4 cycles or BEP for 3 cycles

**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.

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

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

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

See Postchemotherapy Management (TEST-8)

Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
POSTCHEMOTHERAPY MANAGEMENT

Stage IB, IS, IIA, IIB treated with primary chemotherapy

- Negative markers, residual mass → Open nerve-sparing RPLND\(^k\) or Surveillance (category 2B)
- Negative markers, Normal CT scan, no mass → Open nerve-sparing RPLND\(^k\) (category 2B) or Surveillance (category 2B)

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.

\(^k\)Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
**POSTSURGICAL MANAGEMENT**

Stage IA, IB, IIA, IIB treated with open nerve-sparing RPLND

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

- **pN1**
  - Compliant
    - Surveillance
  - Noncompliant
    - Chemotherapy: EP for 2 cycles or BEP for 2 cycles

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

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

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

See Follow-up for Nonseminoma (TEST-11)

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**

**Good Risk**
- Stage IIC: Primary chemotherapy: EP for 4 cycles or BEP for 3 cycles.
- Poor risk: Stage IIIC: Primary chemotherapy: BEP for 4 cycles or VIP for 4 cycles in selected patients.
- Brain metastases: Primary chemotherapy + RT ± surgery, if clinically indicated.

**Primary Treatment**
- Complete response, negative markers: Surveillance (category 2B) or Open nerve-sparing RPLND (category 2B).
- Partial response, residual masses with normal AFP and beta-hCG levels: Surgical resection of all residual masses.
- Incomplete response: See Second Line Therapy (TEST-12).

**Chemotherapy Regimens**
- EP = Etoposide/cisplatin
- BEP = Bleomycin/etoposide/cisplatin
- TIP = Paclitaxel/ifosfamide/cisplatin
- VeIP = Vinblastine/ifosfamide/cisplatin
- VIP = Etoposide/ifosfamide/cisplatin

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.

See Follow-up for Nonseminoma (TEST-11)

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

See Risk Classification (TEST-A).
See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-B).
See Second Line or Subsequent Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-C).
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.
**FOLLOW-UP FOR NONSEMINOMA**

### Surveillance for Stage IA, IB Testicular Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Months between visits, markers, chest x-ray</th>
<th>Months between abdominal/pelvic CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-2</td>
<td>2-3</td>
</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>5</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>6+</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

### Surveillance After Complete Response to Chemotherapy and/or RPLND

<table>
<thead>
<tr>
<th>Year</th>
<th>Months between visits, markers, chest x-ray (category 2B for chest x-ray frequency)</th>
<th>Months between abdominal/pelvic CT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-3</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>2-3</td>
<td>6-12</td>
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<tr>
<td>4</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>6+</td>
<td>12</td>
<td>As clinically indicated</td>
</tr>
</tbody>
</table>

*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.

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**Recurrence, See Salvage Therapy (TEST-12)**

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

**RECURRENCE**

**SECOND LINE THERAPY**

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

  ▶ Chemotherapy
  - Conventional dose therapy (VeIP or TIP) or
  - High-dose chemotherapy

  • Incomplete response or relapse

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

  ▶ Chemotherapy
  - 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

- Prior chemotherapy

  ▶ High-dose chemotherapy (preferred if not previously given) or
  ▶ Clinical trial

  • 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

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**See Second Line or Subsequent Chemotherapy Regimens for Germ Cell Tumors (TEST-C).**
### RISK CLASSIFICATION

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


1 Markers used for risk classification are post-orchiectomy.

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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 days

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
Repeat every 21 days

VIP
Etoposide 75 mg/m² IV on Days 1-5
Mesna 120 mg/m² slow IV push before ifosfamide on Day 1, then
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 days

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

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 hours 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 days

**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 hours after each ifosfamide dose on Days 2 - 5
- Cisplatin 25 mg/m² IV on Days 2 - 5
- Repeat every 21 days

### High-dose chemotherapy regimens

**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 cycles

Paclitaxel 200 mg/m² IV over 24 hours

- Ifosfamide 2000 mg/m² 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/m² IV Days 1 - 3
- Administer with peripheral blood stem cell support at 14 - 21 day intervals for 3 cycles

### Palliative chemotherapy regimen

**GEMOX**
- Gemcitabine 1000 mg/m² IV on Days 1 and 8 followed by
- Oxaliplatin 130 mg/m² IV on Day 1
- Repeat every 21 days

or

- Gemcitabine 1250 mg/m² IV on Days 1 and 8 followed by
- Oxaliplatin 130 mg/m² IV on Day 1
- Repeat every 21 days

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See Chemotherapy References (TEST-C 2 of 2)
SECOND LINE OR SUBSEQUENT CHEMOTHERAPY REGIMENS FOR
METASTATIC GERM CELL TUMORS

CHEMOTHERAPY REFERENCES


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.
Staging

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.

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
### Staging

#### Table 1 (continued)

**American Joint Committee on Cancer (AJCC)**

**TNM Staging System for Testis Cancer (7th ed., 2010)**

#### ANATOMIC STAGE/PROGNOSTIC GROUPS

<table>
<thead>
<tr>
<th>Group</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>S (Serum Tumor Markers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>pTis</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage I</td>
<td>pT1-4</td>
<td>N0</td>
<td>M0</td>
<td>SX</td>
</tr>
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**Serum Tumor Markers (S)**

- SX: Marker studies not available or not performed
- SO: Marker study levels within normal limits
- S1: LDH $< 1.5 \times N^*$ and hCG (mIU/mL) $< 5,000$ and AFP (ng/ml) $< 1,000$
- S2: LDH $1.5-10 \times N$ or hCG (mIU/mL) 5,000-50,000 or AFP (ng/ml) 1,000-10,000
- S3: LDH $> 10 \times N$ or hCG (mIU/mL) $> 50,000$ or AFP (ng/ml) $> 10,000$

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

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

An estimated 8,400 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 (TEST-1).

If an intratesticular mass is identified, further evaluation includes measurement of the serum concentrations of alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), and beta-human chorionic gonadotropin (beta-hCG) and a chest radiograph. Elevated values of beta-hCG, LDH, or AFP should be followed up with repeated tests to allow precise staging. 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 orchectomy is considered the primary treatment for most patients who present with a suspicious testicular mass. 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. Biopsy may also be considered if a suspicious intratesticular abnormality, such as a hypoechoic mass or macrocalcifications, is identified on ultrasound. In contrast, if microcalcifications without any other abnormality can be observed, testicular biopsy is not necessary. These studies, and others as clinically indicated, determine the clinical stage and direct patient management. If clinical signs of metastases are present, magnetic resonance imaging (MRI) of the brain and bone scanning are indicated (TEST-2 and TEST-5).

Further management is dictated by histology, a diagnosis of seminoma or nonseminoma, and stage (ST-1). 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 (ST-1). This classification categorized patients with seminoma and non-seminoma GCT into good-, intermediate-, or poor-risk groups (see TEST-A).

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 (TEST-3). Between 15% and 20% of patients with seminoma, experience relapse during surveillance if they do not undergo adjuvant radiation therapy after orchidectomy. The median time to relapse is approximately 12 months, but relapses can occur more than 5 years after orchidectomy.
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. 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 an alternative to radiation therapy (category 1) for patients with stages IA and IB disease. Oliver et al 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. 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. 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. 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 (TEST-3).

**Seminoma Stages IIC and III**

Patients with stage IIC or III disease are those considered at good or intermediate risk (TEST-3). All stage IIC and stage III disease is considered good risk except for stage III disease with non-pulmonary visceral metastases, which is considered intermediate risk (TEST-A). Standard chemotherapy is used for both groups of patients, but for patients with good risk, either 4 cycles of EP are recommended or 3 cycles of bleomycin, etoposide, and cisplatin (BEP). In contrast, 4 cycles of BEP are recommended for those with intermediate risk disease. 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 (TEST-4). Patients are then classified according to the presence or absence of a residual mass and the status of serum tumor markers. Patients with no residual mass and normal markers need no further treatment and undergo surveillance. In patients with a residual mass with normal markers, a positron emission tomography (PET) scan is recommended to assess for residual viable tumor. To reduce the incidence of false-positive results, the PET scan is typically performed no less than 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) or four cycles of VelIP (vinblastine, ifosfamide, cisplatin).

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. 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. 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 (TEST-12). 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.

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 is defined in TEST-A. Stage-dependent treatment options after inguinal orchietomy 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. 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.

Nonseminoma Stage IA

Two management options exist for patients with stage IA disease after orchietomy: (1) surveillance (in compliant patients) or (2) open nerve-sparing RPLND (TEST-6). The cure rate with either approach exceeds 95%. However, the high cure rate associated with surveillance depends on adherence to periodic follow-up examinations and subsequent chemotherapy for the 20% to 30% of patients who experience relapse.

Noncompliant patients are treated with open RPLND. The open nerve-sparing RPLND is typically performed within 4 weeks of a CT scan and within 7 to 10 days of repeat serum marker testing to ensure accurate presurgical staging. If the dissected lymph nodes are not involved with a tumor (pN0), no adjuvant chemotherapy is given after open nerve sparing RPLND. However, if the resected lymph nodes involve tumor, the decision whether to use adjuvant chemotherapy is based on the degree of nodal involvement and the ability of the patient to comply with surveillance (TEST-9). Chemotherapy is preferred over surveillance in patients with pN2 or pN3 disease. Recommended regimens include either EP or BEP; 2 cycles of either regimen are recommended for patients with pN1 or pN2 disease. 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 (TEST-11). Nonseminoma Stage IB

After orchietomy, 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.

A trial by Albers et al randomized stage I patients after orchietomy, to undergo RPLND (n = 191) or one adjuvant course of BEP (n = 191). 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) (TEST-8).

Surveillance alone may be offered to compliant patients with T2 disease (category 2B) (TEST-6). Vascular invasion is a significant predictor of relapse when orchiectomy is followed by surveillance alone.2 Surveillance is generally not recommended for T2 disease with vascular invasion because of the 50% chance of relapse. Exceptions are made according to individual circumstances in compliant patients. When surveillance is opted in selected patients with T2 disease, both the patient and the physician must be compliant with follow-up recommendations.

**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 (TEST-6). 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 (TEST-8).

**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 (TEST-7).

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 or surveillance (TEST-7). 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 (TEST-7). When tumor markers are negative, the CT findings determine the proper course of treatment. If abnormal radiographic findings are limited to sites within the lymphatic drainage 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 (TEST-9). The second option is to treat with primary chemotherapy with either 4 cycles of EP or 3 cycles of BEP (TEST-7), followed by open nerve sparing RPLND or surveillance (TEST-8).

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%.31-47

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 (TEST-9). 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. 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 (TEST-A). Also, patients with an extragonadal primary site, whether retroperitoneal or mediastinal, are treated with initial chemotherapy. Classifications of risk status emerged from chemotherapy research designed to decrease the toxicity of the regimens while maintaining maximal efficacy.

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

The high cure rate and toxicity associated with cisplatin, vinblastine, and bleomycin regimens resulted in efforts to stratify patients and tailor therapy according to risk. Extent of disease and 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 (ST-1). This classification categorized patients as good-, intermediate-, or poor-risk.

**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, and either eliminating or reducing the dose of bleomycin. Presently, 2 regimens are considered standard treatment programs in the United States for good-risk GCTs: 4 cycles of EP or 3 cycles of BEP (TEST-B). Either regimen is well tolerated and cures approximately 90% of patients with good risk.

**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. 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.
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. The panel recommends 4 cycles of etoposide, ifosfamide, and cisplatin (VIP regimen) for patients who may not tolerate bleomycin. 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 (TEST-11). Patients who experience an incomplete response to first-line therapy or unresectable disease at surgery are treated with second-line therapy (TEST-12).

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 (TEST-12). Standard second line therapy includes conventional dose chemotherapy or high dose chemotherapy (TEST-12). 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. The conventional dose regimen include cisplatin and ifosfamide combined with either vinblastine or paclitaxel (TEST-C). 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


