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Testicular Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Note:** Consider Clinical Trials as treatment options for eligible patients.

### Initial Evaluation

- History and physical
- Lifestyle risk assessment
- Alpha-fetoprotein (AFP)
- Beta-hCG (quantitative)
- Sodium, potassium, chloride, CO₂, BUN, creatinine, magnesium, total bilirubin, AST, ALT, alkaline phosphatase, albumin, calcium, uric acid, phosphorus, and total LDH
- Scrotal ultrasound
- Chest x-ray

### Tumor Histology

- **Solid intratesticular mass on ultrasound?**
  - Yes
    - Radical inguinal orchiectomy
    - Evaluate contralateral testicle
    - Discuss sperm banking
  - No
    - Consider other etiologies

- **Nonseminomatous germ cell tumor or mixed histology**
  - See workup and clinical stage for nonseminoma on Page 3

- **Pure seminoma**
  - (and normal AFP)
  - See workup and clinical stage for pure seminoma on Page 4

- **Non-germ cell testicular tumors**
  - Management according to tumor type

1See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
Mixed or Nonseminomatous Germ Cell Tumor Histology

- Repeat AFP, beta-hCG, and LDH
- CT abdomen and pelvis with contrast
- CT chest if embryonal carcinoma-predominant or abnormal chest x-ray, or abnormal CT of abdomen/pelvis
- Bone scan if clinically indicated
- Brain imaging if clinically indicated
- Discuss sperm banking

Tumor markers normalize with appropriate half-life?

Yes → Imaging negative for metastasis?

Yes → Clinical Stage I

“Average risk Stage I”:
Stage IA (no lymphovascular invasion)

No → Clinical Stage IS

“High risk Stage I”:
tumor has lymphovascular invasion or embryonal predominant or Stage IB

Treat as “Good Prognosis”
metastatic nonseminoma germ cell tumor (See Page 5)

No → Symptomatic from metastases (brain, lung, retroperitoneal mass)?

Yes → Consider emergency chemotherapy

No → Stages: IIA, IIB, IIC, IIIA

“Good Prognosis”

For IIA, IIB, and IIC, See Page 7

Stage IIB

“Intermediate Prognosis”

For IIIA and IIBB, See Page 8

Stage IIIC

“Poor Prognosis”

See Page 9

1 See Appendix A for International Classifications of Germ Cell Cancer

2 It is acceptable to administer emergency chemotherapy to selected patients with advanced metastatic nonseminomatous germ cell tumor on the basis of clinical presentation before orchiectomy, and without a tissue diagnosis.
HISTOLOGY

Pure seminoma histology

FURTHER WORK-UP

- Repeat AFP, beta-hCG, and LDH
- CT abdomen and pelvis with contrast
- CT chest if abnormal chest x-ray or involved lymph nodes on CT of abdomen/pelvis
- Bone scan if clinically indicated
- Brain imaging if clinically indicated
- Discuss sperm banking

Pure seminoma: workup and clinical stage

Post-operative beta-hCG or LDH elevated?

- Yes
  - Imaging negative for metastasis?
    - Yes
      - Consider occult metastasis or consider PET scan
    - No
      - Clinical Stage I
      - See Page 6
  - No
    - Extra-pulmonary metastases?
      - Yes
        - “Intermediate Prognosis”
        - See Page 11
      - No
        - Metastases in lymph nodes or lungs only “Good Prognosis”
        - See Page 10

AFP within normal limits?

- Yes
  - No
    - Suspect unrelated source of non-specific AFP?
      - Yes
        - Nonseminomatous Germ Cell Tumor
      - No
        - Follow algorithm for Nonseminomatous Germ Cell Tumor

Suspect unrelated source of non-specific AFP?

- Yes
  - No
    - Imaging negative for metastasis?
      - Yes
        - Post-operative beta-hCG or LDH elevated?
      - No
        - Clinical Stage I
        - See Page 6

AFP within normal limits?

1 See Appendix A for International Classifications of Germ Cell Cancer

Note: Consider Clinical Trials as treatment options for eligible patients.
Clinical Stage I Nonseminoma: post-orchiectomy management

MANAGEMENT OPTIONS

TUMOR MARKERS

1. Any pT/Tx
2. N0
3. M0
4. S1-3

Stage IS:
- Beta-hCG or AFP elevated
- Metastatic workup negative

Consider sperm banking

High Risk – probability of recurrence is approximately 50%
- Consider sperm banking

Embryonal carcinoma predominant?

Yes
- Surveillance (in compliant patients, pT1-2)
- Adjuvant chemotherapy (1-2 cycles BEP)

No

Average Risk – probability of recurrence is approximately 30%
- Consider sperm banking

Consider management options:
- Surveillance (in compliant patients, pT1-2)
- Prophylactic RPLND
- Adjuvant chemotherapy (1-2 cycles BEP)

Consider management options:
- Surveillance (in compliant patients)
- Prophylactic RPLND

See appropriate surveillance schedule based on treatment

1 High Risk Features (in the primary tumor):
   a. Lymphovascular invasion
   b. Invasion of tunica vaginalis
   c. Invasion of spermatic cord or scrotum (pT3-4)
   d. Embryonal carcinoma predominant

2 Medical oncologist should discuss options with patient based on clinical data

BEP = bleomycin, etoposide, and cisplatin
RPLND = retroperitoneal lymph node dissection

Note: Consider Clinical Trials as treatment options for eligible patients.
Clinical Stage I Pure Seminoma: post-orchiectomy management

TUMOR MARKERS

- Any pT/Tx
- N0
- M0
- S1-3

Stage IS:
- Beta-hCG or AFP elevated
- Metastatic workup negative

Consider sperm banking

Primary tumor greater than 4 cm or pT3-4?

No

Yes

Management Options

Consider management options:
Surveillance or single-dose carboplatin AUC = 7 or AUC = 7 x 2 cycles for all others

See appropriate surveillance schedule based on treatment

Most patients with clinical stage IA pure seminoma can be offered three options:
- Surveillance in compliant patients who are committed to long term follow-up or
- Radiotherapy to para-aortic with or without ipsilateral iliac lymph nodes or
- Adjuvant carboplatin single dose, AUC = 7 or AUC = 7 x 2 cycles

Note: Consider Clinical Trials as treatment options for eligible patients.
Testicular Cancer

Stage IIA, IIB, IIC Nonseminoma: post-orchiectomy management

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**Note:** Consider Clinical Trials as treatment options for eligible patients.

### PRETREATMENT WORKUP

<table>
<thead>
<tr>
<th>TNM STAGE</th>
<th>WORKUP</th>
</tr>
</thead>
</table>
| Any pT/Tx | - Baseline pulmonary function testing  
- Consider baseline audiometry testing  
- Consider sperm banking |
| N1-3      |        |
| M0        |        |
| S0-1      |        |

### TREATMENT

#### Stage IIA, IIB

- **Good Prognosis**
  - Total LDH less than 1.5 times upper limit of normal and  
  - Beta-hCG less than 5,000 mIU/mL and  
  - AFP less than 1,000 ng/mL?

- **Intermediate Prognosis**
  - Total LDH 1.5-10 times upper limit of normal or  
  - Beta-hCG 5,000-50,000 mIU/mL or  
  - AFP 1,000-10,000 ng/mL

- **Poor Prognosis**
  - Total LDH greater than 10 times upper limit of normal or  
  - Beta-hCG greater than 50,000 mIU/mL or  
  - AFP greater than 10,000 ng/mL

#### Stage IIC

- **Post-orchiectomy management**
  - Surgical option: retroperitoneal lymph node dissection
  - Stage IIB: Etoposide and cisplatin (EP) for 2 cycles
  - Stage IIA: Surveillance

#### TREATMENT

- Bleomycin, etoposide, and cisplatin (BEP) for 3 cycles or  
- Etoposide and cisplatin for 4 cycles

See Page 8 for treatment of Stage III

See Page 12 for post-chemotherapy management
Testicular Cancer  
Stage IIIA, IIIB Nonseminoma: post-orchiectomy management

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Note: Consider Clinical Trials as treatment options for eligible patients.

TNM STAGE

IIC, IIIA and IIIB:
• Any pT/Tx
• Any N, M1a, S0-2, or N1-3, M0, S2
(May be good or intermediate prognosis by tumor markers)

PRETREATMENT WORKUP

• Baseline pulmonary function testing
• Consider baseline audiometry testing
• Consider sperm banking

IIC, IIIA Good Prognosis
• Total LDH less than 1.5 times upper limit of normal and
• Beta-hCG less than 5,000 mIU/mL and
• AFP less than 1,000 ng/mL

Yes

IIIB Intermediate Prognosis
• Total LDH 1.5-10 times upper limit of normal or
• Beta-hCG 5,000-50,000 mIU/mL or
• AFP 1,000-10,000 ng/mL

No

TREATMENT

• Bleomycin, etoposide, and cisplatin for 3 cycles or
• Etoposide and cisplatin for 4 cycles

See Page 12 for post-chemotherapy management

NOTE: See Page 9 for treatment of Stage IIIC

Note: Consider Clinical Trials as treatment options for eligible patients.
Stage IIIC (poor prognosis) Nonseminoma: Initial Management

**TNM STAGE**

**IIIC, Poor Prognosis:**
- Any pT/Tx, Any N, M1b\(^1\), Any S
- Total LDH greater than 10 times upper limit of normal or
- Beta-hCG greater than 50,000 mIU/mL or
- AFP greater than 10,000 ng/mL

To avoid delay in the start of chemotherapy, the diagnosis can be made on clinical grounds. Orchiectomy can be deferred.

**TREATMENT**

To Respiratory distress or symptomatic brain metastases?

- Yes
  - Patient with respiratory distress
    - Vincristine and cisplatin
    - Etoposide and cisplatin (limit to 3 days in unstable patient)

- No
  - Patient with symptomatic brain metastases
    - Primary chemotherapy with or without surgery if clinically indicated

1 M1b - Distant metastases other than to non-regional lymph nodes and lungs

2 Plateau: The observed rate of decline in tumor markers should be compared to the expected serum half-lives of 5-7 days (AFP) and 2-3 days (beta-hCG). It is common to see a slower rate of decline after the second cycle of chemotherapy. A continued rate of decline that is much less than the expected half life and does not normalize should be interpreted as a plateau. The decision to stop chemotherapy should be based on clinical judgement, taking into consideration the clinical status of the patient, which of the markers are elevated, extent of elevation, and after ruling out potential sources of spurious elevation.

Note: Consider Clinical Trials as treatment options for eligible patients.
Testicular Cancer

Seminoma: Treatment and Follow-up

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Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL STAGE/TREATMENT

- **IA or IB**
  - Adjuvant carboplatin
  - No adjuvant therapy
- **IS**
  - Radiation therapy
- **IIA or IIB**
  - Radiation therapy
- **IIC or III**
  - See management for advanced seminoma on Page 11

FOLLOW-UP

- History and physical, tumor markers (AFP, beta-hCG, LDH) every 3 months for years 1 and 2, then every 4 months for year 3, then every 6 months for years 4-7, then annually for up to 10 years
- CT abdomen/pelvis annually for years 1-3
- Chest x-ray at alternate visits

RECURRENT

- Tumor recurrence
  - Treat according to histology and stage (post-orchietomy management)

Tumor recurrence

No adjuvant therapy

- History and physical, tumor markers (AFP, beta-hCG, LDH), every 3 months for years 1 and 2, then every 4 months for year 3, then every 6 months for years 4-7, then annually for up to 10 years
- CT abdomen/pelvis every 6 months for years 1-3, then annually for up to 10 years
- Chest x-ray at alternate visits

Tumor recurrence

- History and physical, tumor markers (AFP, beta-hCG, LDH), and chest x-ray every 4 months for year 1, then every 6 months for year 2, then annually for up to 10 years
- CT abdomen/pelvis annually for years 1-3

Tumor recurrence

- History and physical, tumor markers (AFP, beta-hCG, LDH), and chest x-ray every 3-4 months for years 1-3, then every 6 months for year 4, then annually for up to 10 years
- CT abdomen/pelvis every 6 months for year 1, then annually for years 2 and 3

Tumor recurrence

- History and physical, tumor markers (AFP, beta-hCG, LDH), and chest x-ray every 4-6 months for years 1-3, then every 6 months for year 4, then annually for up to 10 years
- CT abdomen/pelvis every 6 months for year 1, then annually for years 2 and 3

Tumor recurrence
Testicular Cancer  
Management for Advanced Seminoma

CLINICAL STAGE/TREATMENT

- Good risk: IIC or III
  - EP for 4 cycles

- Intermediate risk: VIP for 4 cycles

RESPONSE TO TREATMENT

- Complete response
  - History and physical, tumor markers (AFP, beta-hCG, LDH), abdominal/pelvic CT every 3 months for years 1 and 2, then every 4 months for year 3, then every 6 months for years 4-7, then annually for up to 10 years
  - Chest x-ray at alternate visits
  - PET scan as clinically indicated

- Partial response
  - PET
  - PET negative
  - PET positive or not feasible
  - Consider: Radiotherapy, Biopsy, Surveillance if less than 3 cm

- Progression
  - See Page 14 for nonseminoma management of post-chemotherapy tumor recurrence

FOLLOW-UP

Note: Consider Clinical Trials as treatment options for eligible patients.

EP = etoposide and cisplatin
VIP = etoposide, ifosfamide, and cisplatin
1Seminoma that is refractory to chemotherapy is rare and should be managed as nonseminoma
**Testicular Cancer**

**Nonseminoma: Post-chemotherapy management**

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**Note:** Consider Clinical Trials as treatment options for eligible patients.

### Clinical Stage

#### IB (or high risk)
- **IIS**
- **IIA, IIB, IIC**

#### II (or high risk)
- **IIS**
- **IIA, IIB, IIC**

### Response to Chemotherapy

- **Markers negative, Complete response**
  - **IIA, IIB, IIC**
    - **Partial response**
    - **Rising markers, Clinical progression**
      - **Salvage treatment**
      - **See post-chemotherapy recurrence on Page 14**
    - **Retroperitoneal lymph node dissection**
    - **Orchiectomy if not already performed**

- **Residual mass, Markers negative, or plateau**
  - **Retroperitoneal lymph node dissection**
  - **Salvage treatment**
  - **See Surveillance on Page 13**

- **Rising markers or Clinical progression**
  - **Salvage treatment**
  - **See Surveillance on Page 13**

### Follow-Up

- **See Surveillance on Page 13**

---

1 Plateau: The observed rate of decline in tumor markers should be compared to the expected serum half lives of 5-7 days (AFP) and 2-3 days (beta-hCG). It is common to see a slower rate of decline after the second cycle of chemotherapy. A continued rate of decline that is much less than the expected half life and does not normalize should be interpreted as a plateau. The decision to stop chemotherapy should be based on clinical judgement, taking into consideration the clinical status of the patient, which of the markers are elevated, extent of elevation, and after ruling out potential sources of spurious elevation.
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### Table 1: IA, IB Nonseminoma Surveillance

<table>
<thead>
<tr>
<th>Year</th>
<th>Visits, Markers, and Chest X-ray</th>
<th>Abdominal/Pelvic CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Every 1-2 months</td>
<td>Every 4 months</td>
</tr>
<tr>
<td>2</td>
<td>Every 2-3 months</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>3</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>4</td>
<td>Every 4 months</td>
<td>Every 8 months</td>
</tr>
<tr>
<td>5</td>
<td>Every 6 months</td>
<td>Annually</td>
</tr>
<tr>
<td>6 and above</td>
<td>Annually</td>
<td>Annually</td>
</tr>
</tbody>
</table>

### Table 2: Nonseminoma Follow-up after Complete Response to Chemotherapy and/or Retroperitoneal Lymph Node Dissection (RPLND)

<table>
<thead>
<tr>
<th>Year</th>
<th>Visits, Markers, and Chest X-ray</th>
<th>Abdominal/Pelvic CT¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Every 2-3 months</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>2</td>
<td>Every 2-3 months</td>
<td>Every 6-12 months</td>
</tr>
<tr>
<td>3</td>
<td>Every 4 months</td>
<td>Annually</td>
</tr>
<tr>
<td>4</td>
<td>Every 6 months</td>
<td>Annually</td>
</tr>
<tr>
<td>5</td>
<td>Every 6-12 months</td>
<td>Annually</td>
</tr>
<tr>
<td>6 and above</td>
<td>Annually</td>
<td>Every 12-24 months</td>
</tr>
</tbody>
</table>

¹ CT scans for patients treated with chemotherapy. Baseline CT scan for patients status post RPLND
Testicular Cancer  Nonseminoma: Post-chemotherapy tumor recurrence

RESPONSE TO TREATMENT

Nonseminoma - Prior Chemotherapy

Incomplete response or first relapse

Salvage chemotherapy:
- TIP (preferred)
- VeIP
- POMB-ACE
- Consider HDC

Incomplete response and normalization of tumor markers

Resect all residual masses

Complete response and normalization of tumor markers

Consider adjuvant chemotherapy if viable malignant tumor

Response?

Yes

No

Potential for salvage?

Yes

No

Third or subsequent relapse

Consider surgery if solitary site
- Clinical trial (preferred)
- Second or subsequent salvage chemotherapy:
  - Consider HDC
  - TIP
  - Gemcitabine and oxaliplatin
  - POMB-ACE

Palliative chemotherapy or radiotherapy
- Best supportive care

SUBSEQUENT TREATMENT

Incomplete response that is unresectable or second relapse

See Surveillance on Page 13

Note: Consider Clinical Trials as treatment options for eligible patients.

TIP = paclitaxel, ifosfamide, cisplatin
VeIP = vinblastine, ifosfamide, cisplatin, mesna
POMB-ACE = cisplatin, vincristine, methotrexate and bleomycin alternating with actinomycin-D, cyclophosphamide, and etoposide
HDC = high-dose chemotherapy and autologous stem cell transplant

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# APPENDIX A: International Classifications for Germ Cell Cancers

<table>
<thead>
<tr>
<th>PROGNOSIS</th>
<th>NON-SEMINOMA</th>
<th>SEMINOMA</th>
</tr>
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<tbody>
<tr>
<td>GOOD PROGNOSIS</td>
<td>Testes/retroperitoneal primary <strong>and</strong> No non-pulmonary visceral metastases <strong>and</strong></td>
<td>Any primary site <strong>and</strong> No non-pulmonary visceral metastases <strong>and</strong></td>
</tr>
<tr>
<td>All Good Markers:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• AFP</td>
<td>less than 1,000 ng/mL <strong>and</strong></td>
<td>Normal</td>
</tr>
<tr>
<td>• Beta-hCG</td>
<td>less than 5,000 iu/L (1,000 ng/mL) <strong>and</strong></td>
<td>Any value</td>
</tr>
<tr>
<td>• LDH</td>
<td>less than 1.5 times upper limit of normal</td>
<td>Any value</td>
</tr>
<tr>
<td>INTERMEDIATE PROGNOSIS</td>
<td>Testes/retroperitoneal primary <strong>and</strong> No non-pulmonary visceral metastases <strong>and</strong></td>
<td>Any primary site <strong>and</strong> Non-pulmonary visceral metastases <strong>and</strong></td>
</tr>
<tr>
<td>Markers any of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• AFP</td>
<td>greater than or equal to 1,000 and less than or equal to 10,000 ng/mL <strong>or</strong></td>
<td>Normal</td>
</tr>
<tr>
<td>• Beta-hCG</td>
<td>greater than or equal to 5,000 iu/L and less than 50,000 iu/L <strong>or</strong></td>
<td>Any value</td>
</tr>
<tr>
<td>• LDH</td>
<td>greater than or equal to 1.5 times normal and less than 10 times normal</td>
<td>Any value</td>
</tr>
<tr>
<td>POOR PROGNOSIS</td>
<td>Mediastinal primary <strong>or</strong> Non-pulmonary metastases</td>
<td>No patients classified as poor prognosis</td>
</tr>
<tr>
<td>Markers any of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• AFP</td>
<td>greater than 10,000 ng/mL <strong>or</strong></td>
<td></td>
</tr>
<tr>
<td>• Beta-hCG</td>
<td>greater than or equal to 50,000 iu/L (10,000 ng/mL) <strong>or</strong></td>
<td></td>
</tr>
<tr>
<td>• LDH</td>
<td>greater than 10 times normal</td>
<td></td>
</tr>
</tbody>
</table>

1 From the International Germ Cell Consensus Classification from the International Germ Cell Cancer Collaborative Group
SUGGESTED READINGS


This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Genitourinary Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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