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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Testicular Cancer

Version 1.2015

NCCN.org

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

Eric Jonasch, MD/Vice-chair †
The University of Texas
MD Anderson 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

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

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

Brian A. Costello, MD, MS †
Mayo Clinic Cancer Center

Ithaar H. Derweesh, MD ω
UC San Diego Moores Cancer Center

Shilpa Gupta, MD †
Moffitt Cancer Center

Steven L. Hancock, MD § Þ
Stanford Cancer Institute

Jenny J. Kim, MD †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

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

Elaine T. Lam, MD †
University of Colorado Cancer Center

Clayton Lau, MD ω
City of Hope Comprehensive Cancer Center

Ellis G. Levine, MD †
Roswell Park Cancer Institute

Daniel W. Lin, MD ω
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

Elizabeth R. Plimack, MD, MS †
Fox Chase Cancer Center

Edward N. Rampersaud, MD ω
Duke Cancer Institute

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

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

Joel Sheinfeld, MD ω
Memorial Sloan Kettering Cancer Center

Brian Shuch, MD ω
Yale Cancer Center/Smilow Cancer Hospital

Kanishka Sircar, MD ≠
The University of Texas
MD Anderson Cancer Center

Brad Somer, MD †
St. Jude Children's Research Hospital/
University of Tennessee Health Science
Center

Richard B. Wilder, MD §
Moffitt Cancer Center

NCCN
Mary Dwyer, MS
Rashmi Kumar, PhD
Sarika Trikha, PharmD

† Medical oncology
‡ Hematology/Hematology oncology
§ Radiotherapy/Radiation oncology
Þ Internal medicine
ω Urology
≠ Pathology
* Writing Committee Member

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

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 1.2015 Updates Testicular Cancer

Updates in Version 1.2015 of the NCCN Guidelines for Testicular Cancer from Version 1.2014 include:

New to the Guidelines

- **Follow-up**
  - **The follow-up recommendations for both pure seminoma (TEST-A) and nonseminomatous germ cell tumor (NSGCT) (TEST-B) were extensively revised. For seminoma, the recommendation was removed from the algorithms and placed in tables.**

Seminoma

TEST-3

- **Stage IA, IB**
  - **Primary treatment**
    - ◊ **For single-agent carboplatin, the category was changed from a 1 to a 2A.**
    - ◊ **The dose for RT was added, "20 Gy," and the category was changed from a 1 to a 2A.**
  - **The follow-up recommendations were removed from page and directed to new "Follow-up for Seminoma" section.**

TEST-4

- **For Stage IIA**
  - **Primary treatment, the RT recommendation was revised, "RT to include para-aortic and ipsilateral iliac lymph nodes to a dose of 30 ~~to 36~~ Gy (preferred)."**
- **For Stage IIB**
  - **Primary treatment, the RT recommendation was revised, "RT *in select non-bulky cases* to include para-aortic and ipsilateral iliac lymph nodes to a dose of ~~30 to~~ 36 Gy."**
- **The follow-up recommendations after RT were removed from the page and directed to new "Follow-up for Seminoma" section.**

TEST-5

- **Post chemotherapy follow-up recommendations were removed from the page and directed to new "Follow-up for Seminoma" section.**

Continued on next page

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NCCN Guidelines Version 1.2015 Updates Testicular Cancer

Updates in Version 1.2015 of the NCCN Guidelines for Testicular Cancer from Version 1.2014 include:

Nonseminoma

- Follow-up for nonseminoma links to corresponding tables were added throughout the section.

TEST-9

- Stage IB was removed from the postchemotherapy management page.
- Stage IIA, IIB treated with primary chemotherapy
  - Postchemotherapy management for negative markers, no mass, or residual mass <1 cm on CT scan:
    - ◊ Surveillance was changed from a category 2B to a 2A.
    - ◊ Nerve-sparing bilateral RPLND was modified by adding, "in selected cases."

TEST-11

- Post-chemotherapy management
  - For a complete response, negative markers,
    - ◊ If original stage was Stage IS, the surveillance recommendation was changed from category 2B to a 2A.
    - ◊ If original stage was Stage IIA, S1; Stage IIB, S1; Stage IIC; or Stage IIIA, "Surveillance" was changed from a category 2B to a 2A and "Bilateral RPLND ± nerve-sparing" was modified by adding, "in selected cases."

TEST-12

- Second-line therapy
  - For unfavorable prognosis and late relapse, after second-line therapy, the decision points "complete response" and "incomplete response or persistent disease" with corresponding treatment options replaced "persistent disease or relapse."

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- For Stage IIA/B, the modified dog-leg field dose was revised, "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.~~"

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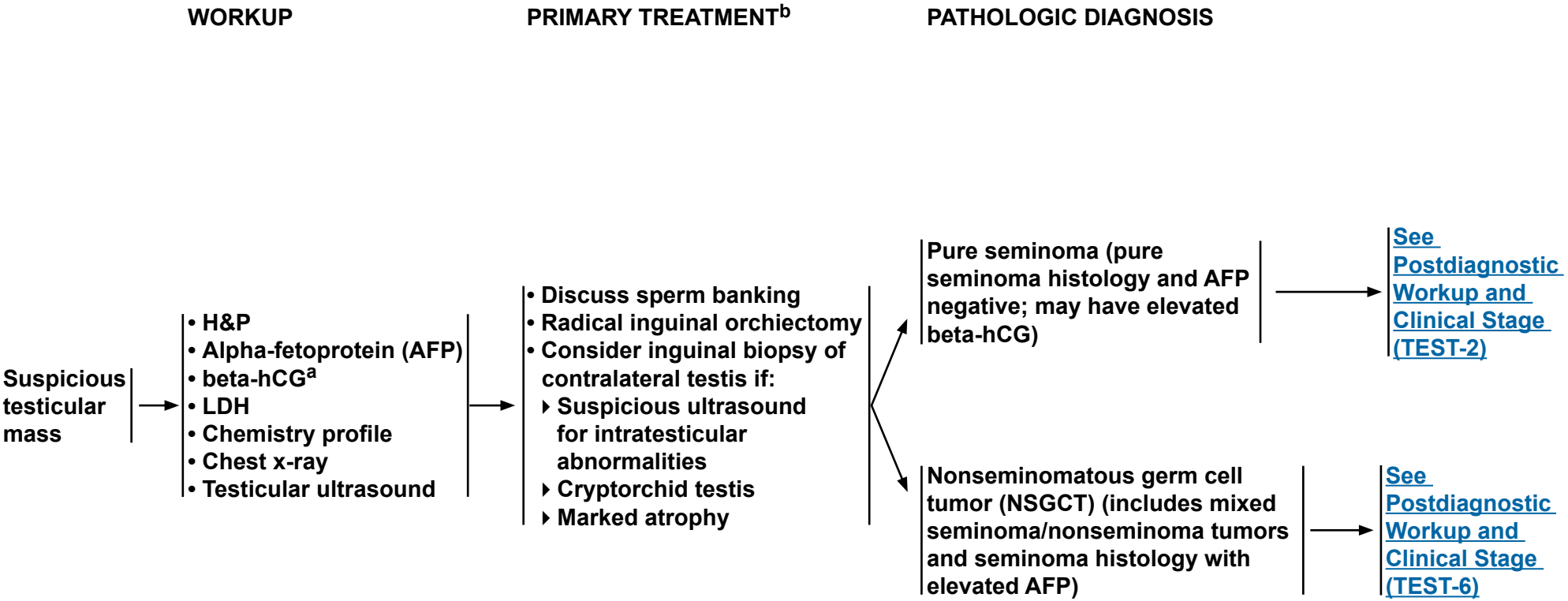

[a]Quantitative analysis of beta subunit.
[b]Though rare, when a patient presents with rapidly increasing beta-hCG and symptoms related to disseminated disease and a testicular mass, chemotherapy can be initiated immediately without waiting for a biopsy diagnosis.

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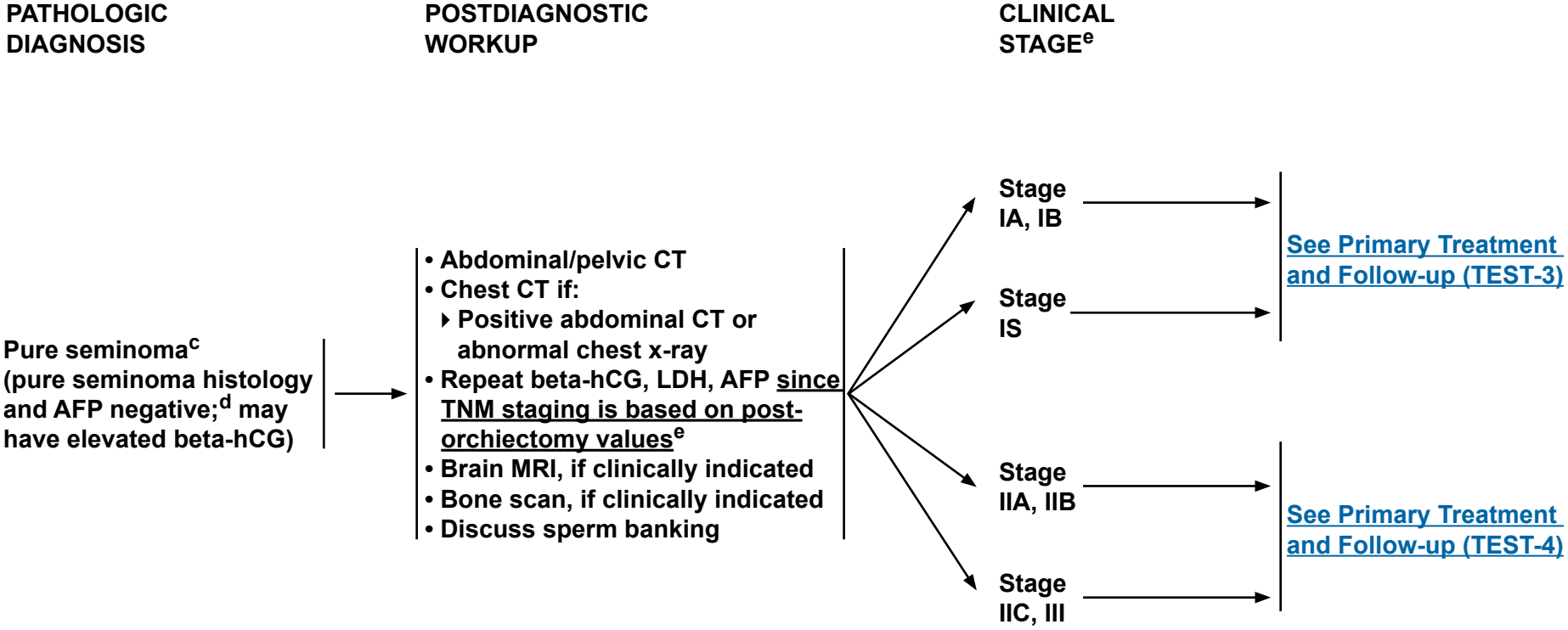

[c]Mediastinal primary seminoma should be treated by risk status used for gonadal seminomas with etoposide/cisplatin for 4 cycles or bleomycin/etoposide/cisplatin for 3 cycles.
[d]If AFP positive, treat as nonseminoma.
[e]Elevated values should be followed after orchiectomy with repeated determination to allow precise staging.

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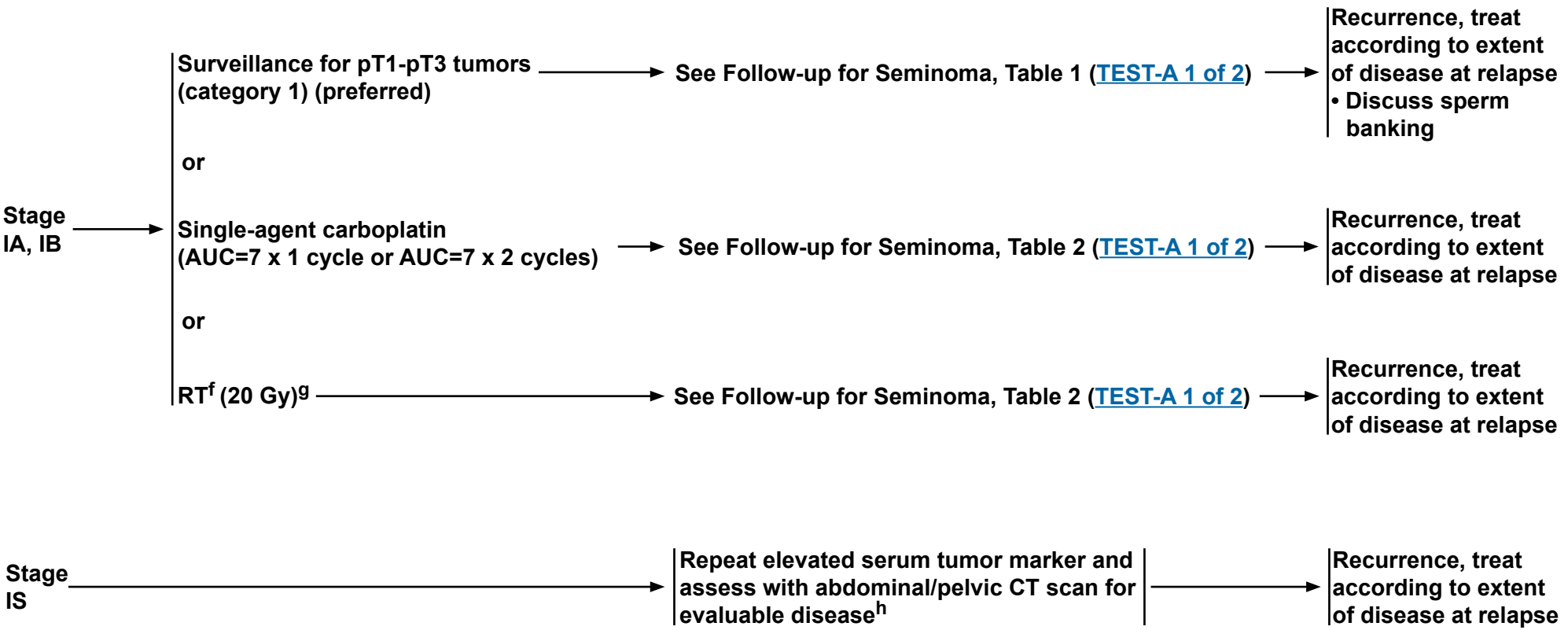

[f] See Principles of Radiotherapy for Pure Testicular Seminoma (TEST-C).
[g] For Stage I seminoma, long-term follow-up studies indicate an increase in late toxicities with radiation treatment. See Discussion.
[h] For further information on Stage IS, see Discussion.

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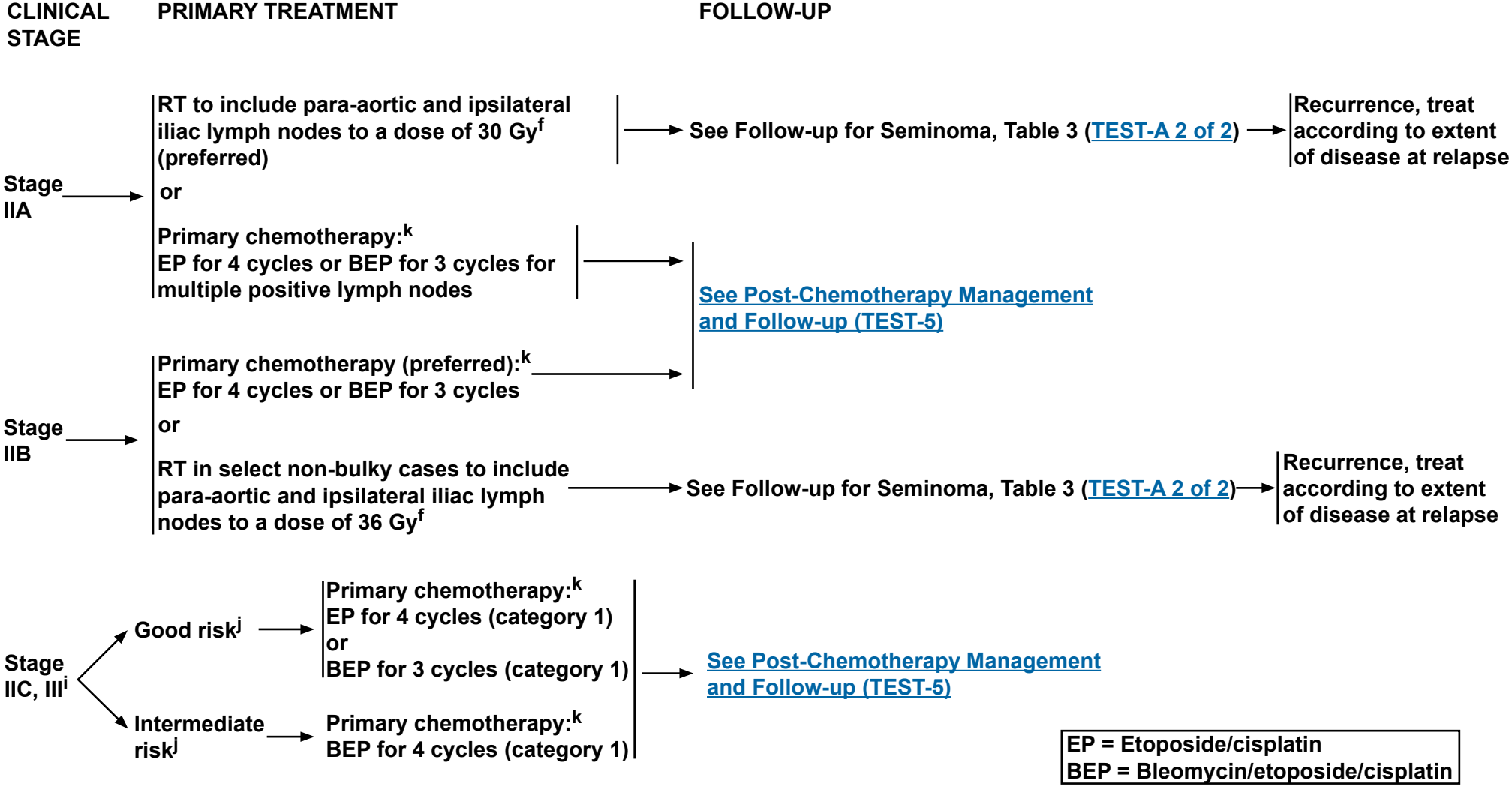

[f] See Principles of Radiotherapy for Pure Testicular Seminoma (TEST-C).
[i] All stage IIC and stage III seminoma is considered good-risk disease except for stage III disease with non-pulmonary visceral metastases (eg, bone, liver, or brain), which is considered intermediate risk.
[j] See Risk Classification for Advanced Disease (TEST-D).
[k] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).

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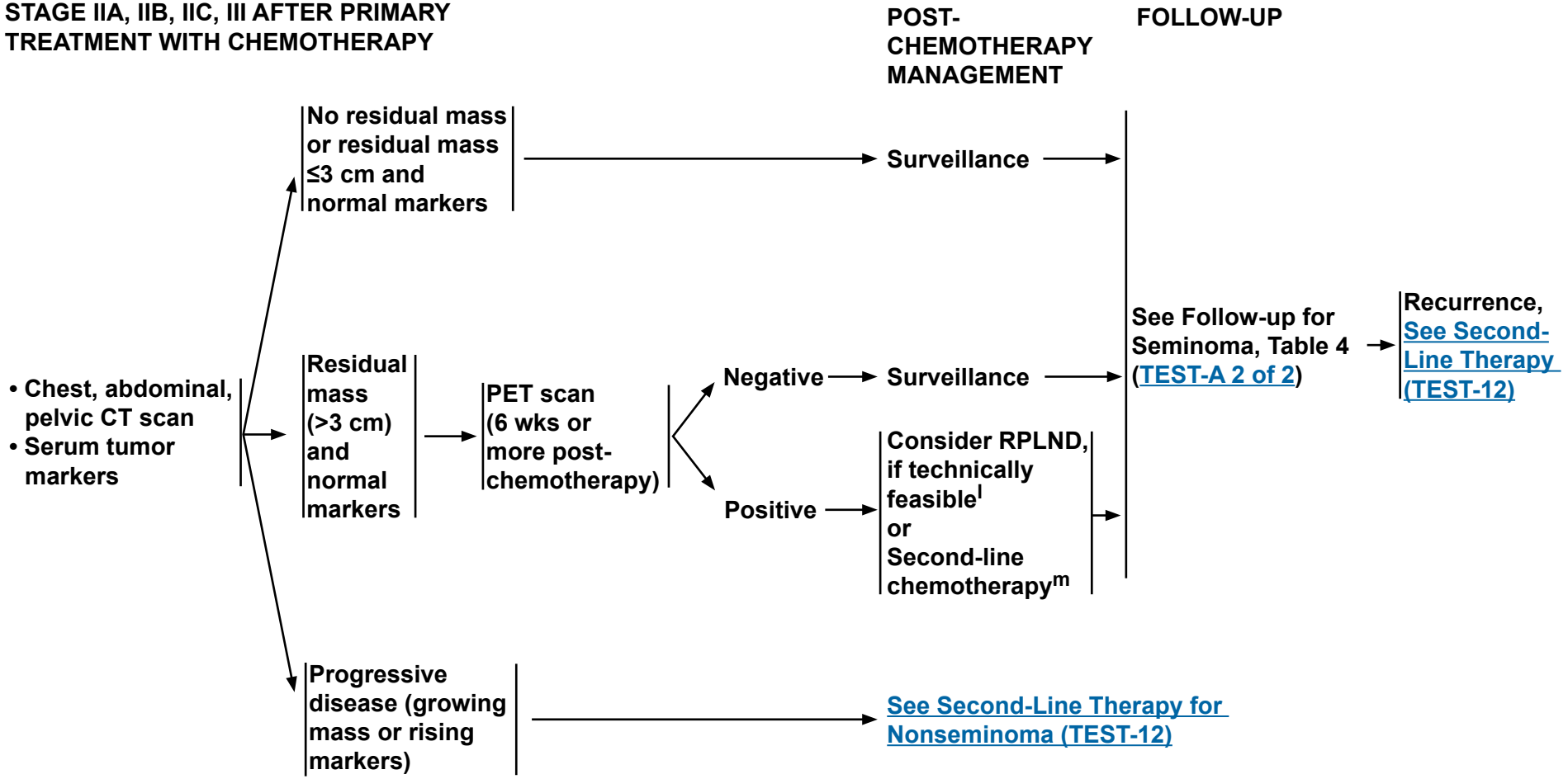
STAGE IIA, IIB, IIC, III AFTER PRIMARY TREATMENT WITH CHEMOTHERAPY



[l]If viable seminoma found by retroperitoneal lymph node dissection (RPLND), see TEST-11 (residual embryonal, yolk sac, choriocarcinoma, or seminoma elements).
[m]See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).

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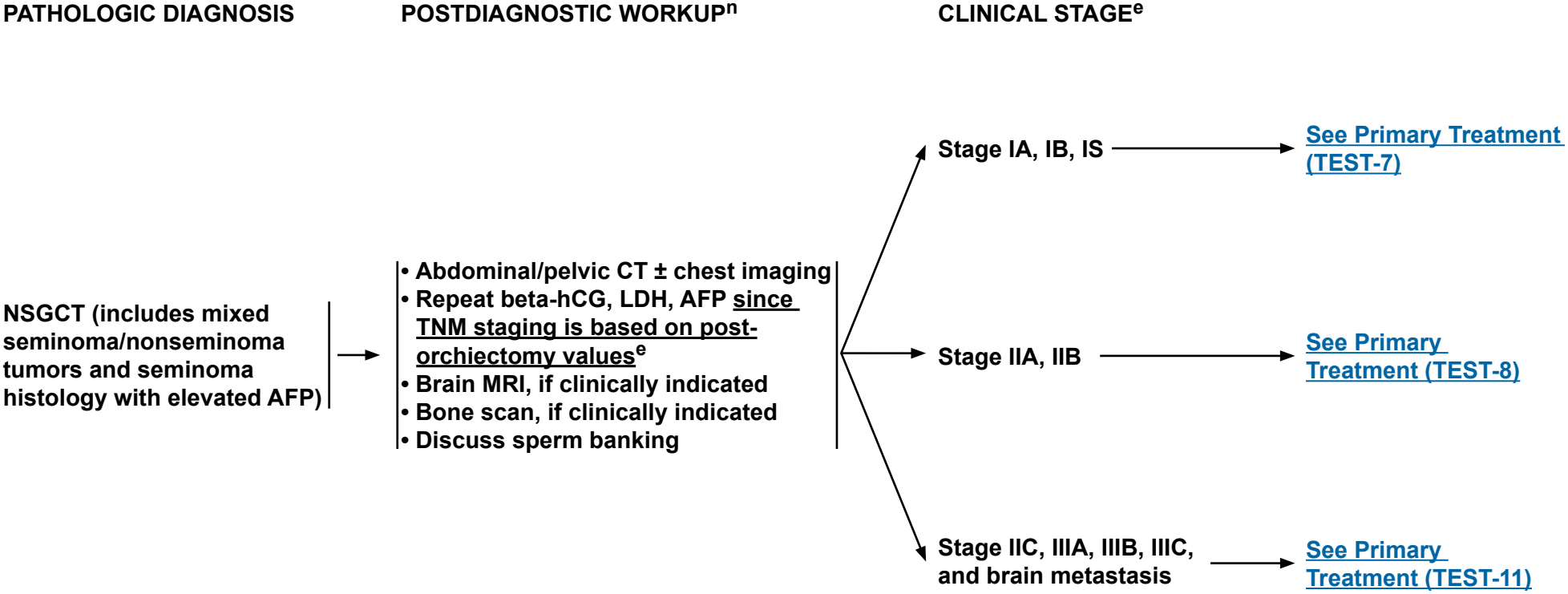

[e]Elevated values should be followed after orchiectomy with repeated determination to allow precise staging.
[n]PET scan is not clinically indicated for nonseminoma.

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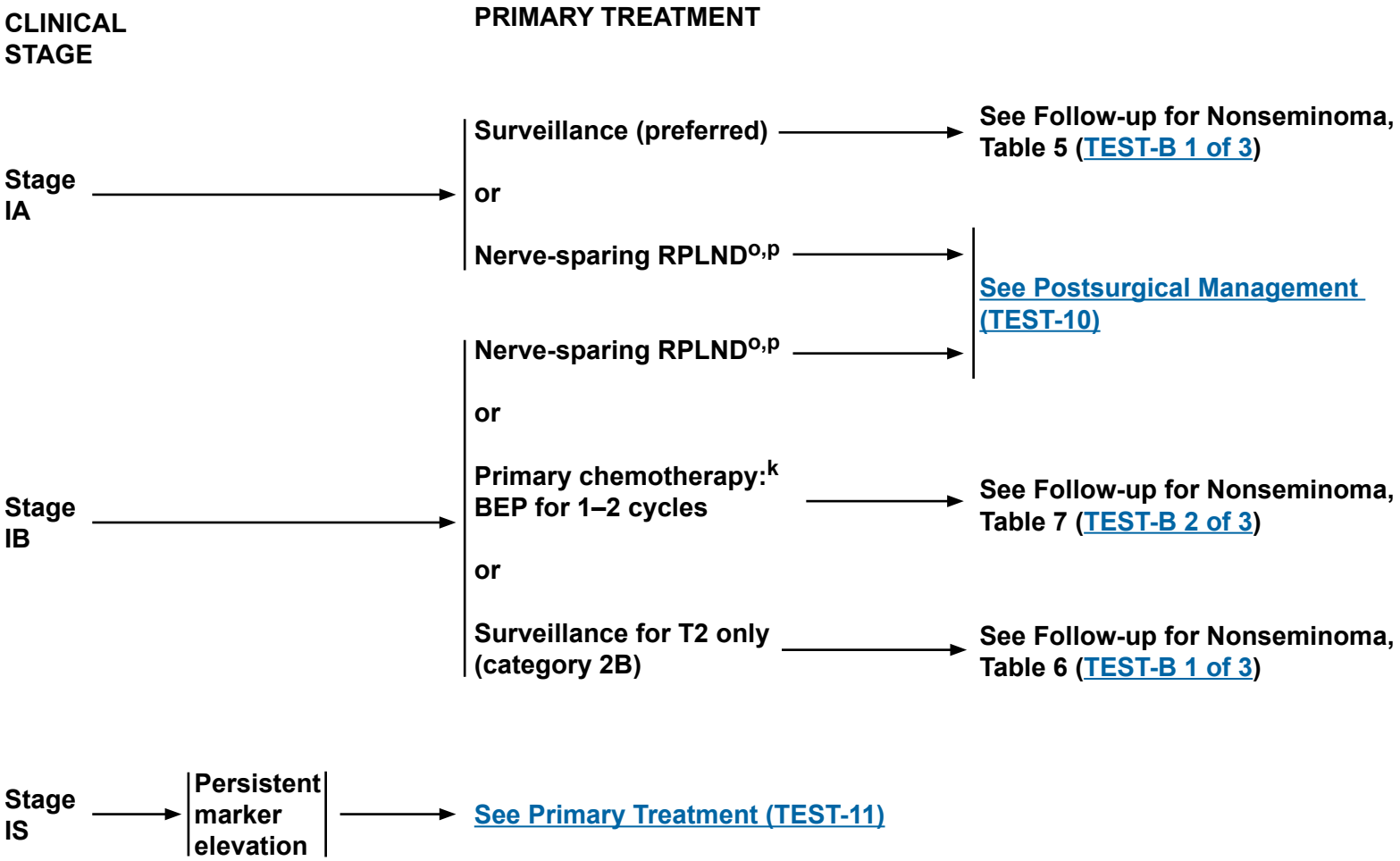

[k] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[o] Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.
[p] See Principles of Surgery for Germ Cell Tumors (TEST-H).

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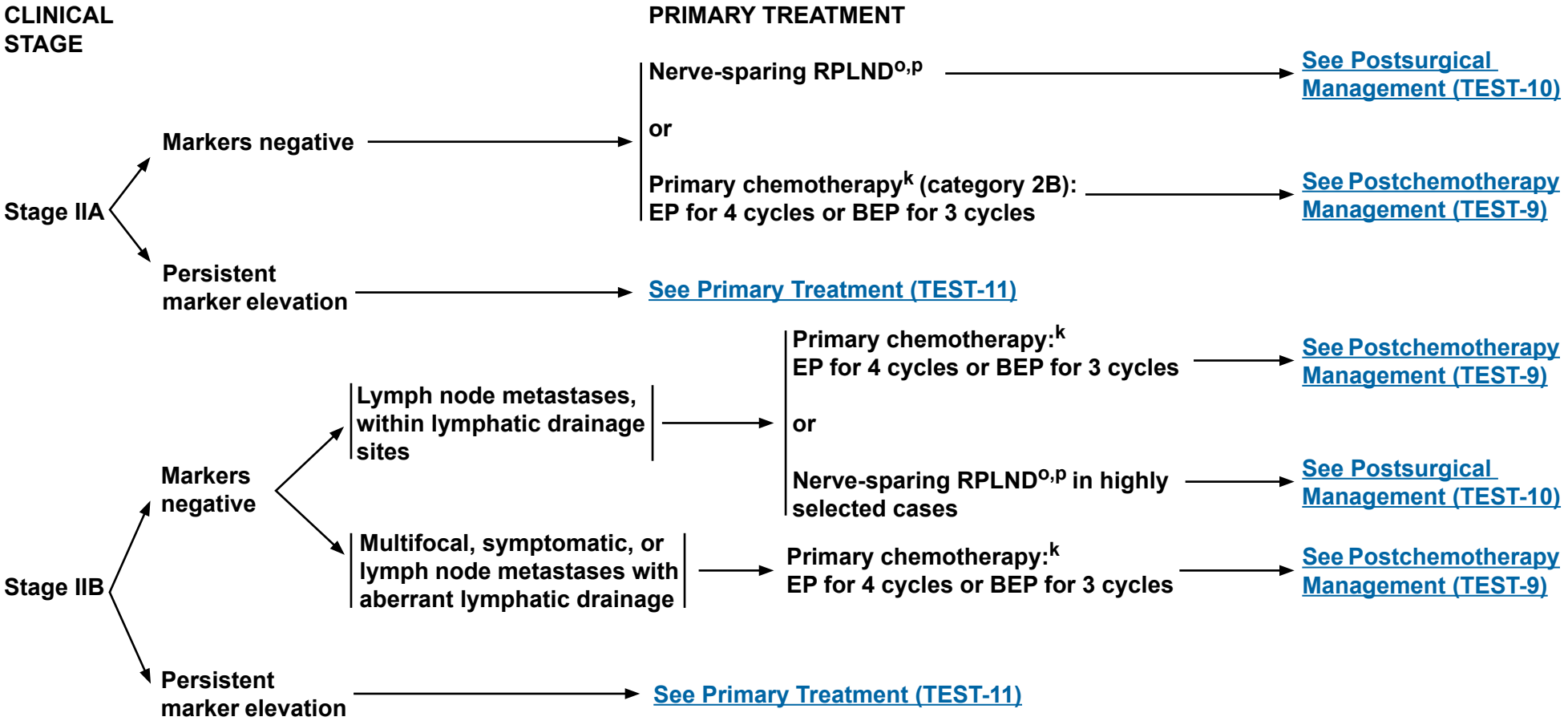

EP = Etoposide/cisplatin
BEP = Bleomycin/etoposide/cisplatin

[k] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[o] Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.
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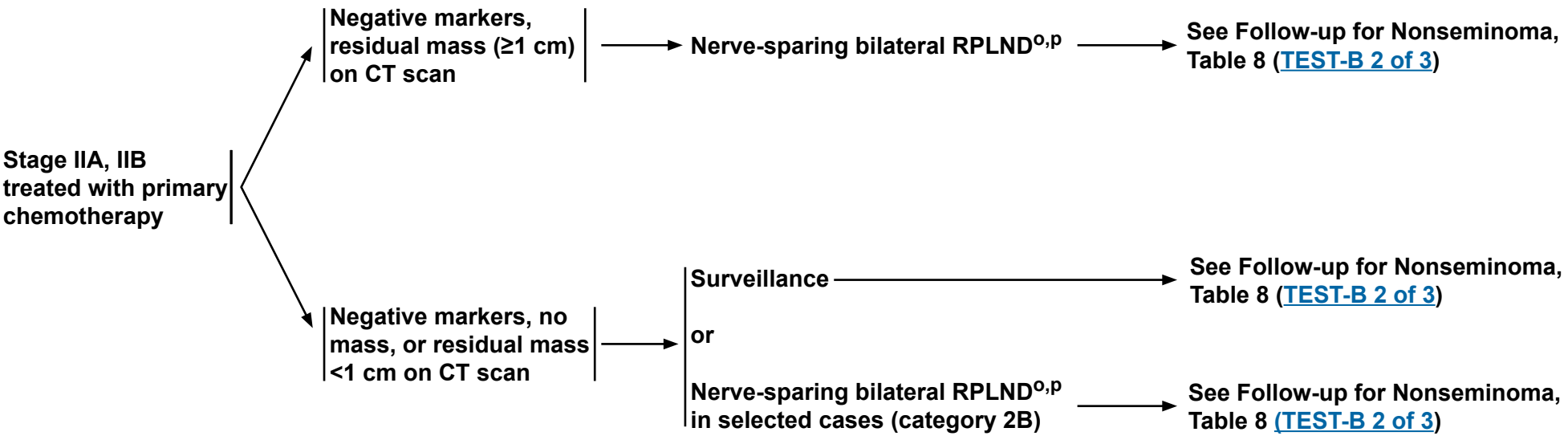
POSTCHEMOTHERAPY MANAGEMENT



[o]Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.
[p]See Principles of Surgery for Germ Cell Tumors (TEST-H).

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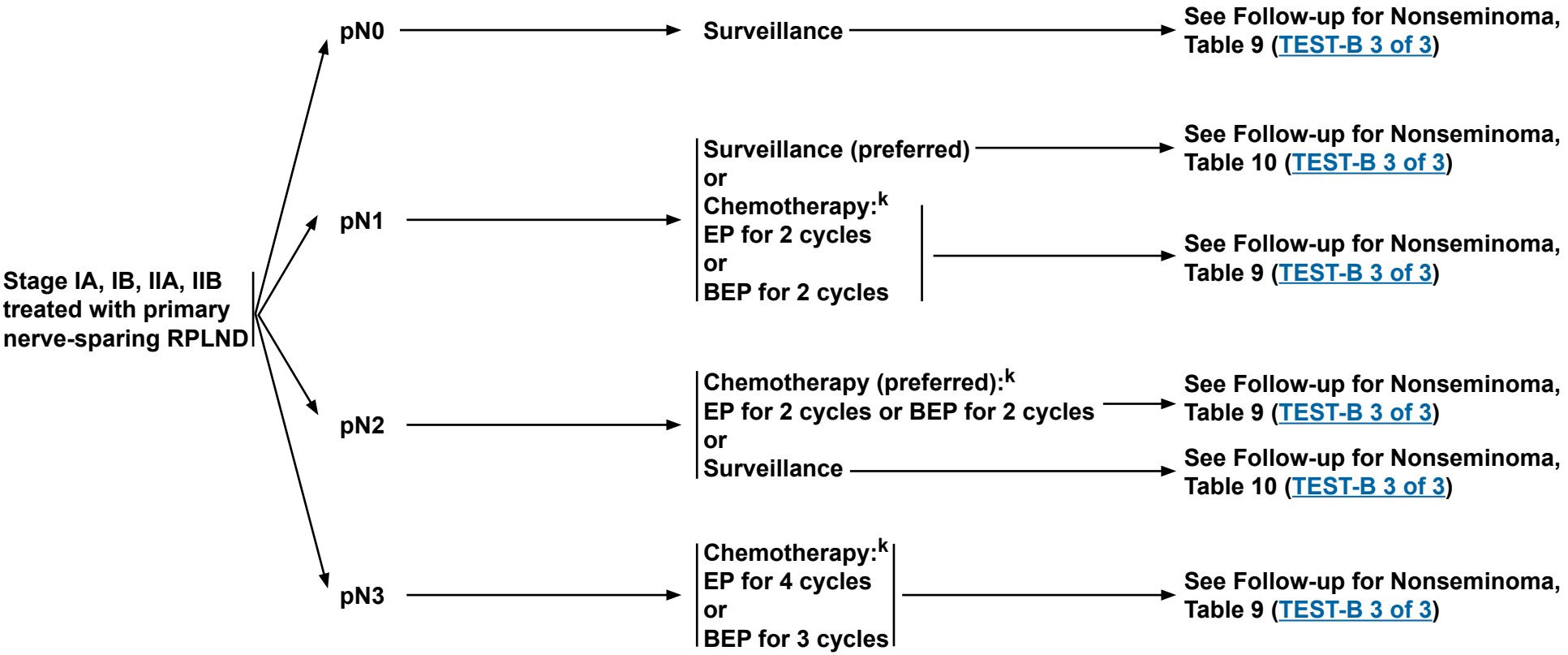
POSTSURGICAL MANAGEMENT



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

[k] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).

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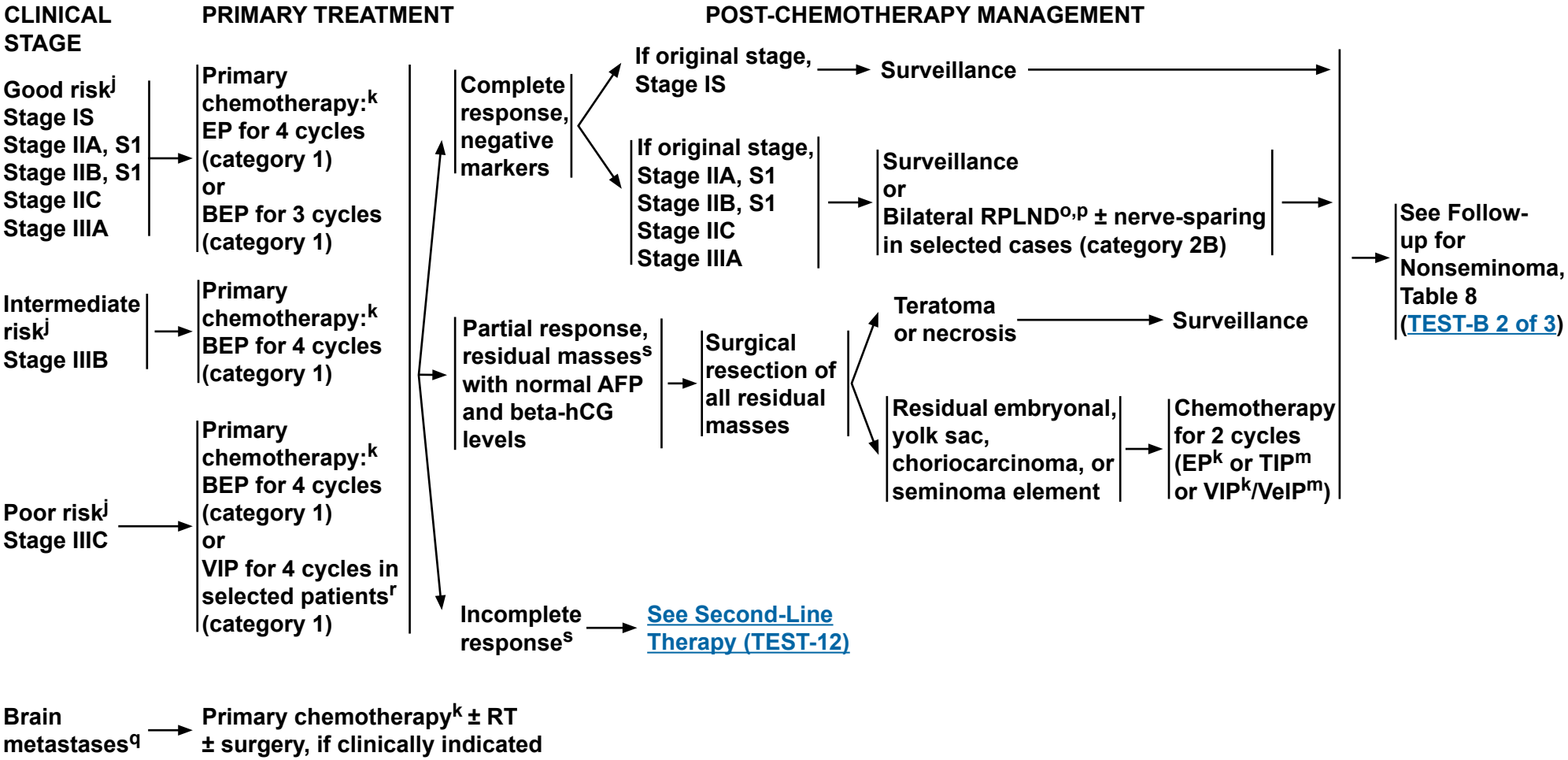

[j] See Risk Classification for Advanced Disease (TEST-D).
[k] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[m] See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).

[o] Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.
[p] See Principles of Surgery for Germ Cell Tumors (TEST-H).
[q] Patients should receive adequate treatment for brain metastases, in addition to cisplatin-based chemotherapy.
[r] Patients who may not tolerate bleomycin.
[s] There is limited predictive value for PET scan for residual masses.

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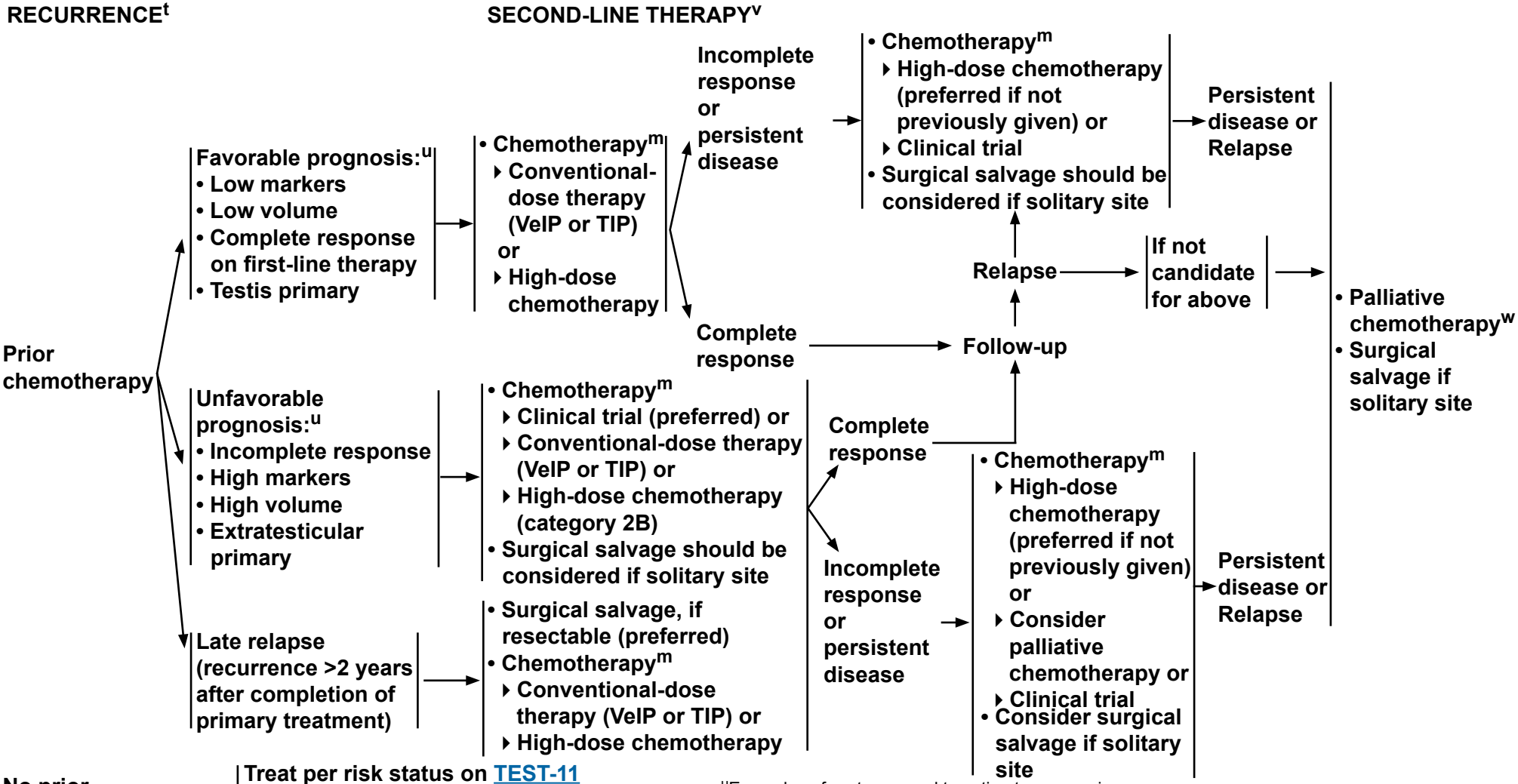

[m] See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).

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

[u] Examples of systems used to estimate prognosis are:
1) Lorch A, Beyer J, Bascoul-Mollevi C, et al. J Clin Oncol 2010;28:4906-4911.
2) Einhorn LH, Williams SD, Chamness A, et al. New Engl J Med 2007;357:340-348.
3) Motzer RJ, Geller NL, Tan CC, et al. Cancer 1991;67:1305-1310.

[v] Includes best supportive care.

[w] See Subsequent Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-G).

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FOLLOW-UP FOR SEMINOMA

The follow-up for seminoma tables are to provide guidance, and should be modified for the individual patient based upon sites of disease, biology of disease, and length of time on treatment. Reassessment of disease activity should be performed in patients with new or worsening signs or symptoms of disease, regardless of the time interval from previous studies.

Table 1 Clinical Stage I Seminoma: Surveillance after Orchiectomy

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 3–6 mo	Every 6–12 mo	Every 6–12 mo	Annually	Annually
Abdominal/ Pelvic CT	At 3, 6, and 12 mo	Every 6–12 mo	Every 6–12 mo	Every 12–24 mo	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients.				

If Recurrence, treat according to extent of disease at relapse

Table 2 Clinical Stage I Seminoma: Surveillance after Adjuvant Treatment (Chemotherapy or Radiation)

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 6–12 mo	Every 6–12 mo	Annually	Annually	Annually
Abdominal/ Pelvic CT	Annually	Annually	Annually	------	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients.				

If Recurrence, treat according to extent of disease at relapse

[1]Serum tumor markers are optional.
[2]Testicular ultrasound for any equivocal exam.

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FOLLOW-UP FOR SEMINOMA

Table 3 Clinical Stage IIA and Non-Bulky IIB Seminoma: Surveillance after Radiotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal/ Pelvic CT	At 3 mo, then at 6–12 mo	Annually	Annually	As clinically indicated	
Chest x-ray[3]	Every 6 mo	Every 6 mo	------		

If Recurrence, treat according to extent of disease at relapse

Table 4 Bulky Clinical Stage IIB and Stage III Seminoma: Surveillance Post-Chemotherapy with No Residual Mass or Residual Mass ≤3 cm and Normal Tumor Markers

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[2]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT[4]	• Abdominal/pelvic CT at 3–6 months, then as clinically indicated • PET scan as clinically indicated				
Chest x-ray[3]	Every 2 mo[5]	Every 3 mo[5]	Annually	Annually	Annually

If Recurrence, see TEST-12.

[1]Serum tumor markers optional.
[2]Testicular ultrasound for any equivocal exam.
[3]Chest x-ray may be used for routine follow-up but chest CT is preferred in the presence of thoracic symptoms.
[4]Patients with PET-negative residual mass measuring >3 cm following chemotherapy should undergo an abdominopelvic CT scan every 6 months for the first year then annually for five years.
[5]Add chest CT if supradiaphragmatic disease present at diagnosis.

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FOLLOW-UP FOR NONSEMINOMA

The follow-up tables for nonseminoma are to provide guidance, and should be modified for the individual patient based upon sites of disease, biology of disease, and length of time on treatment. Reassessment of disease activity should be performed in patients with new or worsening signs or symptoms of disease, regardless of the time interval from previous studies.

Table 5 Clinical Stage IA, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Every 4–6 mo	Every 6–12 mo	Annually	---	---
Chest x-ray[2]	At mo 4 and12	Annually	Annually	Annually	Annually

If Recurrence, see TEST-12.

Table 6 Clinical Stage IB, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Every 4 mo	Every 4–6 mo	Every 6 mo	Annually	---
Chest x-ray[2]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually

If Recurrence, see TEST-12.

[1]Testicular ultrasound for any equivocal exam.
[2]Chest x-ray may be used for routine follow-up but chest CT is preferred in the presence of thoracic symptoms.

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FOLLOW-UP FOR NONSEMINOMA

Table 7 Clinical Stage IB NSGCT: Treated with 1–2 Cycles of Adjuvant BEP Chemotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 3 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Annually	Annually	---	---	---
Chest x-ray[2]	Every 6–12 mo	Annually	---	---	---

If Recurrence, see TEST-12.

Table 8 Clinical Stage II-III NSGCT: Surveillance After Complete Response to Chemotherapy ± Post-chemotherapy RPLND

	Year (at month intervals)				
	1	2	3	4	5
H&P and marker[1]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal/ Pelvic CT[3]	Every 6 mo	Annually	---	---	---
Chest x-ray[2,4]	Every 6 mo	Every 6 mo	Annually[5]	Annually[5]	---

If Recurrence, see TEST-12.

[1]Testicular ultrasound for any equivocal exam.
[2]Chest x-ray may be used for routine follow-up but chest CT is preferred in the presence of thoracic symptoms.
[3]Patients who undergo RPLND and are found to have pN0 disease (no tumor or teratoma) need only 1 CT scan at postoperative month 4.
[4]Chest CT if supradiaphragmatic disease at baseline.
[5]Chest x-ray is optional at month 36 and 48.

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FOLLOW-UP FOR NONSEMINOMA

Table 9 Pathologic Stage IIA/B NSGCT: Post-Primary RPLND and Treated with Adjuvant Chemotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 6 mo	Every 6 mo	Annually	Annually	Annually
Abdominal/ Pelvic CT	After RPLND	As clinically indicated			
Chest x-ray[2]	Every 6 mo	Annually	Annually	Annually	Annually

If Recurrence, see TEST-12.

Table 10 Pathologic Stage IIA/B NSGCT: Post-Primary RPLND and NOT Treated with Adjuvant Chemotherapy[6]

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	At 3–4 mo[7]	As clinically indicated			
Chest x-ray[2]	Every 2–4 mo	Every 3–6 mo	Annually	Annually	Annually

If Recurrence, see TEST-12.

[1]Testicular ultrasound for any equivocal exam.
[2]Chest x-ray may be used for routine follow-up but chest CT is preferred in the presence of thoracic symptoms.
[6]Patients with clinical stage II-A/II-B nonseminoma who undergo primary RPLND and are found to have pN0 disease (no tumor or teratoma, pathologic Stage I) should revert to the surveillance schedule for low-risk NSGCT with the exception that only 1 CT scan is needed postoperatively around month 4 (Table 5).
[7]This schedule assumes a complete resection has taken place.

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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) three-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 once the orchiectomy wound has fully healed.
  - 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 the NCCN Guidelines for Antiemesis. Antiemetic prophylaxis is encouraged at least two hours prior to each treatment, and some cases may require more frequent dosing.

Preparation for Radiotherapy

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

Treatment Planning Principles

- A non-contrast 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.

For Stage I, see TEST-C 2 of 5
For Stage IIA, IIB, see TEST-C 3 of 5
For References, see TEST-C 5 of 5

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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 fractions. Daily 2.0-Gy 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 T-11.[13]
      - – The inferior border should be placed at the inferior border of vertebral body L-5.[10,14]
    - ◊ Lateral borders:
      - – Conventionally, PA-strip fields are approximately 10 cm wide, encompassing the tips of the transverse processes of the PA 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 T-12. The right and left kidney D50% should be ≤8 Gy (ie, 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 (ie, 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 1.2-1.9-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 TEST-C 4 of 5).[3]

Special Considerations:

- Ipsilateral pelvic surgery (eg, 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.

For Stage IIA, IIB, see TEST-C 3 of 5
For References, see TEST-C 5 of 5

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Stage IIA-IIB

- Patients should not receive primary RT if they have a horseshoe (pelvic) kidney, inflammatory bowel disease, or a history of RT.
- For clinical stage IIA-B patients, treatment is delivered in two 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 fractions; daily 2.0-Gy[17].
  - Target: The fields should include the retroperitoneal and proximal ipsilateral iliac lymph nodes.
    - ◊ Modified dog-leg fields as described by Classen et al are preferred.[18]
      - – Care should be taken to ensure coverage of the ipsilateral common, external, and proximal internal iliac lymph nodes down to the top of the acetabulum.
      - – The fields can be set up using bony landmarks or by contouring the vascular structures, as for stage I.
        - ▪ The superior border should be placed at the bottom of vertebral body T-11.[19]
        - ▪ The inferior border should be placed at the top of the acetabulum.[18]
        - ▪ The medial border for the lower aspect of the modified dog-leg fields extends from the tip of the contralateral transverse process of the fifth lumbar vertebra toward the medial border of the ipsilateral obturator foramen.
        - ▪ The lateral border for the lower aspect of the modified dog-leg fields is defined by a line from the tip of the ipsilateral transverse process of the fifth lumbar vertebra to the superolateral border of the ipsilateral acetabulum.
        - ▪ Preferably, one should contour the aorta and inferior vena cava from the bottom of the T-11 vertebra inferiorly and ipsilateral iliac arteries and veins down to the top of the acetabulum. One should provide a 1.2- to 1.9-cm margin on these vascular structures for 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 2, see TEST-C 4 of 5).[3]
        - ▪ It is not necessary to include the ipsilateral inguinal nodes or the inguinal scar in the AP-PA fields unless the patient has a history of ipsilateral pelvic surgery (eg, inguinal herniorrhaphy or orchiopexy).

- 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.[18]
  - 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 TEST-C 4 of 5).

For Stage I, see TEST-C 2 of 5
For References, see TEST-C 5 of 5

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Figure 1

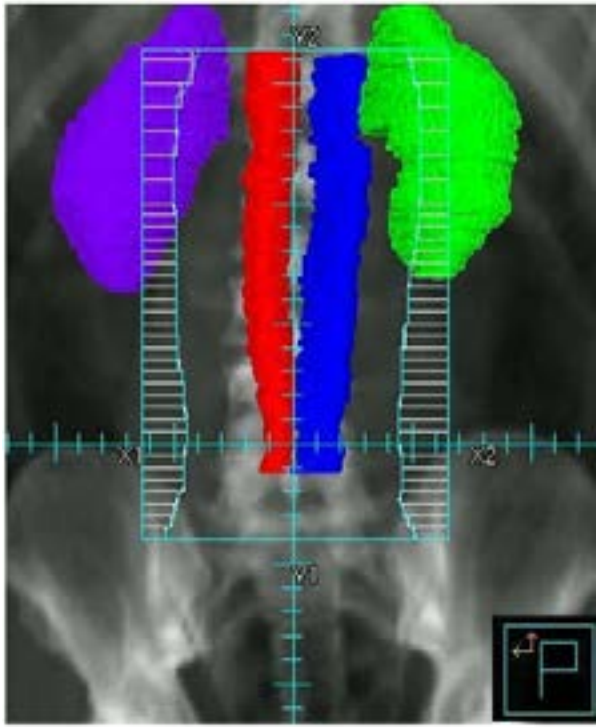


Figure 2

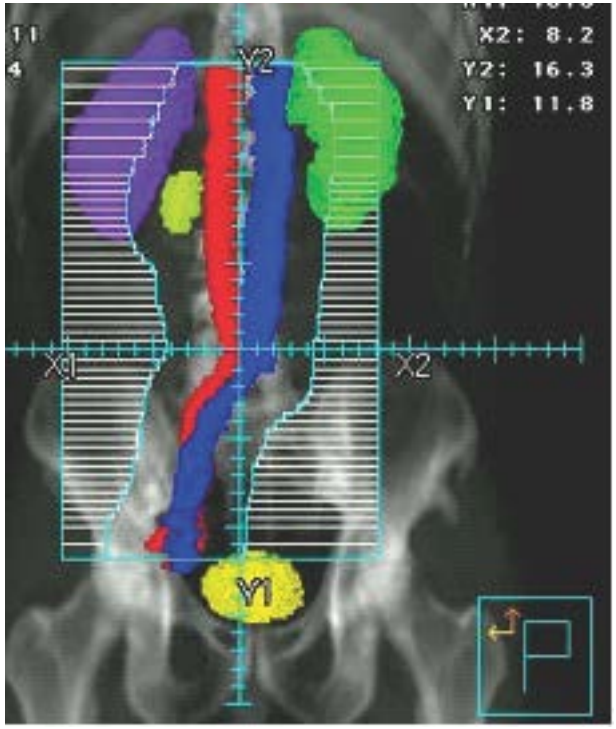
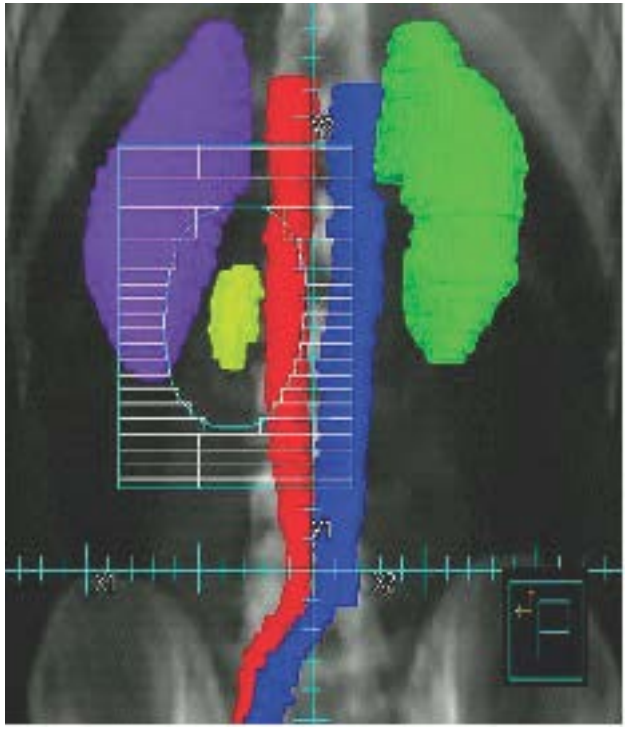


Figure 3



For Stage I, see TEST-C 2 of 5
For Stage IIA, IIB, see TEST-C 3 of 5
For References, see TEST-C 5 of 5

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

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

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

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

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

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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[1]

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, and 16
Repeat every 21 days[2]

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[3]

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

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[2]

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[3]

Paclitaxel 200 mg/m² IV over 24 hours on Day 1
Ifosfamide 2000 mg/m² over 4 hours with mesna protection on Days 2–4
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- to 21-day intervals for 3 cycles[4]

[1]Loehrer PJ Sr, Lauer R, Roth BJ, et al. Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med 1988;109:540-546.
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SUBSEQUENT CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

Palliative Chemotherapy Regimens*

Gemcitabine/oxaliplatin
Gemcitabine/paclitaxel
Gemcitabine/paclitaxel/oxaliplatin
Etoposide (oral)

***See references below for dosing.**

Etoposide (oral)
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Gemcitabine/oxaliplatin/paclitaxel
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Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SURGERY FOR GERM CELL TUMORS

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

Post-Chemotherapy Setting

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

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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

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Continued on next page

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Table 1 (continued)

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

ANATOMIC STAGE/PROGNOSTIC GROUPS

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

Serum Tumor Markers (S)

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

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 1/17/12

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.

Discussion update in progress

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Overview

An estimated 8,590 new cases of testicular cancer will be diagnosed in the United States in 2012.[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 beta-human chorionic gonadotropin (beta-HCG) are critical in diagnosing the 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 very useful for monitoring all stages of nonseminomas. Serum markers are also useful in monitoring metastatic seminomas because elevated marker levels are the early signs of relapse.

LDH is a less specific marker compared to AFP and 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] An elevated serum concentration of beta-HCG, which has a half-life of approximately 1–3 days, may also be present with seminomatous and nonseminomatous tumors. The elevations of beta-HCG need to be interpreted with caution as 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% 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.

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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 the serum tumor markers, and a chest x-ray. 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.[4]

Serum tumor markers are critical in the assignment of prognosis and management during treatment as well. Serum tumor markers are prognostic factors and contribute to diagnosis and staging.[5] 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.

Biopsy may also be considered if a suspicious intratesticular abnormality, such as a hypoechoic mass or macrocalcification, is identified on ultrasound. In contrast, if microcalcifications without any other abnormality can be observed, testicular biopsy is not necessary.

In patients of reproductive age, sperm banking must be discussed.[6, 7] It must be discussed with the patients before undergoing any therapeutic intervention that may compromise fertility, including surgery, radiation therapy, and chemotherapy.[8-10] If banking of sperm is desired, it may be performed either before or after orchiectomy but certainly prior to subsequent therapy.

Inguinal orchiectomy is considered the primary treatment for most patients who present with a suspicious testicular mass.[11] 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.[12] The extent of primary tumor is classified after orchiectomy, and therefore pathological (p) stage is assigned to the primary tumor (T).

Further management is dictated by histology, a diagnosis of pure seminoma or nonseminoma (includes mixed seminoma tumors and seminoma histology with elevated AFP), and the stage. 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.

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 post -orchiectomy. Post-orchiectomy markers are utilized to classify the patient according to the IGCCCG risk classification. This classification categorizes patients with pure seminoma and non-seminoma GCT into good-, intermediate-, or poor-risk groups.[13]

Definition of stage and risk classification is done according to the American Joint Committee on Cancer (AJCC) and IGCCCG classification.

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Pure Seminoma

If a GCT is found, an abdominopelvic computed tomographic (CT) scan is performed. Abdominopelvic CT scanning is used to assess the retroperitoneal nodes.[14]

A chest CT is indicated if the abdominopelvic CT shows retroperitoneal adenopathy or the chest x-ray shows abnormal results. A chest CT scan is a sensitive way to evaluate the thorax and mediastinal nodes.[15]

The NCCN panel members recommend a brain MRI or bone scan, only if there is suspicion of metastases to these organs.

Elevated values of beta-HCG, LDH, or AFP should be followed with repeated tests. Serum concentrations of beta-HCG and LDH may be elevated in patients with seminoma. An elevated AFP level indicates nonseminoma, and the patient 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.[16] A number of prospective non-randomized studies of surveillance have been conducted.[17-20] The relapse rate seen in these studies is 15-20% at 5 years, and most of the relapses are first detected in infra-diaphragmatic lymph nodes.[18-20] Some studies report tumor size greater than 4 cm and rete testis invasion as a risk factor in predicting relapse in patients.[19, 21, 22] A validation study by Chung et al revealed that tumor size >4 cm and rete testis invasion were not predictors of relapse.[23, 24] Therefore, the NCCN panel members discourage risk-adapted management using tumor size >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 by the NCCN Testicular Cancer panel.

If surveillance is not applicable, alternatives are either adjuvant carboplatin or adjuvant radiotherapy as described below. 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 1 testicular cancer to undergo either radiotherapy or one injection of carboplatin.[25] In the study, carboplatin (area under the cure [AUC] X 7) was administered given intravenously. 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 survival rates for both groups were similar.[25] Late relapses and secondary GCTs can occur beyond 5 and 10 years. Therefore, the investigators continued to follow these patients. The updated results reported non-inferiority of single-dose carboplatin versus radiation therapy.[26] 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 = 0.37). There were 2 cases of contralateral GCTs on carboplatin versus 15 on radiation therapy 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.[26]

Discussion
Updated in progress

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Two courses of adjuvant carboplatin have also been reported to reduce the relapse rate.[27] The NCCN Testicular Cancer panel recommends carboplatin AUC X 7 either 1 or 2 cycles as a category 1 recommendation for patients with stages IA and IB pure seminoma.

If radiation therapy is delivered, the NCCN panel recommends a total dose of 20.0 Gy (midplane) in 10 daily 2.0 Gy fractions,[28] given to an infradiaphragmatic area, including para-aortic lymph nodes; in special circumstances, it may include the ipsilateral ilioinguinal nodes.[29-32] Patients for whom radiation therapy is generally not given include those with patients 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 para-aortic nodes is also a category 1 recommendation in the NCCN Testicular Cancer Guidelines, though active surveillance is preferred (see page entitled “Principles of Radiotherapy for Treatment of Pure Seminoma” in the algorithms).

Follow-up after primary treatment for pure seminoma stages IA and IB
For follow-up, it is important to distinguish the different risk of recurrence associated with each treatment modality (surveillance versus adjuvant therapy). An analysis of more than 5,000 stage I seminoma patients 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 for patients on surveillance includes a history and physical, with measurement of post -orchiectomy serum tumor markers (AFP, beta-HCG, and LDH), performed every 3 to 4 months for 1-2 years, every 6-12 months for years 3-4, and annually thereafter.[34, 35]

There is controversy regarding how many imaging studies must be performed in patients on active surveillance. The NCCN panel recommends abdominal/ pelvic CT every 6 months for years 1-2, every 6-12 months for year 3, and then annually for years 4-5. The most common site of relapse in patients managed by surveillance or adjuvant chemotherapy is the retroperitoneal nodes. Chest x-rays may be obtained as clinically indicated for years 1-5. A clinical trial in UK, entitled TRISST (MRC TE24/TRial of Imaging and Schedule in Seminoma Testis), 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.[36]

The risk of recurrence 5 years after adjuvant treatment is <0.3% annually.[33] Follow-up of patients treated with carboplatin includes a history and physical, with measurement of post -orchiectomy serum tumor markers (AFP, beta-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 NCCN panel recommends abdominal/pelvic CT annually for the first 3 years after RT or carboplatin. In a recently published meta-analysis of 2,466 patients, Mead et al reported that recurrence rarely occurred after more than 3 years from treatment with either RT or carboplatin.[16] Relapse occurred after 3 years only in 4 out of the 2,466 patients (0.2%).[16] They recommend that CT scans of the pelvis and chest can be omitted in these patients as a part of routine follow-up. The NCCN panel recommends that chest x-rays be obtained only as clinically indicated.

Follow-up of patients treated with radiotherapy includes a history and physical, with measurement of post -orchiectomy serum tumor markers

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(AFP, beta-HCG, and LDH). Follow-up should be performed every 4 months for 1-2 years, and then annually for 3-10 years.[33] Para-aortic radiation therapy is recommended when patients with stage I seminoma are irradiated (see page entitled "Principles of Radiotherapy for Treatment of Pure Seminoma" in the algorithms). Patients treated with para-aortic radiation therapy have a slightly higher rate of pelvic relapse compared with those treated with ''dog-leg'' RT.[30, 33, 37, 38] Some NCCN Institutions obtain a CT scan of the pelvis only every 6 months for 3 years after paraaortic radiotherapy.[33] Other NCCN institutions 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 x-rays 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

By the AJCC definition, stage IS requires persistent elevation of serum tumor markers (LDH, AFP, and beta-HCG) following 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 NCCN 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, and stage IIB as disease measuring 2 to 5 cm in maximum diameter.

Radiotherapy has been the mainstay of treatment in stage IIA and IIB seminoma patients.[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 NCCN Testicular Cancer panel recommends radiation therapy to an infradiaphragmatic area, including para-aortic and ipsilateral iliac lymph nodes in two anteroposterior-posteroanterior phases. The initial phase consists radiation to modified dog-leg fields consisting of a dose of 20.0 Gy (midplane) in 10 daily 2.0 Gy fractions[29] 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 page entitled "Principles of Radiotherapy for Treatment of Pure Seminoma" in the algorithms. 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 stage IIB seminoma patients 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

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The recommended follow-up schedules for stage IIA/B patients after radiation therapy include a history and physical with measurement of post-orchiectomy serum tumor markers (AFP, beta-HCG, and LDH), performed every 3 months for year 1, every 6 months for years 2-5, and then annually for years 6-10.

Chest x-ray is recommended every 6 months for the first 2 years. An abdominal CT scan is recommended every 6 months in years 1-2 and annually in year 3 after radiotherapy. In those who have undergone retroperitoneal lymph node dissection (RPLND), it is recommended between 3-6 months post surgery and then as clinically indicated.[39]

The follow-up of stage IIB patients after chemotherapy is similar to follow-up after chemotherapy for patients with stages IIC and III as discussed in the section below entitled "Follow-up for pure seminoma stages IIB, IIC, and III after chemotherapy"

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 non-pulmonary visceral metastases (e.g., bone, liver, or brain), which is considered intermediate risk. Standard chemotherapy is used for both groups of patients. However, for patients with good risk, 3 cycles of BEP[47-49] or 4 cycles of EP [50-52] are recommended. In contrast, more intensive chemotherapy, i.e., 4 cycles of BEP, is recommended for those with intermediate risk disease.[53, 54] All these chemotherapy options are category 1 recommendations according to the NCCN Testicular Cancer panel.

Post-chemotherapy management of pure seminoma stages IIB, IIC, and III

After initial chemotherapy, patients with stage IIB, IIC and III are evaluated with serum tumor markers and a CT scan of the chest abdomen and pelvis. Patients are then classified according to the presence or absence of a residual mass and the status of serum tumor markers. Patients with normal markers and either no residual mass or residual mass of 3 cm or lesser need no further treatment. They should undergo surveillance as discussed in the section below entitled "Follow-up for pure seminoma stages IIB, IIC, and III after chemotherapy"

In cases of residual tumor >3 cm and markers levels that are normal, a PET scan is recommended to assess whether there is residual viable tumor.[55] A PET scan has a high positive and negative predictive value 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 NCCN panel recommends a PET scan in patients with seminoma, a residual mass >3 cm and normal levels of markers, approximately 6 weeks after chemotherapy in order to decide 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 section below entitled "Follow-up for pure seminoma stages IIB, IIC, and III after chemotherapy".

Since a positive PET scan is strong indicator of residual active tumor, resection should be considered. Therefore, if technically feasible,

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RPLND may be considered (category 2A). The other option if resection is not feasible is second-line chemotherapy (category 2A). Cisplatin-based combination chemotherapy is used for second-line treatment.[64-66] The regimens are four cycles of TIP (paclitaxel, ifosfamide, cisplatin)[67] or four cycles of VeIP (vinblastine, ifosfamide, cisplatin).[65, 66]

According to the NCCN Guidelines, second-line therapy for seminoma and nonseminoma is similar. It is discussed below in the section entitled "Second-line therapy for Metastatic Germ Cell Tumors". The follow-up of these patients is also described below.

Follow-up for pure seminoma stages IIB, IIC, and III after chemotherapy
Recommended follow-up schedules include a history and physical with chest x-ray and measurement of post- orchiectomy 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 cases except in those who have undergone RPLND. In this situation, it is recommended between 3-6 months post-surgery and then as clinically indicated.[68] A PET scan may be performed as clinically indicated.

Nonseminoma

Similar to the workup for seminoma, if non-seminoma is found, CT of abdomen and pelvis should be performed with chest imaging if needed. MRI of the brain and 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 nonseminoma patients.[69, 70]

Elevated values of beta-HCG, LDH, or AFP should be followed up with repeated tests. Nonseminoma includes mixed seminoma tumors and seminoma histology with elevated AFP. Post-orchiectomy serum markers are important to classify the patient with nonseminoma according to the IGCCCG risk classification into good-, intermediate- and poor-risk groups.[13]

In patients of reproductive age, sperm banking must be discussed.[6, 7] It must be discussed with the patients before undergoing any therapeutic intervention that may compromise fertility, including surgery, radiation therapy, or chemotherapy.[8-10] If sperm banking is desired, it may be performed either before or after orchiectomy, but certainly prior to 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.[71]

Nonseminoma Stage IA

Primary treatment of nonseminoma stage IA
According to the NCCN Testicular Cancer panel, two management options exist for patients with stage IA disease after orchiectomy: (1) surveillance[72-76] (2) nerve-sparing RPLND. The cure rate with either approach exceeds 95%. However, the high cure rate associated with surveillance depends on adherence to periodic follow-up examinations and subsequent chemotherapy for the 20% to 30% of patients who experience relapse. Patients who choose surveillance should agree to

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be compliant for follow-up. When RPLND is performed, it should be done using a nerve-sparing technique.[77, 78] According to the NCCN 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. 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 an option for patients 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.[79-85] 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 NCCN Guidelines, the long term follow-up tests for stage IA patients, electing primary surveillance, post-RPLND, or post-chemotherapy include serum marker assessment, chest x-ray, and an abdominal CT scan. The frequency of these tests is outlined in the NCCN Testicular Cancer treatment algorithms on page entitled “Follow-up for Nonseminoma”.

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 two cycles of BEP as primary treatment for stage I nonseminoma patients have been reported with relapse-free survival in greater than 95% of patients.[76, 82, 86-90] Based on these studies the NCCN panel considers 2 cycles of BEP as primary chemotherapy as a category 2A recommendation. Late consequences of cisplatin-based chemotherapy have been reported based on long-term follow-up of patients.[91-96] A trial by Albers et al randomized stage I patients after orchiectomy, to undergo unilateral RPLND (n = 191) or one adjuvant course of BEP (n = 191).[97] 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* =.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 comparator arm in this trial (unilateral RPLND) is not the standard treatment approach. Therefore while the results of this study are promising however this merits further investigation comparing 1 cycle of BEP versus 2 cycles with longer follow-up. The NCCN 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.[11] 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

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patients with T2 disease, both the patient and the physician must be compliant with follow-up recommendations.

Management of nonseminoma stage 1B after primary treatment
The adjuvant treatment following primary nerve- sparing RPLND for patients with IB is similar to that described for stage IA in the section above entitled “Management of nonseminoma stage 1A after RPLND”

Management after primary chemotherapy in patients with normal values of serum tumor markers may be nerve-sparing RPLND or surveillance. The NCCN Testicular Cancer panel considers, nerve- sparing bilateral RPLND a category 2A recommendation for patients with residual mass of 1 cm or greater and category 2B if the residual mass is less than 1 cm. Surveillance is category 2B for both populations. The long term follow-up tests in the current NCCN Guidelines for those electing surveillance include serum marker assessment, chest x-ray, and abdominal CT scan. The frequency of these tests is outlined in the NCCN Testicular Cancer treatment algorithms on page entitled “Follow-up for nonseminoma”.

Nonseminoma Stage IS

Patients with stage IS disease exhibit a persistent elevation of serum tumor markers post-orchiectomy but no radiographic evidence of disease. The elevated levels of AFP and beta-HCG after orchiectomy must be interpreted with caution as they might be due to reasons other that disseminated nonseminoma such as hepatobiliary disease, marijuana use, and hypogonadism.

Primary treatment of nonseminoma stage IS
The consensus recommendation of the NCCN panel 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.[98, 99]

Management of stage 1S nonseminoma post-primary treatment
The management of patients with stage IS nonseminoma after primary treatment with chemotherapy is similar to the management schema outlined for good risk nonseminoma patients including stages IIB, IIC and IIIA described in sections below (see page MS-11).

Nonseminoma Stage IIA

Primary treatment of nonseminoma stage IIA
Treatment for patients with stage IIA nonseminoma depends on post-orchiectomy serum tumor marker levels.

For patients with normal post-orchiectomy levels of AFP and HCG, the NCCN panel considers either primary RPLND (category 2A) or chemotherapy (category 2B) and as treatment options for stage IIA.[100-104] 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 HCG levels, the NCCN panel recommends induction chemotherapy. The data supporting this comes from 2 retrospective studies of patients with low stage nonseminoma treated by RPLND.[105, 106] The presence of elevated postorchiectomy AFP or HCG levels was associated with a high risk of relapse.[105, 106]

Management after primary chemotherapy and RPLND is discussed in sections below.

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

The NCCN Testicular Cancer panel considers nerve-sparing bilateral RPLND a category 2A recommendation for patients with residual mass of 1 cm or greater and category 2B 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.[107] Referral to high volume centers must be considered for RPLND post-chemotherapy. Surveillance however is category 2B for both populations.

After primary nerve-sparing RPLND, the treatment options include either surveillance or chemotherapy. The treatment choice depends on treatment depends on the number of positive lymph nodes identified. For example, since RPLND is likely a curative procedure in patients with pathological 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%-90% of pN1 patients,[106, 108, 109] therefore the NCCN panel prefers surveillance over chemotherapy for patients with pN1 disease. The risk of relapse in patients with p N2-N3 disease is > 50%.[106, 108, 110] With 2 cycles of adjuvant cisplatin based chemotherapy, the risk of relapse after RPLND is generally <1%.[106, 111, 112] The NCCN 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 consists of 2 cycles of BEP or 2 cycles of EP,[113] resulting in a nearly 100% relapse-free survival rate. For pN3, the NCCN panel recommend longer chemotherapy course consisting of either 4 cycles of EP or 3 cycles of BEP.

If stage IIA patients have persistent marker elevation (i.e., stage IIA, S1), the primary treatment is chemotherapy as described for good-risk nonseminoma in sections below (see page MS-11).

Nonseminoma Stage IIB

Primary treatment of nonseminoma stage IIB
Treatment for patients with stage IIB nonseminoma depends also on both post-orchiectomy tumor marker levels *and* radiographic findings. When tumor markers are negative, the CT findings determine the proper course of treatment. If abnormal radiographic findings are limited to sites within the lymphatic drainage in the retroperitoneum (i.e., the landing zone), two management options are available. One option is to perform nerve- sparing RPLND and to consider adjuvant treatment as described for patients with stage IIA disease. The second option is to treat with primary chemotherapy with either 4 cycles of EP or 3 cycles of BEP, followed by 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.[101] The reported relapse free survival with either approach is close to 98%.[108, 113-118]

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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 stage IIB patients 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 sections below (see section below). 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 post-primary outlined above for patients with stage IIA nonseminoma.

Advanced Metastatic Nonseminoma

The primary chemotherapy regimens of choice for patients with advanced disease depends on the IGCCCG risk classification.[13] This classification categorizes patients as good-, intermediate-, or poor-risk.[13] 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 IIIA. Treatment for good-risk GCTs were designed to decrease toxicity while maintaining maximal efficacy. Randomized clinical trials showed that this can be achieved by either substituting etoposide for vinblastine[119, 120] or by eliminating or reducing the dose of bleomycin.[119, 121] Presently, two regimens are recommended by the NCCN Testicular Cancer panel: 4 cycles of EP[51]or 3 cycles of BEP[47, 49, 122, 123] (both category 2A). Either regimen is well tolerated and cures approximately 90% of patients with good risk.[124]

Primary treatment of intermediate-risk (stage IIIB) nonseminoma
For patients with intermediate risk, the cure rate is approximately 70% with standard therapy using 4 cycles of BEP.[125, 126] For patients with intermediate risk (stage IIIB), 4 cycles of BEP is a category 2A recommendation by the NCCN Testicular Cancer panel.

Primary treatment of poor-risk (stage IIIC) nonseminoma
In patients with poor-risk GCTs (stage IIIC), between 20% and 30% of all patients with metastatic GCTs are not cured with conventional cisplatin therapy and less than one half experience a durable complete response to 4 cycles of BEP, and therefore treatment in a clinical trial is preferred.[124]. The NCCN panel lists enrolling these patients in clinical trials as their preferred treatment option.

The standard chemotherapy regimen for poor-risk patients is 4 cycles of BEP. The regimen containing etoposide, ifosfamide, cisplatin (VIP) was compared to BEP and found to be more toxic, compared with BEP but equally effective. Therefore 4 cycles of VIP may be used for those who may not tolerate bleomycin.[127]

Post-chemotherapy 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 the NCCN Testicular Cancer treatment algorithms on page entitled “Follow-up for Nonseminoma”.

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If a complete response to chemotherapy is found by radiographic imaging, and the tumor markers are negative, the NCCN panel lists 2 management options exist: surveillance (category 2B) or bilateral RPLND using nerve-sparing technique if possible (category 2B).[63]

If a residual mass is found and the serum tumor markers (AFP and beta-HCG) have normalized, then all sites of residual disease are resected.[128-130] 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, is found in the residual mass, 2 cycles of conventionally dosed chemotherapy (EP, VeIP [paclitaxel, ifosfamide, cisplatin], or TIP [vinblastine, ifosfamide, cisplatin]) are administered.

After patients are rendered disease-free, standard surveillance is initiated. The frequency of these follow-up tests is outlined in the NCCN Testicular Cancer treatment algorithms on page entitled “Follow-up for Nonseminoma”.

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

Second Line Therapy for Metastatic Germ Cell Tumors

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.[131-133] 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.[131] Standard second-line therapy includes conventional dose chemotherapy or high -dose chemotherapy. The conventional dose regimen include cisplatin and ifosfamide combined with either vinblastine or paclitaxel.[134] If the patient experiences an incomplete response or relapses after second-line conventional dose chemotherapy, the preferred third-line option, if the second- line therapy included conventional dose chemotherapy, would be high-dose chemotherapy[135, 136] 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 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; conventional-dose second line therapy (with VeIP or TIP); high-dose chemotherapy (category 2B). Alternatively, the patients may be put on best supportive care or salvage surgery if feasible.

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The high- dose regimens include high-dose carboplatin plus etoposide followed by autologous stem cell transplant[132, 137] or paclitaxel, ifosfamide followed by high-dose carboplatin plus etoposide with stem cell support.[138]

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.[139] 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.

The palliative chemotherapy options for patients with intensively pretreated, cisplatin-resistant, or refractory germ cell tumor are combinations of gemcitabine with paclitaxel and /or oxaliplatin.[140-145]

The recommendation for gemcitabine and oxaliplatin is based on data from phase II studies.[140-142] 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 and gemcitabine combination is a safe for patients with cisplatin-refractory testicular GCTs and may offer a chance of long-term survival.[140-142]

Gemcitabine and paclitaxel is another option that has shown promising results in a phase II study[144] and long term follow-up results with this combination show long disease-free survival in the rare patients that progressed after high-dose chemotherapy, and had not received prior paclitaxel or gemcitabine.[145]

A phase II study of patients with treatment-refractory germ-cell tumors found the combination of gemcitabine, oxaliplatin, paclitaxel to be effective with acceptable toxicity.[143]

For palliative therapy, the NCCN Testicular Cancer panel recommends gemcitabine with oxaliplatin[140-142]; gemcitabine with paclitaxel[144, 145]; gemcitabine with oxaliplatin and paclitaxel[143] (all are category 2A recommendations).

Treatment of Brain Metastases

The prognosis of patients with bran metastasis is poor.[146] Primary chemotherapy (using a cisplatin-based regimen) with radiotherapy is indicated for patients in whom brain metastases are detected.[147, 148] If clinically indicated and feasible, surgical resection of the metastasis should also be performed.

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