National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Testicular Cancer

Version 1.2019 — October 22, 2018

NCCN.org

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NCCN Guidelines Version 1.2019
Testicular Cancer

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Discussion

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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference

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Updates in Version 1.2019 of the NCCN Guidelines for Testicular Cancer from Version 2.2018 include:

Global Changes
- The NCCN Categories of Preference have been applied to all of the suggested treatment regimens.
- Stage IA and IB for Nonseminoma were changed to "Stage I without risk factors" and "Stage I with risk factors," respectively.

TEST-2
- Footnote e revised: "If AFP *elevated* ~~positive~~, treat as nonseminoma."
- Footnote j: "See Principles of Imaging (TEST-I)" was added.
- Footnote removed: "The panel recommends using the AJCC Staging 7th edition for subclassifying and making treatment decisions about stage I tumors (See ST-1 and ST-2)" (also for TEST-3, TEST-6, TEST-7)

TEST-3
- Category 1 was removed from Surveillance for pT1-pT3 tumors
- Footnote l revised: "Recommend ~~chest~~/abdomen/pelvic CT scan *and chest x-ray or CT scan* within the 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scan was done previously. *See Principles of Imaging (TEST-I)."* (also for TEST-7, TEST-11)
- Footnote m is new.

TEST-4
- Footnote u revised: Intermediate risk in seminoma is based on metastases to organs other than the lungs (stage IIIC). Stage IIIB does not apply to pure seminomas. Patients with elevated AFP have nonseminomas and *in* patients with a serum bHCG ~~above~~ >1000 IU/L *consider the possibility of a NSGCT and re-review surgical specimen with pathology and consider discussion with a high-volume center.* ~~are also generally presumed to have a nonseminoma.~~ LDH *and bHCG alone* should not be used to stage or risk stratify patients with pure seminoma.
- Footnote w is new.

TEST-5
- Follow-up for "Positive for viable seminoma" split into two pathways: "Complete resection" and "Incomplete resection or Progression".
  - "2 cycles adjuvant chemotherapy" was added after "Complete resection."
- Footnote x is new.

TEST-6
- Footnote dd is new (also for TEST-7 and TEST-10)

TEST-7
- Stage I with risk factors: "category 2B" was removed from Surveillance.
- Footnote ee is new.

TEST-8
- Stage IIA, Markers negative: "category 2B" was removed from Primary chemotherapy.

TEST-11
- Footnote ii revised: "Consider consultation with high-volume center ~~for poor-risk disease~~."
- Post-Chemotherapy Management for Partial and Incomplete response were moved to a new page (TEST-12)

TEST-12
- Footnote oo is new.
- Footnote pp is new.

TEST-15
- Third-Line Therapy for "Prior high-dose chemotherapy": "MMR testing" was added.

Continued

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Testicular Cancer

Updates in Version 1.2019 of the NCCN Guidelines for Testicular Cancer from Version 2.2018 include:

TEST-A
- Footnote e is new.

TEST-B
- Footnote removed: "The panel recommends using the AJCC Staging 7th edition for subclassifying and making treatment decisions about stage I tumors (See ST-1 and ST-2)"
- Footnote c is new.
- Footnote e is new.
- Footnote f revised: "Patients who undergo RPLND and are found to have pN0 disease (no tumor or teratoma) need only 1 CT scan at postoperative month *3*–4 *and then as clinically indicated.*"

TEST-B (1 of 3)
- Stage IA and IB were changed to "Stage I without risk factors" and "Stage I with risk factors," respectively
- Table 5
  - Abdominal ± Pelvic CT interval for years 4 and 5 updated to "As clinically indicated"
- Table 6
  - Abdominal ± Pelvic CT interval for year 5 updated to "As clinically indicated"
  - Chest x-ray intervals were updated to be consistent with Abdominal ± Pelvic CT intervals.

TEST-B (2 of 3)
- "or Primary RPLND" was added to title of Table 7.

TEST-B (3 of 3)
- Table 10: Abdominal/Pelvic CT interval for year 2 changed from "As clinically indicated" to "Annually"

TEST-C
- Principles of Radiotherapy for Pure Testicular Seminoma was extensively reorganized

TEST-G
- High-dose chemotherapy regimens were duplicated on this page from TEST-F for addition of the NCCN Categories of Preference.
- Footnote a is new.
- Footnote b revised: "See references *on TEST-G (2 of 2)* ~~below~~ for dosing."

TEST-I
- Principles of Imaging is new.

Staging (ST-1)
- Staging definitions and tables from the AJCC Staging 7th edition were removed.

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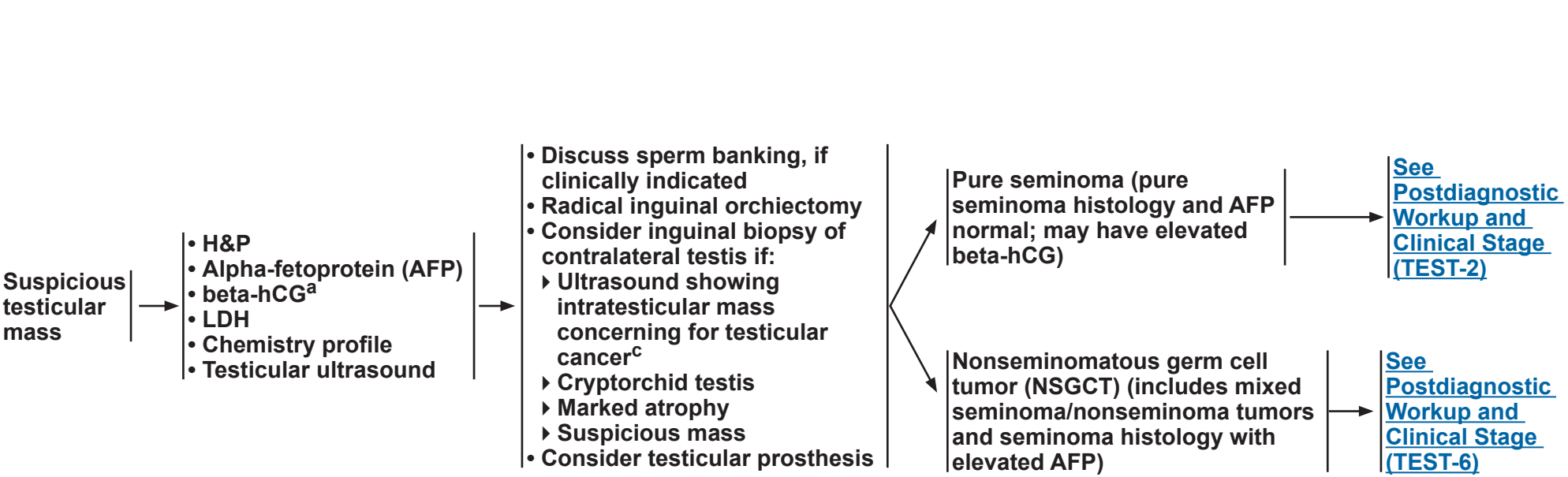

[a] Quantitative analysis of beta subunit.
[b] Though rare, when a patient presents with rapidly increasing beta-hCG or AFP and symptoms are related to disseminated disease and a testicular mass, chemotherapy can be initiated immediately without waiting for a biopsy diagnosis.
[c] Biopsies are not recommended for microcalcifications.

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

Pure seminoma[d]
(pure seminoma histology and AFP normal;[e] may have elevated beta-hCG)

→

- **Abdominal/pelvic CT[f]**
- **Chest x-ray**
- **Chest CT[f] if:**
  - **Positive abdominal CT or abnormal chest x-ray**
- **Repeat beta-hCG, LDH, AFP since TNM staging is based on post-orchiectomy values[g]**
- **Brain MRI,[h] if clinically indicated[i]**
- **Recommend sperm banking, if clinically indicated**

→

Stage IA, IB →
Stage IS →
See Primary Treatment and Follow-up (TEST-3)

Stage IIA,[j] IIB →
Stage IIC, III →
See Primary Treatment and Follow-up (TEST-4)

[d] 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.
[e] If AFP elevated, treat as nonseminoma.
[f] With contrast.
[g] Elevated values should be followed after orchiectomy with repeated determination to allow precise staging. Follow declining markers until normalization or plateau. Staging is based on marker levels at the time that the patient starts postorchiectomy therapy (for example, for patients starting chemotherapy for disseminated disease, prognostic category and staging should be assigned based on the serum tumor marker levels on day 1 of cycle 1 of chemotherapy).
[h] With and without contrast.
[i] Eg, beta-hCG >5000 IU/L, or extensive lung metastasis.
[j] For select cases of clinical stage IIA disease with borderline retroperitoneal lymph nodes, waiting 4–6 weeks and repeating imaging (chest/abdomen/pelvic CT with contrast) to confirm staging before initiating treatment can be considered. See Principles of Imaging (TEST-I).

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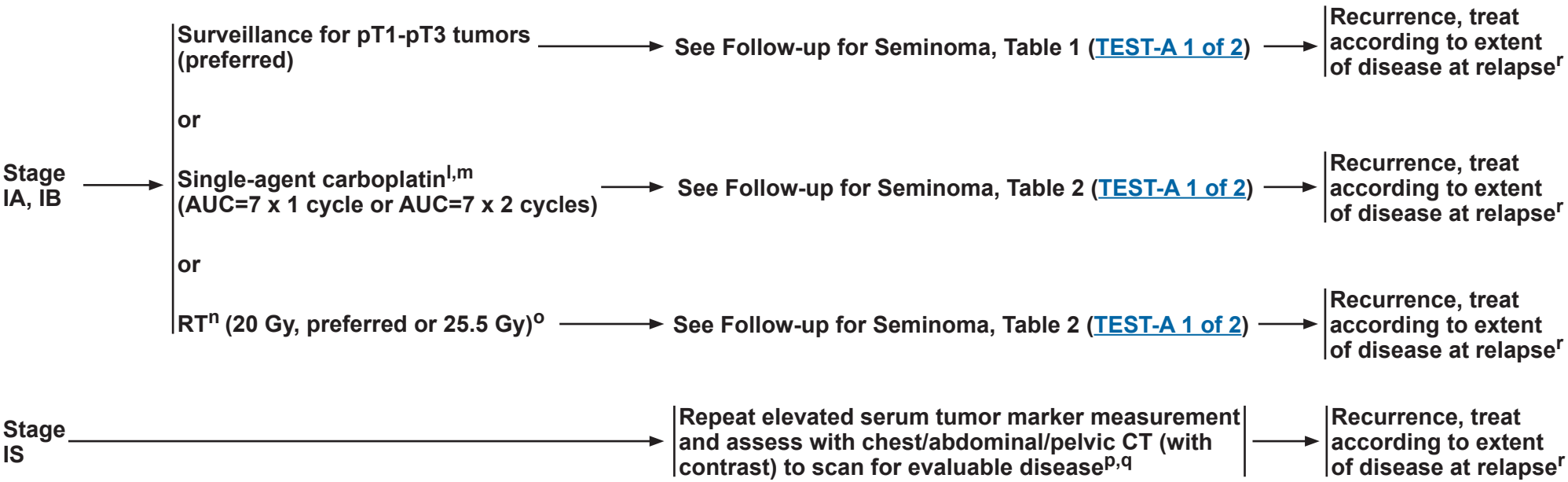

[k] Discuss sperm banking prior to chemotherapy or radiation treatment.
[l] Recommend abdomen/pelvic CT scan and chest x-ray or CT scan within the 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scan was done previously. See Principles of Imaging (TEST-I).
[m] There are limited long-term follow-up data on the toxicity and efficacy of carboplatin. A recent population-based study suggested patients with larger tumors, rete testis involvement, or both derive a smaller reduction in relapse rate with 1 cycle of carboplatin than previously reported (see Discussion).
[n] See Principles of Radiotherapy for Pure Testicular Seminoma (TEST-C).
[o] For stage I seminoma, long-term follow-up studies indicate an increase in late toxicities with radiation treatment. See Discussion.
[p] For further information on Stage IS, see Discussion.
[q] Elevated tumor markers increase the risk of disease outside of the retroperitoneum. Therefore, systemic therapy should be encouraged.
[r] Patients should not be treated based upon an elevated LDH alone.

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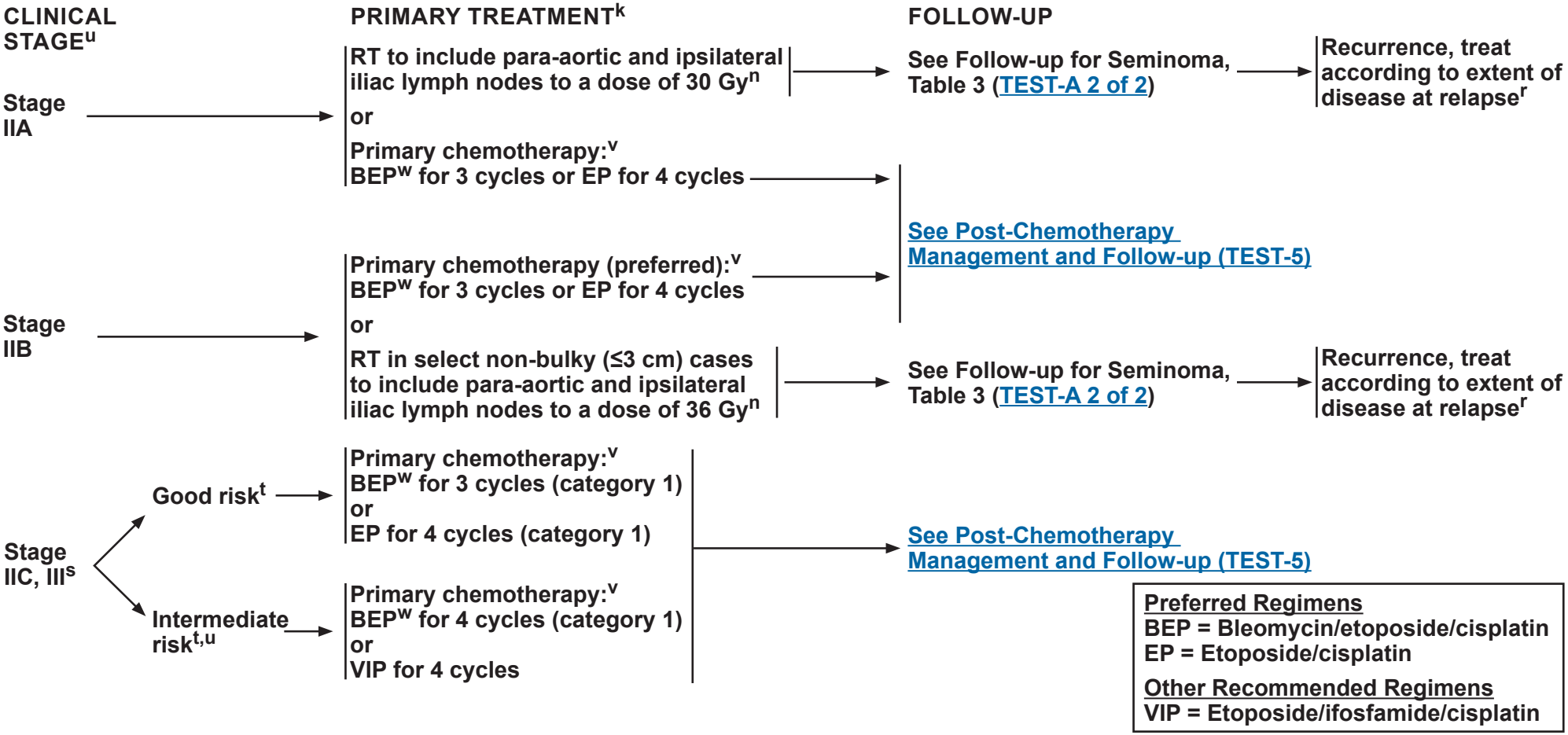

Preferred Regimens
BEP = Bleomycin/etoposide/cisplatin
EP = Etoposide/cisplatin

Other Recommended Regimens
VIP = Etoposide/ifosfamide/cisplatin

[k] Discuss sperm banking prior to chemotherapy or radiation treatment.
[n] See Principles of Radiotherapy for Pure Testicular Seminoma (TEST-C).
[r] Patients should not be treated based upon an elevated LDH alone.
[s] All stage IIC and stage III seminomas are considered good-risk disease except for stage III disease with non-pulmonary visceral metastases (eg, bone, liver, brain), which is considered intermediate risk.
[t] See Risk Classification for Advanced Disease (TEST-D).
[u] Intermediate risk in seminoma is based on metastases to organs other than the lungs (stage IIIC). Stage IIIB does not apply to pure seminomas. Patients with elevated AFP have nonseminomas. In patients with a serum bHCG >1000 IU/L, consider the possibility of an NSGCT, re-review surgical specimen with pathology, and consider discussion with a high-volume center. LDH and bHCG alone should not be used to stage or risk stratify patients with pure seminoma.
[v] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[w] Consider a bleomycin-free regimen in patients with reduced or borderline GFR and in patients over the age of 50.

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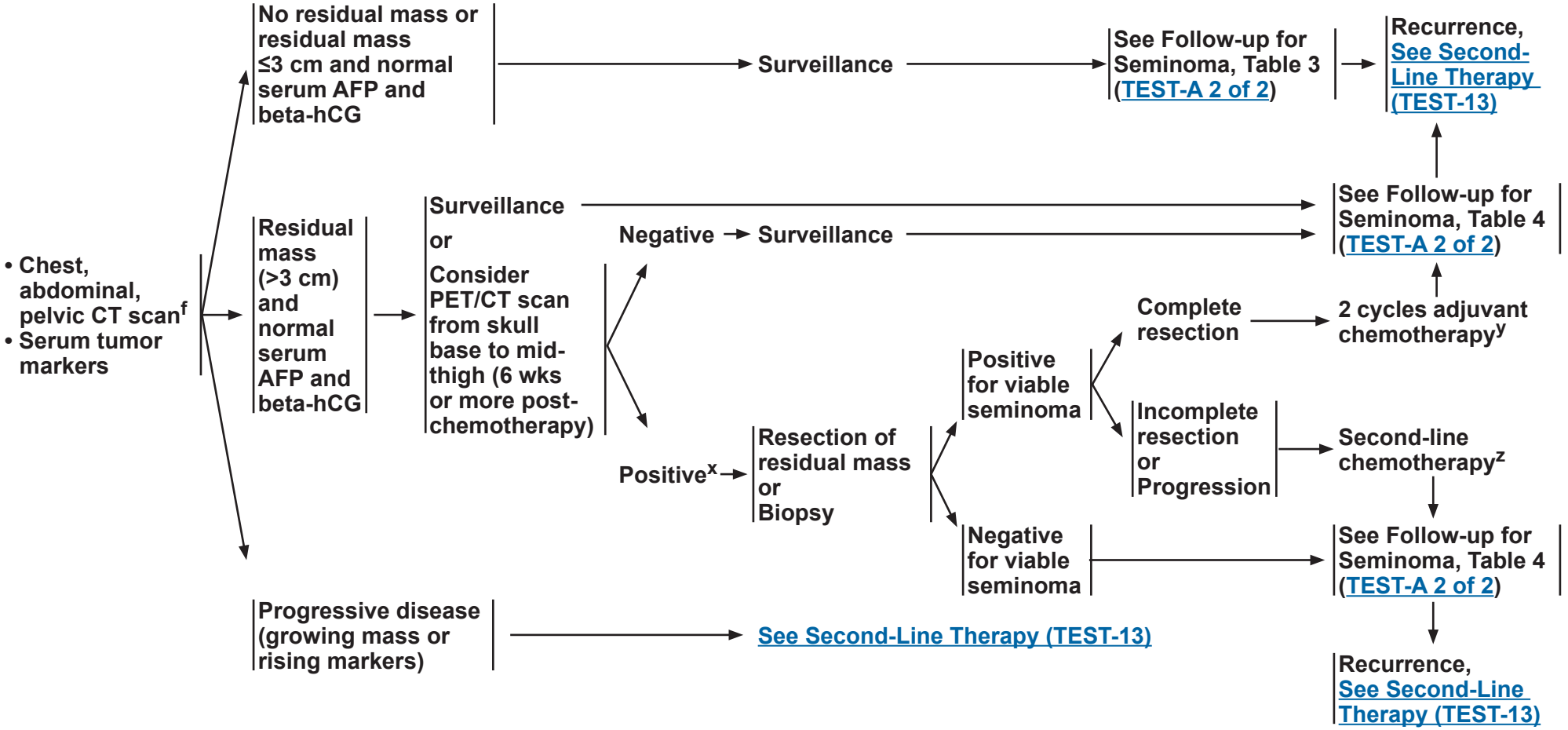
STAGE IIA, IIB, IIC, III AFTER PRIMARY TREATMENT WITH CHEMOTHERAPY

POST-CHEMOTHERAPY MANAGEMENT

FOLLOW-UP



[f] With contrast.
[x] If PET/CT is borderline, consider surveillance and repeat PET/CT. See Principles of Imaging (TEST-I).
[y] If complete resection of all residual disease, consider chemotherapy for 2 cycles (EP or TIP or VIP or VeIP). If resection incomplete, full course of second-line therapy is recommended (see TEST-13). If a biopsy is performed and is positive, consider surgery if complete resection is possible or full course of second-line chemotherapy.
[z] See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).

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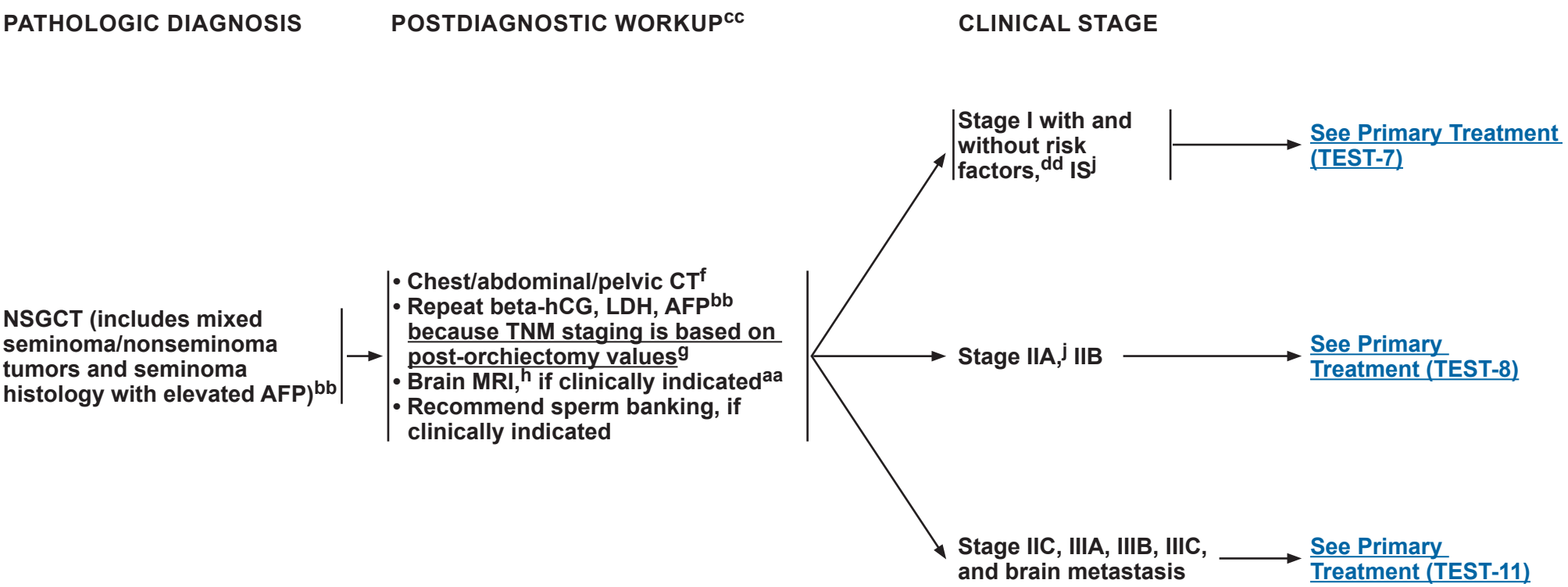

[f] With contrast.
[g] Elevated values should be followed after orchiectomy with repeated determination to allow precise staging. Follow declining markers until normalization or plateau. Staging is based on marker levels at the time that the patient starts postorchiectomy therapy (for example, for patients starting chemotherapy for disseminated disease, prognostic category and staging should be assigned based on the serum tumor marker levels on day 1 of cycle 1 of chemotherapy).
[h] With and without contrast.
[j] For select cases of clinical stage IIA disease with borderline retroperitoneal lymph nodes, waiting 4–6 weeks and repeating imaging (chest/abdomen/pelvic CT with contrast) to confirm staging before initiating treatment can be considered. See Principles of Imaging (TEST-I).
[aa] Eg, beta-hCG >5000 IU/L, extensive lung metastasis, choriocarcinoma, neurologic symptoms, non-pulmonary visceral metastasis, or AFP >10,000 ng/mL.
[bb] Mildly elevated AFP levels may not indicate presence of germ cell tumor. Decisions to treat should not be based on AFP values <20 ng/mL.
[cc] PET/CT scan is not clinically indicated for nonseminoma.
[dd] Risk factors include lymphovascular invasion or invasion of spermatic cord or scrotum.

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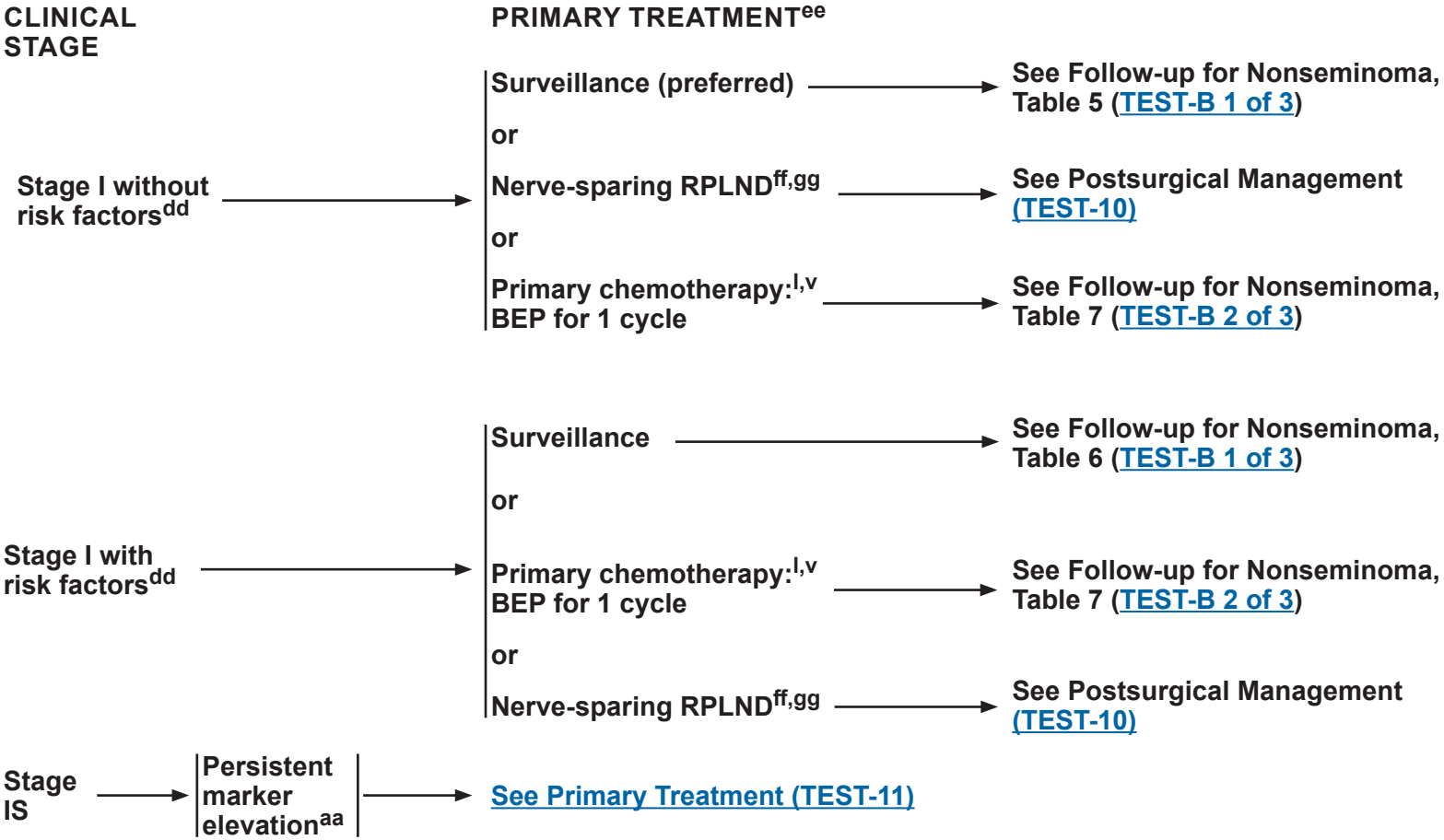

[l] Recommend abdomen/pelvic CT scan and chest x-ray or CT scan within the 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scan was done previously. See Principles of Imaging (TEST-I).
[v] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[aa] Mildly elevated AFP levels may not indicate presence of germ cell tumor. Decisions to treat should not be based on AFP values <20 ng/mL.
[dd] Risk factors include lymphovascular invasion or invasion of spermatic cord or scrotum.
[ee] Treatment options listed based on preference, see Discussion.
[ff] Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.
[gg] See Principles of Surgery for Germ Cell Tumors (TEST-H).

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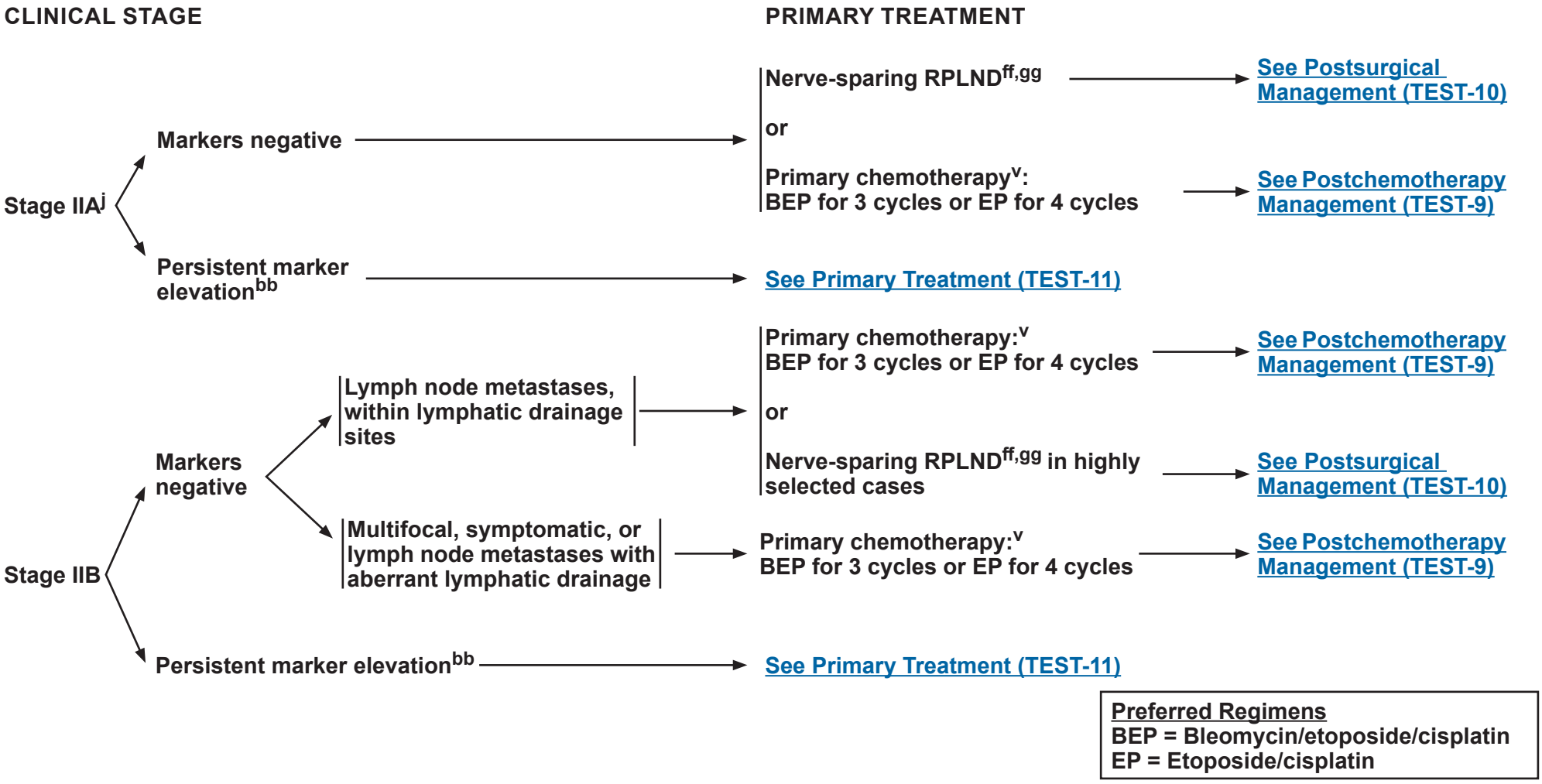

Preferred Regimens
BEP = Bleomycin/etoposide/cisplatin
EP = Etoposide/cisplatin

[j] For select cases of clinical stage IIA disease with borderline retroperitoneal lymph nodes, waiting 4–6 weeks and repeating imaging (chest/abdomen/pelvic CT with contrast) to confirm staging before initiating treatment can be considered. See Principles of Imaging (TEST-I).
[v] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[bb] Mildly elevated AFP levels may not indicate presence of germ cell tumor. Decisions to treat should not be based on AFP values <20 ng/mL.
[ff] RPLND is recommended within 4 weeks of CT scan and 7–10 days of markers.
[gg] See Principles of Surgery for Germ Cell Tumors (TEST-H).

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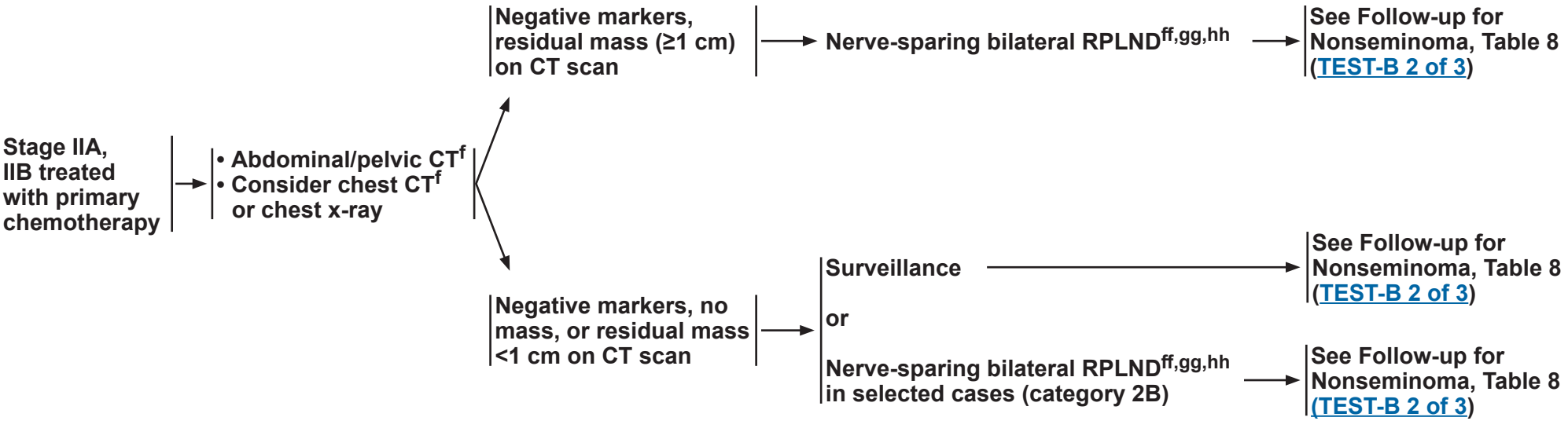
POSTCHEMOTHERAPY MANAGEMENT



[f] With contrast.
[ff] RPLND is recommended within 4 weeks of CT scan and 7–10 days of markers.
[gg] See Principles of Surgery for Germ Cell Tumors (TEST-H).
[hh] Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy.

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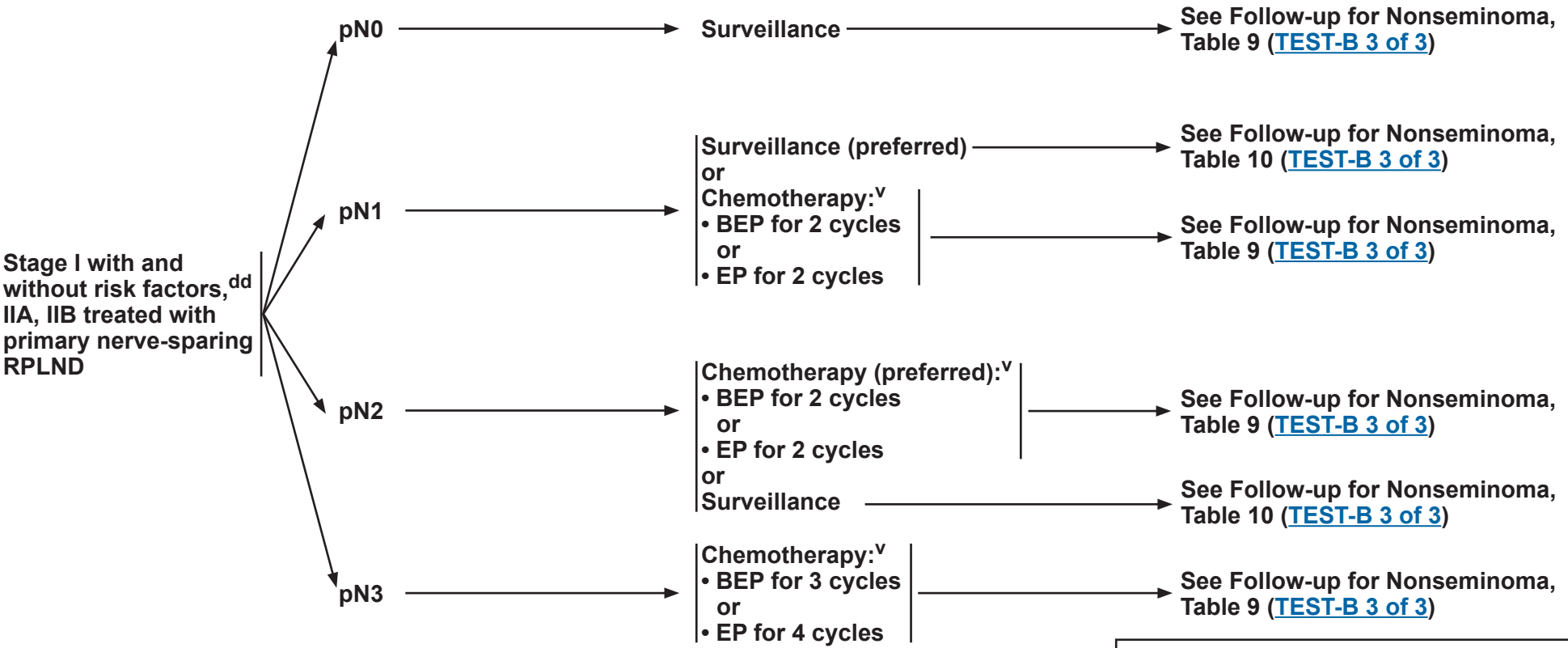
POSTSURGICAL MANAGEMENT



pN1, pN2
Preferred Regimens
EP = Etoposide/cisplatin
Other Recommended Regimens
BEP = Bleomycin/etoposide/cisplatin

pN3
Preferred Regimens
BEP = Bleomycin/etoposide/cisplatin
EP = Etoposide/cisplatin

[v] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[dd] Risk factors include lymphovascular invasion or invasion of spermatic cord or scrotum.

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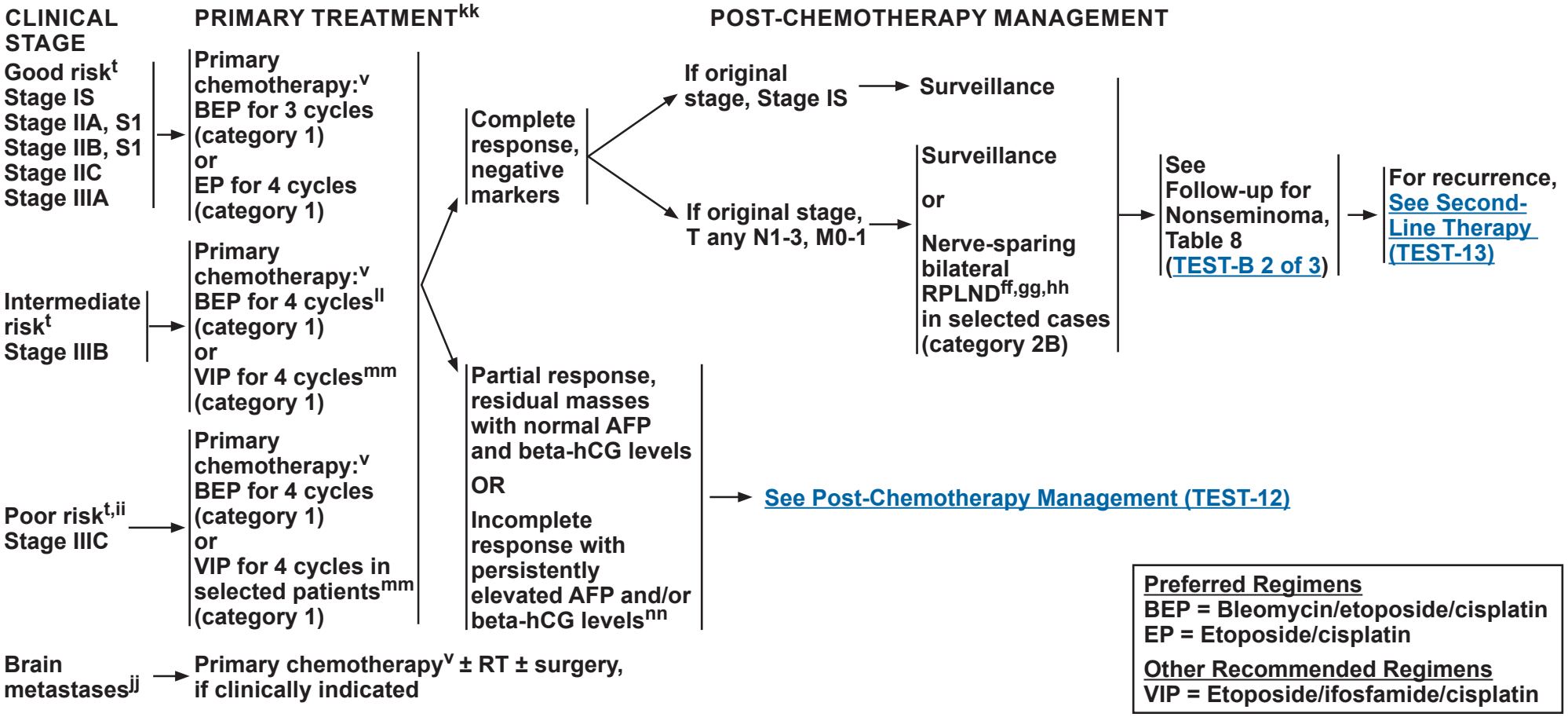

Preferred Regimens
BEP = Bleomycin/etoposide/cisplatin
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Other Recommended Regimens
VIP = Etoposide/ifosfamide/cisplatin

[t] See Risk Classification for Advanced Disease (TEST-D).
[v] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[ff] RPLND is recommended within 4 weeks of CT scan and 7–10 days of markers.
[gg] See Principles of Surgery for Germ Cell Tumors (TEST-H).
[hh] Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy.
[ii] Consider consultation with a high-volume center
[jj] Patients should receive adequate treatment for brain metastases, in addition to cisplatin-based chemotherapy.
[kk] To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.
[ll] If intermediate risk is based on LDH 1.5–3 times the upper limit of normal, then BEP for 3 cycles can be considered.
[mm] Patients who may not tolerate bleomycin.
[nn] Salvage chemotherapy should be reserved for patients with rising AFP, beta-hCG, or other evidence of progressive disease.

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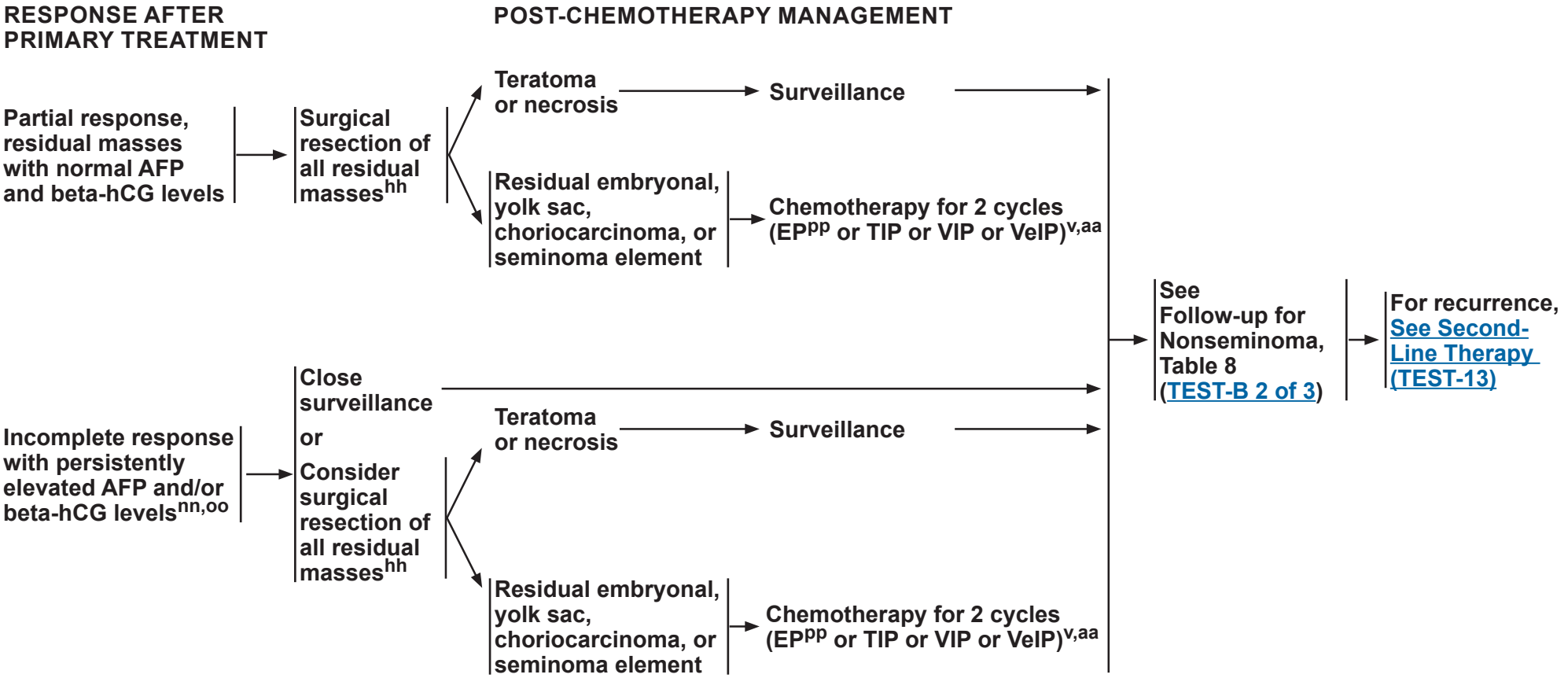

Preferred Regimens
EP[pp] = Etoposide/cisplatin
TIP = Paclitaxel/ifosfamide/cisplatin
VIP = Etoposide/ifosfamide/cisplatin
VeIP = Vinblastine/ifosfamide/cisplatin

[v] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[aa] See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).
[hh] Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy.
[nn] Salvage chemotherapy should be reserved for patients with rising AFP, beta-hCG, or other evidence of progressive disease.
[oo] Recommend referral to a high-volume center.
[pp] Consider EP for low-volume residual disease.

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RECURRENCE[qq]

SECOND-LINE THERAPY[kk,ss]

Prior chemotherapy

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

→
- Clinical trial (preferred)
- Chemotherapy[y]
  - Conventional-dose therapy (VeIP or TIP)
  - High-dose chemotherapy
- Recommend sperm banking if clinically indicated

Unfavorable prognosis:[rr]
- Incomplete response
- High markers
- High volume
- Extratesticular primary

→
- Chemotherapy[z]
  - Clinical trial (preferred)
  - Conventional-dose therapy (VeIP or TIP) or
  - High-dose chemotherapy
- Consider surgical salvage if solitary site
- Recommend sperm banking if clinically indicated

Late relapse (recurrence >2 years after completion of primary treatment)

→
- Surgical salvage, if resectable (preferred)
- Chemotherapy[z]
  - Conventional-dose therapy (VeIP or TIP)
  - High-dose chemotherapy
- Recommend sperm banking if clinically indicated

→ Post Second-Line Therapy (TEST-14)

No prior chemotherapy →

Treat per risk status on TEST-11
and
Recommend sperm banking

Preferred Regimens
- High-dose chemotherapy[z]
- TIP = Paclitaxel/ifosfamide/cisplatin
- VeIP = Vinblastine/ifosfamide/cisplatin

[z] See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).
[kk] To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.
[qq] It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.
[rr] Examples of systems used to estimate prognosis are: 1) Fossa SD, Cvancarova, Chen L, et al. J Clin Oncol 2011;29:963-970; 2) Fedyanin M, Tryakin A, Kanagavel D, et al. Urol Oncol 2013;31:499-504; and 3) Masterson TA, Carver BS, Shayegan B, et al. Urology 2012;79:1079-1084.
[ss] Includes best supportive care.

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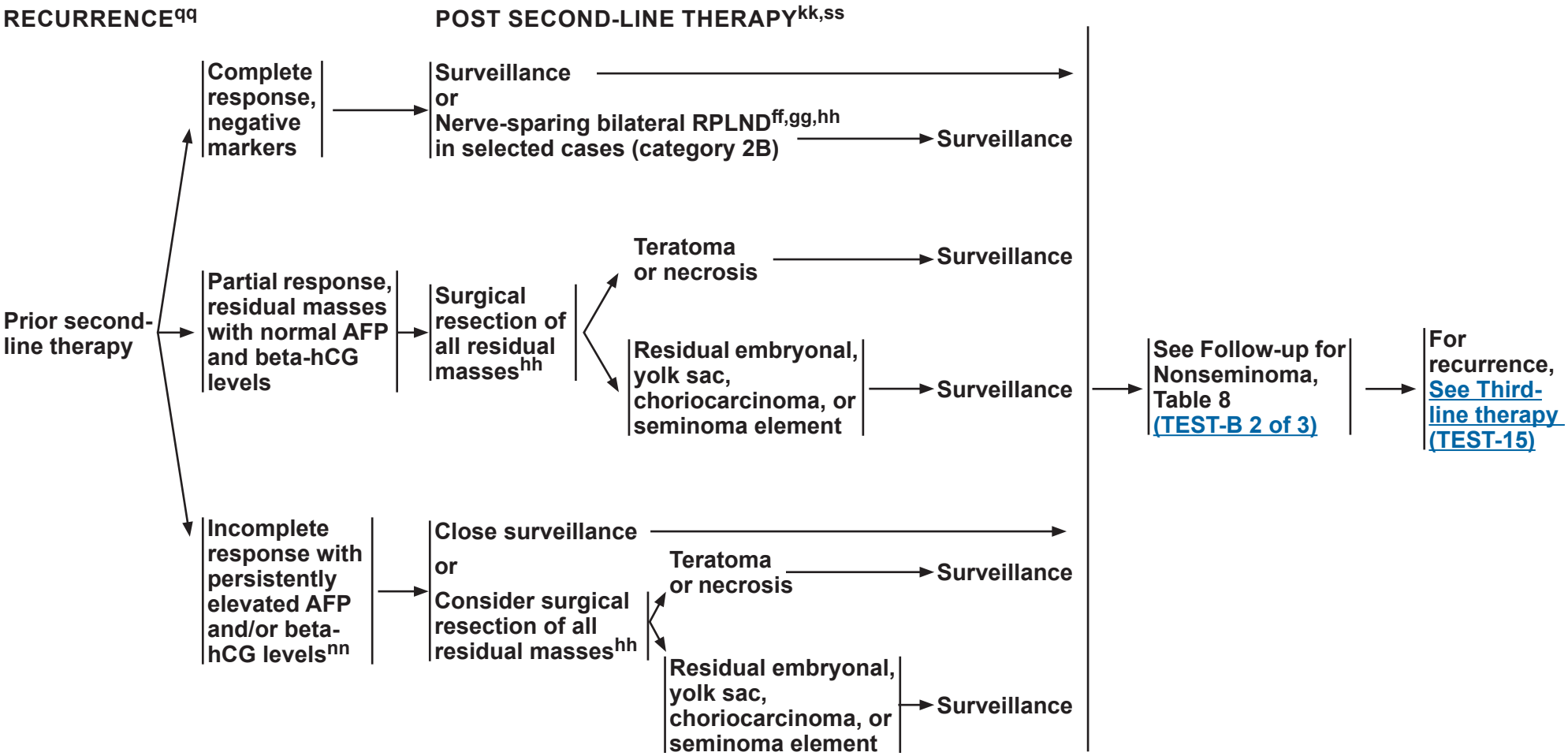

[ff] RPLND is recommended within 4 weeks of CT scan and 7–10 days of markers.
[gg] See Principles of Surgery for Germ Cell Tumors (TEST-H).
[hh] Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy.
[kk] To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.
[nn] Salvage chemotherapy should be reserved for patients with rising AFP, beta-hCG, or other evidence of progressive disease.
[qq] It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.
[ss] Includes best supportive care.

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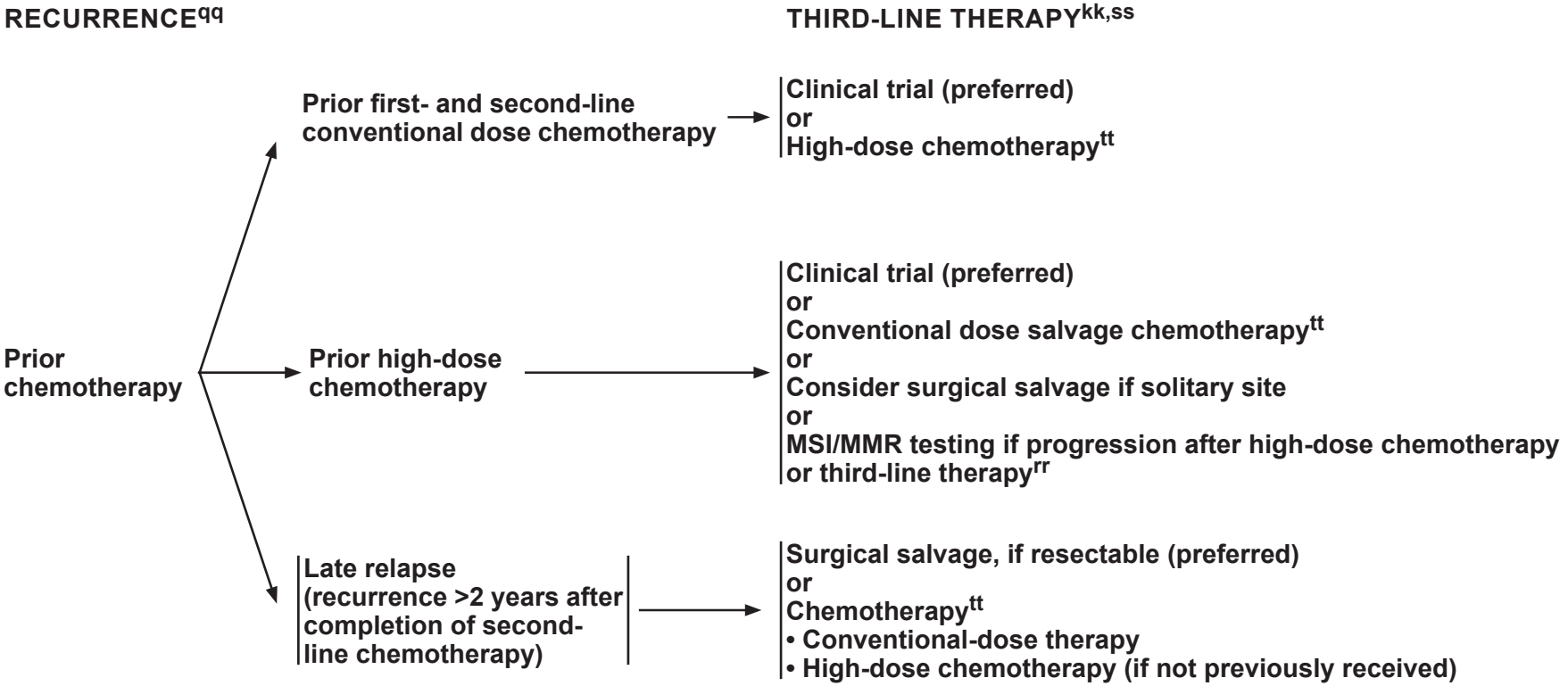

[kk] To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.
[qq] It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.
[ss] Includes best supportive care.
[tt] See Third-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-G).

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

FOLLOW-UP FOR SEMINOMA

No single follow-up plan is appropriate for all patients. The follow-up for seminoma tables are to provide guidance, and should be modified for the individual patient based on sites of disease, biology of disease, and length of time on treatment *and may be extended beyond 5 years at the discretion of the physician*. 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. Further study is required to define optimal follow-up duration.

Table 1 Clinical Stage I Seminoma: Surveillance After Orchiectomy

	Year (at month intervals)				
	1	2	3	4	5[d]
H&P[a,b]	Every 3–6 mo	Every 6–12 mo	Every 6–12 mo	Annually	Annually
Abdominal ± Pelvic CT[c,e]	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 with contrast 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[d]
H&P[a,b]	Every 6–12 mo	Every 6–12 mo	Annually	Annually	Annually
Abdominal ± Pelvic CT[c,e]	Annually	Annually	Annually	——	
Chest x-ray	As clinically indicated, consider chest CT with contrast in symptomatic patients.				

If Recurrence, treat according to extent of disease at relapse

[a] Serum tumor markers are optional.
[b] Testicular ultrasound for any equivocal exam.
[c] With or without contrast.
[d] CT is not recommended beyond 5 years unless clinically indicated.
[e] In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include all the nodes that need to be assessed. The same imaging modality (CT or MRI) should be used throughout surveillance. See Principles of Imaging (TEST-I).

Note: All recommendations are category 2A unless otherwise indicated.
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FOLLOW-UP FOR SEMINOMA

Table 3 Clinical Stage IIA and Non-Bulky IIB Seminoma: Surveillance After Radiotherapy or Post-Chemotherapy[f]

	Year (at month intervals)				
	1	2	3	4	5[d]
H&P[a,b]	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal ± Pelvic CT[e,g]	At 3 mo, then at 6–12 mo	Annually	Annually	As clinically indicated	
Chest x-ray[h]	Every 6 mo	Every 6 mo	—		

If Recurrence, treat according to extent of disease at relapse

Table 4 Bulky Clinical Stage IIB, IIC, and Stage III Seminoma: Surveillance Post-Chemotherapy

	Year (at month intervals)				
	1	2	3	4	5[d]
H&P and markers[b]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT[e,g,h,i,j,k]	Every 4 mo	Every 6 mo	Annually	Annually	As clinically indicated
Chest x-ray[h]	Every 2 mo[l]	Every 3 mo[l]	Annually	Annually	Annually

If Recurrence, see TEST-13.

[a] Serum tumor markers are optional.
[b] Testicular ultrasound for any equivocal exam.
[d] CT is not recommended beyond 5 years unless clinically indicated.
[e] In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include all the nodes that need to be assessed. The same imaging modality (CT or MRI) should be used throughout surveillance. See Principles of Imaging (TEST-I).
[f] Assuming no residual mass or residual mass <3 cm and normal tumor markers.
[g] With contrast.
[h] Chest x-ray may be used for routine follow-up, but chest CT with contrast is preferred in the presence of thoracic symptoms.
[i] Patients with PET-negative residual mass measuring >3 cm following chemotherapy should undergo an abdominal/pelvic CT scan with contrast every 6 months for the first year then annually for 5 years.
[j] Patients with residual masses may require more frequent imaging based on clinical judgment.
[k] PET/CT scan skull base to mid-thigh as clinically indicated.
[l] Add chest CT with contrast if supradiaphragmatic disease present at diagnosis.

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

FOLLOW-UP FOR NONSEMINOMA

No single follow-up plan is appropriate for all patients. The follow-up for nonseminoma tables are to provide guidance, and should be modified for the individual patient based on sites of disease, biology of disease, and length of time on treatment *and may be extended beyond 5 years at the discretion of the physician*. 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. Further study is required to define optimal follow-up duration.

Table 5 Clinical Stage I without risk factors, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[a]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal ± Pelvic CT[b,c]	Every 4–6 mo	Every 6–12 mo	Annually	As clinically indicated	
Chest x-ray[d]	At mo 4 and 12	Annually	Annually	Annually	Annually

If Recurrence, see TEST-13.

Table 6 Clinical Stage I with risk factors, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[a]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal ± Pelvic CT[b,c]	Every 4 mo	Every 4–6 mo	Every 6 mo	Annually	As clinically indicated
Chest x-ray[d]	Every 4 mo	Every 4–6 mo	Every 6 mo	Annually	As clinically indicated

If Recurrence, see TEST-13.

[a] Testicular ultrasound for any equivocal exam.
[b] With contrast.
[c] In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include all the nodes that need to be assessed. The same imaging modality (CT or MRI) should be used throughout surveillance. See Principles of Imaging (TEST-I).
[d] Chest x-ray may be used for routine follow-up, but chest CT with contrast is preferred in the presence of thoracic symptoms.

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

FOLLOW-UP FOR NONSEMINOMA

Table 7 Clinical Stage IA/B NSGCT: Treated with 1 Cycle of Adjuvant BEP Chemotherapy or Primary RPLND

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[a]	Every 3 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal ± Pelvic CT[b,c]	Annually	Annually[e]	—	—	—
Chest x-ray[d]	Every 6–12 mo	Annually	—	—	—

If Recurrence, see TEST-13.

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[a]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal ± Pelvic CT[b,c,f]	Every 6 mo	Every 6–12 mo	Annually	—	—
Chest x-ray[d,g]	Every 6 mo	Every 6 mo	Annually[h]	Annually[h]	—

If Recurrence, see TEST-13.

[a] Testicular ultrasound for any equivocal exam.
[b] With contrast.
[c] In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include all the nodes that need to be assessed. The same imaging modality (CT or MRI) should be used throughout surveillance. See Principles of Imaging (TEST-I).
[d] Chest x-ray may be used for routine follow-up, but chest CT with contrast is preferred in the presence of thoracic symptoms.
[e] Optional for patients treated with primary RPLND.
[f] Patients who undergo RPLND and are found to have pN0 disease (no tumor or teratoma) need only 1 CT scan at postoperative month 3–4 and then as clinically indicated.
[g] Chest CT with contrast if supradiaphragmatic disease at baseline.
[h] Chest x-ray is optional at months 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[a]	Every 6 mo	Every 6 mo	Annually	Annually	Annually
Abdominal/ Pelvic CT[b,c,f]	4 mo after RPLND	As clinically indicated			
Chest x-ray[d]	Every 6 mo	Annually	Annually	Annually	Annually

If Recurrence, see TEST-13.

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

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

If Recurrence, see TEST-13.

[a] Testicular ultrasound for any equivocal exam.
[b] With contrast.
[c] In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include all the nodes that need to be assessed. The same imaging modality (CT or MRI) should be used throughout surveillance. See Principles of Imaging (TEST-I).
[d] Chest x-ray may be used for routine follow-up, but chest CT with contrast is preferred in the presence of thoracic symptoms.
[f] Patients who undergo RPLND and are found to have pN0 disease (no tumor or teratoma) need only 1 CT scan at postoperative month 3–4 and then as clinically indicated.
[i] 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).
[j] 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.
- 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).[1] 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.[2]
- 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 with 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 2 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.[3,4]
- If sperm banking is desired, it should be performed prior to imaging and the delivery of adjuvant therapy.

General Treatment Information

- 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.

Stage I (TEST-C 2 of 5)
Stage IIA, IIB (TEST-C 3 of 5)
References

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Stage I

- **Dose: For stages IA, IB: Recommended radiation dose regimens are listed in the below table for the minority of patients who prefer adjuvant treatment, realizing that there is a high likelihood of salvage should a relapse occur during surveillance.[5]**

Table 1

Total Dose (Gy)	Dose per Fraction (Gy)	Number of Fractions
20 (preferred)	2.0	10
25.5	1.5	17
19.8	1.8	11
21.6	1.8	12

- **Para-aortic (PA)-Strip Fields[6] - 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).[7,8]**
    - ◊ **Superior and inferior borders: Borders may be determined by bony anatomy.**
    - ◊ **The superior border should be placed at the bottom of vertebral body T-10/11.[9]**
    - ◊ **The inferior border should be placed at the inferior border of vertebral body L-5.[6,10]**
    - ◊ **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).[1] 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).[1]**
      - ▪ **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 (IVC) may be contoured on the CT scan; one should allow a 1.2- to 1.9-cm margin on the aorta and IVC to include the para-aortic, paracaval, interaortocaval, and preaortic nodes in the clinical target volume.[7,11] 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.[12] 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).[1]**

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.[8,13]**

Stage IIA-IIB (TEST-C 3 of 5)
References

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Stage II

- 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 20–25.5 Gy (see Table 1 on TEST-C 2 of 5 for dose fractionation options).
    - Boost gross disease to achieve a total dose of approximately:

Table 2: Boost to Gross Disease

Stage	Total Dose (Gy)	Dose per Fraction (Gy)
IIA	30	1.8–2.0 Gy per fraction
IIB	36	1.8–2.0 Gy per fraction

  - 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.[14]
    - 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-10/11.[15]
      - The inferior border should be placed at the top of the acetabulum.[14]
      - 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 IVC from the bottom of the T-10/11 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.[7,11] 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.[12] 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).[1]
      - 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 1.8–2 Gy fractions to a cumulative total dose of approximately 30 Gy for stage IIA and 36 Gy for stage IIB.[14]
  - 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).

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Stage I (TEST-C 2 of 5)
References

PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Treatment Modalities

- **Linear accelerators with >6 MV photons should be used when possible.**

Target Volumes by Stage (or location)

Figure 1:
Stage I RT Field

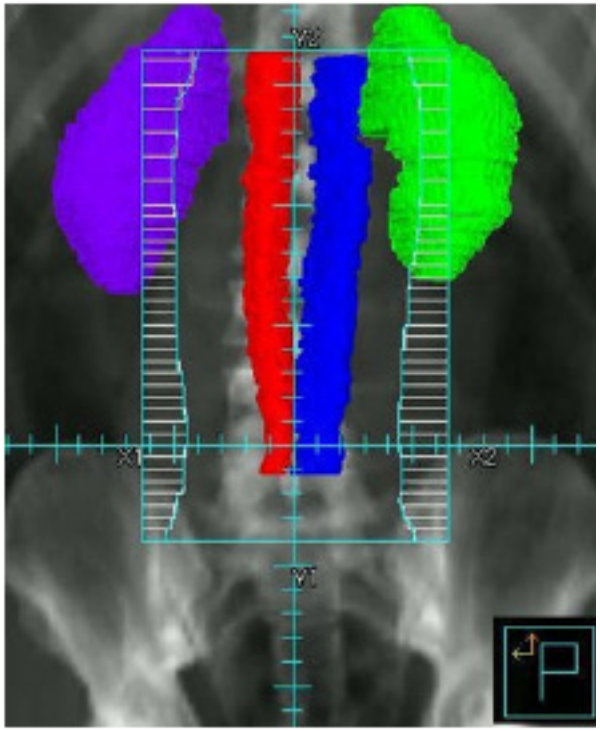


Figure 2:
Stage II RT Large field

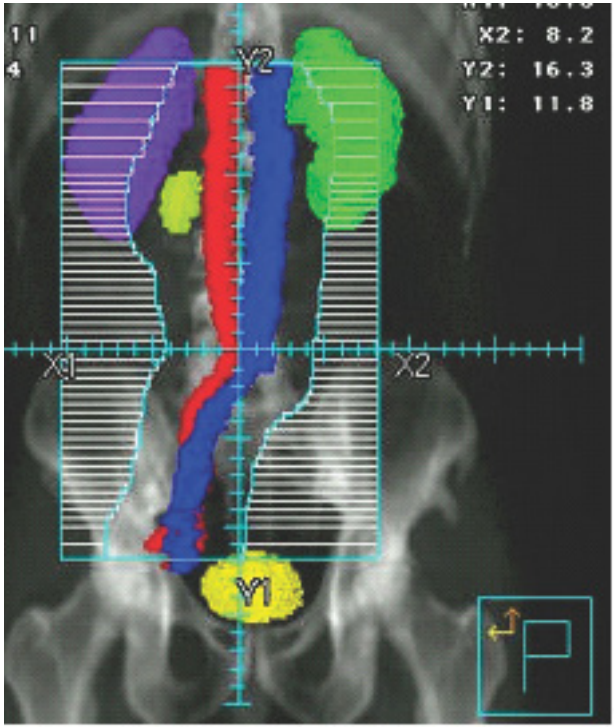
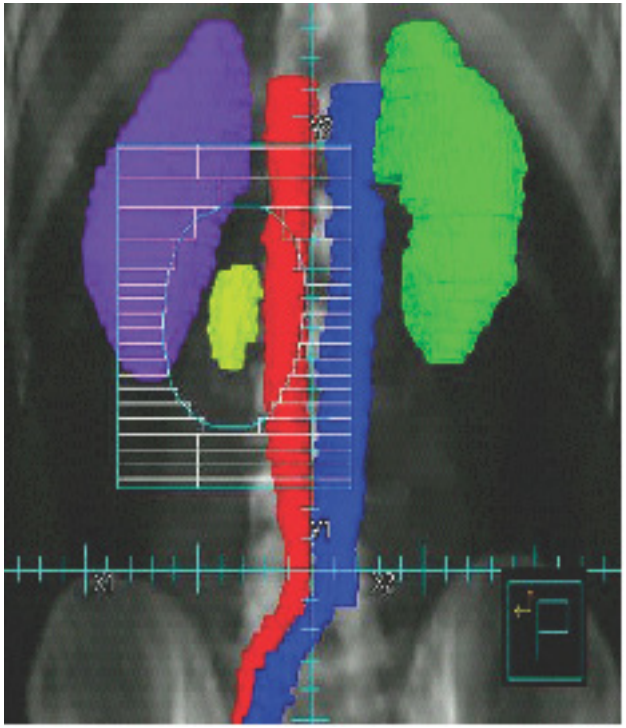


Figure 3:
Stage II Cone-down Field



Stage I (TEST-C 2 of 5)
Stage IIA, IIB (TEST-C 3 of 5)
References

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA
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Note: All recommendations are category 2A unless otherwise indicated.
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RISK CLASSIFICATION FOR ADVANCED DISEASE (post-orchiectomy)[a]

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.

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

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PRIMARY CHEMOTHERAPY REGIMENS FOR GERM CELL TUMORS

Preferred Regimens

- **BEP**
  Etoposide 100 mg/m^2 IV on Days 1–5
  Cisplatin 20 mg/m^2 IV on Days 1–5
  Bleomycin 30 units IV weekly on Days 1, 8, and 15 or Days 2, 9, and 16
  Repeat every 21 days[2]

- **EP**
  (Option only for good-risk patients [see TEST-D], patients with pathologic stage II disease, and patients with viable GCT at surgery following first-line chemotherapy)
  Etoposide 100 mg/m^2 IV on Days 1–5
  Cisplatin 20 mg/m^2 IV on Days 1–5
  Repeat every 21 days[1]

Other Recommended Regimens

- **VIP[3]**
  (Option only for intermediate or poor-risk patients or patients with viable GCT at surgery following first-line chemotherapy [See TEST-5 and TEST-11])
  Etoposide 75 mg/m^2 IV on Days 1–5
  Mesna 240 mg/m^2 IV over 15 minutes before ifosfamide,
  then at 4 and 8 hours from the start of each ifosfamide dose daily on Days 1–5
  Ifosfamide 1200 mg/m^2 on Days 1–5
  Cisplatin 20 mg/m^2 IV on Days 1–5
  Repeat every 21 days[4]

[1] Xiao H, Mazumdar M, Bajorin DF, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. J Clin Oncol 1997;15:2553-2558.
[2] Saxman SB, Finch D, Gonin R, Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: The Indiana University Experience. J Clin Oncol 1998;16:702-706.
[3] VIP, TIP, VeIP: These regimens are high risk for febrile neutropenia and granulocyte colony-stimulating factors (G-CSFs) should be used (See NCCN Guidelines for Myeloid Growth Factors).
[4] Nichols CR, Catalano PJ, Crawford ED, et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 1998;16:1287-1293.

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SECOND-LINE CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

Conventional-Dose Chemotherapy Regimens

Preferred Regimens

- **TIP**[1]
  Paclitaxel 250 mg/m^2 IV on Day 1
  Ifosfamide 1500 mg/m^2 IV on Days 2–5
  Mesna 300 mg/m^2 IV over 15 minutes before ifosfamide, then at 4 and 8 hours from the start of each ifosfamide dose daily on Days 2–5
  Cisplatin 25 mg/m^2 IV on Days 2–5
  Repeat every 21 days[3]

- **VeIP**[1]
  Vinblastine 0.11 mg/kg IV Push on Days 1–2
  Mesna 240 mg/m^2 IV over 15 minutes before ifosfamide, then at 4 and 8 hours from the start of each ifosfamide dose daily on Days 1–5
  Ifosfamide 1200 mg/m^2 IV on Days 1–5
  Cisplatin 20 mg/m^2 IV on Days 1–5
  Repeat every 21 days[2]

High-Dose Chemotherapy Regimens

Preferred Regimens

- **Carboplatin 700 mg/m^2 (body surface area) IV**
  Etoposide 750 mg/m^2 IV
  Administer 5, 4, and 3 days before peripheral blood stem cell infusion for 2 cycles[4]

- **Paclitaxel 200 mg/m^2 IV over 24 hours on Day 1**
  Ifosfamide 2000 mg/m^2 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 on Days 1–3
  Etoposide 400 mg/m^2 IV on Days 1–3
  Administer with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles[5]

[1] VIP, TIP, VeIP: These regimens are high risk for febrile neutropenia and granulocyte colony-stimulating factors (G-CSFs) should be used (See NCCN Guidelines for Myeloid Growth Factors).
[2] 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.
[3] Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;23:6549-6555.
[4] Einhorn LH, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 2007;357:340-348.
[5] Feldman DR, Sheinfeld J, Bajorin DF et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. J Clin Oncol 2010;28:1706-1713.

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

THIRD-LINE CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS[a]

High-Dose Chemotherapy NOT Previously Received

Preferred Regimens

High-Dose Chemotherapy

- **Carboplatin 700 mg/m^2 (body surface area) IV**
  Etoposide 750 mg/m^2 IV
  Administer 5, 4, and 3 days before peripheral blood stem cell infusion for 2 cycles[1]
- **Paclitaxel 200 mg/m^2 IV over 24 hours on Day 1**
  Ifosfamide 2000 mg/m^2 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 on Days 1–3
  Etoposide 400 mg/m^2 IV on Days 1–3
  Administer with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles[2]

Other Recommended Regimens[b]

- **Gemcitabine/paclitaxel/oxaliplatin[3]**
- **Gemcitabine/oxaliplatin[4-6]**
- **Gemcitabine/paclitaxel[7,8]**
- **Etoposide (oral)[9]**

Useful in Certain Circumstances[b]

- **Pembrolizumab (for MSI-H/dMMR tumors)[10,11]**

High-Dose Chemotherapy Previously Received

Preferred Regimens[b]

- **Gemcitabine/paclitaxel/oxaliplatin[3]**
- **Gemcitabine/oxaliplatin[4-6]**
- **Gemcitabine/paclitaxel[7,8]**
- **Etoposide (oral)[9]**

Useful in Certain Circumstances[b]

- **Pembrolizumab (for MSI-H/dMMR tumors)[10,11]**

[a] If VIP or TIP received as second-line therapy, high-dose chemotherapy is the preferred third-line option.
[b] See references on TEST-G (2 of 2) for dosing.

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

THIRD-LINE CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS
REFERENCES

[1] Einhorn LH, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 2007;357:340-348.
[2] Feldman DR, Sheinfeld J, Bajorin DF et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. J Clin Oncol 2010;28:1706-1713.
[3] Bokemeyer C, Oechsle K, Honecker F, et al; German Testicular Cancer Study Group. Combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel in patients with cisplatin-refractory or multiply relapsed germ-cell tumors: A study of the German Testicular Cancer Study Group. Ann Oncol 2008;19:448-453.
[4] Pectasides D, Pectasides M, Farmakis D, et al. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumors: a phase II study. Ann Oncol 2004;15:493-497.
[5] Kollmannsberger C, Beyer J, Liersch R, et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: A study of the German Testicular Cancer Study Group. J Clin Oncol 2004;22:108-114.
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[7] Einhorn LH, Brames MJ, Juliar B, Williams SD. Phase II study of paclitaxel plus gemcitabine salvage chemotherapy for germ cell tumors after progression following high-dose chemotherapy with tandem transplant. J Clin Oncol 2007;25:513-516.
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[11] Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520.

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

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. Referral to high-volume centers with experience in performing RPLNDs should be considered.**
- **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 a consistent independent predictor 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 patients with metastatic NSGCT 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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PRINCIPLES OF IMAGING

Staging

Pure Seminoma and Nonseminoma

- **Abdominal/pelvic CT scan with contrast and chest x-ray or CT scan is recommended within 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scan was performed previously. (TEST-3, TEST-7)**
  - **Chest CT should be performed if abdominal/pelvic CT or chest x-ray is abnormal.**

Treatment Response Assessment

Pure Seminoma

- **Consider PET/CT scan (skull base to mid-thigh) for a residual mass >3 cm post primary chemotherapy. (TEST-5)**
- **PET/CT scan should be performed at least 6 weeks following completion of chemotherapy.**
  - **A negative PET/CT following chemotherapy is very reassuring. If PET/CT scan is positive, resection or interventional radiology-guided biopsy should be considered. An alternative is to wait an additional 8–12 weeks and repeat PET/CT scan to assess for changes. If the mass is persistently FDG-avid on PET, then resection or biopsy is recommended.**

Surveillance

Pure Seminoma and Nonseminoma (TEST-A and TEST-B)

- **MRI with contrast can be considered in select circumstances in place of an abdominal/pelvic CT.**
  - **MRI protocol should include visualization of retroperitoneal and pelvic nodes.**
- **Use the same imaging modality (CT or MRI) throughout surveillance.**
- **In stage I seminoma and nonseminoma, chest x-rays should be obtained when abdominal/pelvic CT scans are performed. Additional chest imaging is not indicated under normal circumstances. In a retrospective review of nearly 560 patients, 76 patients relapsed with only four patients having disease in the chest, one of whom had an abnormal chest x-ray (but also in the setting of an elevated AFP).[1] Similar data from Daugaard et al showed no role for chest x-ray in detecting relapse.[2] Other series have also called into question the value of chest x-rays in this and other surveillance settings for germ cell tumors.[3,4]**

[1] De La Pena H, Sharma A, Glicksman C, et al. No longer any role for routine follow-up chest x-rays in men with stage I germ cell cancer. Eur J Cancer. 2017;84:354-359.
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[3] Tolan S, Vesprini D, Jewett MA, et al. No role for routine chest radiography in stage I seminoma surveillance. Eur Urol 2010;57:474-479.
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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Testis Cancer 8th ed., 2017

Table 1. **Definitions for T, N, M**

Clinical T	Primary Tumor
cTX	Primary tumor cannot be assessed
cT0	No evidence of primary tumor
cTis	Germ cell neoplasia *in situ*
cT4	Tumor invades scrotum with or without vascular/lymphatic invasion

Note: Except for Tis confirmed by biopsy and T4, the extent of the primary tumor is classified by radical orchiectomy. TX may be used for other categories for clinical staging.

Pathological T	Primary Tumor
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Germ cell neoplasia *in situ*
pT1	Tumor limited to testis (including rete testis invasion) without lymphovascular invasion
pT1a	Tumor smaller than 3 cm in size
pT1b*	Tumor 3 cm or larger in size
pT2	Tumor limited to testis (including rete testis invasion) with lymphovascular invasion OR Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
pT3	Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion
pT4	Tumor invades scrotum with or without lymphovascular invasion

*Subclassification of pT1 applies only to pure seminoma.

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American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Testis Cancer 8th ed., 2017

Table 1 **(continued)**

Clinical N	Regional Lymph Nodes
cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph node metastasis
cN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension OR Multiple lymph nodes, none larger than 2 cm in greatest dimension
cN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension OR Multiple lymph nodes, any one mass larger than 2 cm but not larger than 5 cm in greatest dimension
cN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Pathological N	Regional Lymph Nodes
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than fi ve nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

M		Distant Metastasis
M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-retroperitoneal nodal or pulmonary metastases
	M1b	Non-pulmonary visceral metastases

S	Serum Markers
SX	Marker studies not available or not performed
S0	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

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American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Testis Cancer 8th ed., 2017

Table 2. **AJCC Prognostic Stage Groups**

	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	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

Histologic Grade (G)

- **Germ cell tumors are not graded**

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Discussion

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 indicated.

NCCN Categories of Preference

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Table of Contents

Overview

Testicular cancer is relatively uncommon and accounts for <1% of all male tumors.[1] However, it is the most common solid tumor in men between the ages of 20 and 34 years,[2,3] and the incidence has been steadily increasing over the last 6 decades.[4-7] An estimated 9310 new cases of testicular cancer will be diagnosed in the United States in 2018 resulting in 400 deaths, which reflects the excellent 5-year survival rate for this disease (~95%).[1,2] Testicular germ cell tumors (GCTs) comprise 95% of malignant tumors arising in the testes.[3] GCTs also occasionally originate in extragonadal primary sites (usually the retroperitoneum or anterior mediastinum), and are managed similarly to testicular GCTs with regard to systemic therapy and management of residual masses.[8] Several risk factors for testis cancer development have been identified, including prior history of testis cancer, family history of testis cancer, and cryptorchidism.[3,9,10]

Testicular GCTs are categorized into two main histologic subtypes: seminoma and nonseminoma.[3,11,12] Seminomas are more common, while nonseminomas tend to grow faster and often include multiple cell types. The four types of nonseminomas are embryonal carcinoma, choriocarcinoma, yolk sac tumor, and teratoma.[11] Teratomas are sometimes classified as either mature or immature, but this distinction is of no clear significance in adult men and does not affect management in these patients. Rarely, a teratoma may histologically resemble a somatic cancer, such as a sarcoma or adenocarcinoma, and is then referred to as a teratoma with somatic type malignancy.

The serum tumor markers alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-hCG) are critical in diagnosing testicular GCTs, determining prognosis, and assessing treatment outcome. Serum tumor markers should be determined before and after treatment and throughout the follow-up period. In addition, lactate dehydrogenase (LDH) is important for determining prognosis and is used to help risk-stratify patients starting first-line chemotherapy for disseminated nonseminomatous tumors.[13] LDH, beta-hCG and AFP should be measured on the first day of the first cycle of first-line chemotherapy in these patients. LDH can also be used to monitor for relapse, but is nonspecific resulting in a high false-positive rate. Serum tumor markers are very useful for monitoring all stages of nonseminomas and are also useful in monitoring stage II and III seminomas, because elevated marker levels may be an early sign of relapse.

Beta-hCG is the most commonly elevated serum tumor marker in testicular cancer. Elevated serum concentrations of beta-hCG may be present with both seminomatous and nonseminomatous tumors. However, in patients with beta-hCG levels >1000 IU/L, consider the possibility of a nonseminoma GCT and re-review the surgical specimen with pathology. Consider discussion with a high-volume center experienced in the management of these patients. Additionally, patients with post-orchiectomy beta-hCG levels >5000 IU/L are at an increased risk of having brain metastases and a brain MRI should be performed. It is essential to note that minor elevations of beta-hCG (generally <20 IU/L) need to be interpreted with caution because hypogonadism, hyperthyroidism, and marijuana use may cause serum elevations of beta-hCG.[14-16] Intramuscular injection of 300mg of testosterone cypionate may be administered in these cases of mild beta-hCG elevations of unclear etiology in order to exclude hypogonadism as a cause. Similarly, heterophile antibodies have been reported to result in substantially elevated false-positive beta-hCG results (>400 IU/L), so clinicians should consider repeating the test using a different assay if a false positive is suspected due to the absence of radiographic evidence of disease.[17,18]

Elevated serum AFP is only associated with nonseminomatous GCTs, particularly embryonal or yolk sac carcinomas, and may be seen at any disease stage. When patients with a histologically “pure” seminoma have an elevated level of AFP, it is generally interpreted as meaning the tumor is a mixed GCT and that undetected nonseminomatous GCT elements are present in addition to the seminoma.[13,19-21] However, a small number of people have a chronically elevated serum AFP level and clinicians should be cautious about initiating treatment for a mildly elevated but stable AFP. If an elevation of serum AFP is due to a metastatic GCT, then the AFP typically will be steadily rising.

Although serum LDH concentrations are elevated in about half of men with advanced testicular cancer, LDH is a less specific marker for testicular cancer compared to AFP and beta-hCG. Therefore, decisions about treatment should not generally be based on LDH elevations alone. The primary use of LDH is to risk stratify patients with disseminated nonseminomas on the first day of first-line chemotherapy.[13] LDH should not be used to risk stratify patients with pure seminoma.

Standard care has been established for all disease stages and should be closely followed to maximize the potential for cure and to avoid unnecessary side effects, complications, and late toxicities. Nonseminoma is the more clinically aggressive tumor type. When both seminoma and elements of nonseminoma are present, management follows that of a nonseminoma. Therefore, the diagnosis of a seminoma is restricted to pure seminoma histology and normal serum AFP levels. It is important to note that pediatric GCTs are managed differently from adult GCTs and are not covered in these guidelines. Additionally, testicular tumors arising from the stroma are also not covered in these guidelines, since they account for <5% of cases and standards of care are not well established.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Testicular Cancer, an electronic search of the PubMed database was performed using the following search terms: ‘testicular cancer’ and ‘germ cell tumor.’ The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[22]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and/or discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

Clinical Presentation

Testicular cancer most often presents as a painless or painful testicular nodule, mass, enlargement, or induration (hardening). Often, patients will 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. Other patients may present with enlarged lymph nodes of the lower neck or upper chest (supraclavicular), a retroperitoneal mass, gynecomastia, venous thrombosis, or pulmonary embolism. If testicular cancer is being considered as a possibility, then a transscrotal ultrasound should be performed. If the ultrasound findings show a mass concerning for malignancy, then an inguinal orchiectomy is generally performed to make a diagnosis. Transscrotal biopsies of the testes should not be performed because violating the scrotum can seed the cancer and complicate management.

Workup, Primary Treatment, and Pathologic Diagnosis

Workup

If an intratesticular mass is identified, the workup should include a thorough history and physical examination. Testicular ultrasound serves to confirm the presence of a testicular mass, determine whether a mass is intra- or extratesticular, and to explore the contralateral testis.[23] If a testicular mass concerning for malignancy is confirmed on ultrasound, serum tumor markers, including LDH, AFP, and beta-hCG, need to be assessed as they are used for diagnosis, prognosis, and staging.[12] Marker levels should be assessed both before and after orchiectomy. Elevated levels of beta-hCG, LDH, or AFP should be followed up with repeated tests to allow precise

staging. Testicular GCTs are typically heterogeneous and hypoechoic on ultrasound.

Primary Treatment

Radical inguinal orchiectomy is considered the primary treatment for most patients who present with a testicular mass that is concerning for malignancy on ultrasound.[24] Concurrent insertion of testicular prosthesis may be considered during radical inguinal orchiectomy if desired by the patient.[25-27] In cases where the ultrasound shows an ambiguous abnormality that might be malignant, an open inguinal biopsy can be performed, but such cases are extremely rare. Similarly, an inguinal biopsy of the contralateral testis should be considered if an ambiguous suspicious mass is identified on ultrasound. An open inguinal biopsy of the contralateral testis may also be considered when that testis is cryptorchid or shows marked atrophy.[28] However, biopsies are not recommended for microcalcifications.

Sperm banking should be discussed with patients of reproductive age, if clinically indicated, before undergoing any therapeutic intervention that may compromise fertility, including surgery, radiation therapy (RT), or chemotherapy.[29-32] If sperm banking is desired, it may be performed either before or after orchiectomy, but certainly prior to subsequent therapy.

Further management is dictated by histology, stage, and whether the cancer is a pure seminoma or a nonseminoma (nonseminomas include mixed GCTs that are partially comprised of seminoma and tumors that are histopathologically described as pure seminomas in patients with elevated serum AFP). Though rare, when a patient presents with: 1) rapidly increasing beta-hCG or AFP levels; 2) symptoms related to disseminated disease; and 3) a testicular mass or distribution of metastatic disease consistent with a testicular, retroperitoneal, or mediastinal GCT, chemotherapy may be initiated immediately without waiting for a biopsy diagnosis if the risk of delaying treatment outweighs the benefit of a tissue diagnosis.

Staging

Staging of testicular GCTs is based upon determination of the extent of disease and assessment of post-orchiectomy levels of serum tumor markers.[12] The tumor (T), node (N), and metastasis (M) staging system used by the AJCC is the internationally accepted standard for cancer staging and is a major factor influencing prognosis and treatment decisions. The AJCC TNM staging system incorporates serum tumor marker elevation as a distinct category (S), which is unique to this organ site. The extent of the primary tumor is classified after orchiectomy, and therefore pathologic (p) staging is assigned to the primary tumor (T). The 8th edition of the AJCC Cancer Staging Manual introduced invasion of the epididymis and hilar soft tissue as new pathologic criteria used for T classification of stage I testicular GCTs.[12,33] Due to the excellent clinical outcomes seen in testicular cancer, large-scale follow-up studies have historically used tumor relapse rather than tumor-specific survival to validate the relevance of pathologic parameters used for staging.[12] However, hilar soft tissue and epididymal invasion have not been validated for their association with relapse of stage I disease. Current data only support their association with having advanced-stage disease at the time of diagnosis.[34,35] Therefore, it is the opinion of the panel that these factors should not be used for clinical decision-making in the management of these patients. Instead, the NCCN Guidelines recommend managing patients with stage I nonseminoma based on the presence or absence of lymphovascular invasion (LVI), invasion of the spermatic cord, or invasion of the scrotum, which are risk factors known to be associated with an increased risk of relapse.[36-44] The NCCN Guidelines do not recommend risk-adapted treatment for stage I pure seminoma.

Predominance of embryonal carcinoma has also been proposed as a prognostic indicator of relapse in stage I nonseminoma, with several studies showing that a high volume of embryonal carcinoma in the primary tumor (>50%) is associated with an increased risk of relapse.[38,45-52] However, very few patients have a high volume of embryonal carcinoma without also having LVI, and the value of embryonal carcinoma predominance in predicting relapse in the absence of LVI is unclear.[38,45,48,52] Therefore, predominance of embryonal carcinoma is not used by the

NCCN Guidelines to risk stratify stage I nonseminoma patients. Stage I nonseminoma patients with a high volume of embryonal carcinoma and no evidence of LVI are neither high-risk nor low-risk and should be considered for adjuvant therapy.

To assess for metastatic disease, imaging studies of the chest, abdomen, and pelvis should be performed. Such studies typically include CT scans of the abdomen and pelvis and CT scan or x-ray of the chest. PET scans should not be used to stage testicular GCTs. In select patients, brain MRI should also be performed; these patients include those with neurologic symptoms, post-orchiectomy serum beta-hCG >5000 IU/L, or extensive lung metastases. In patients who had elevated serum tumor markers prior to orchiectomy, it is important to obtain the half-life kinetics of the tumor markers after orchiectomy if the markers are declining because a slower-than-expected decline often indicates the presence of metastatic disease.

Risk Classification for Advanced Disease

In 1997, the International Germ Cell Cancer Consensus Group (IGCCCG) defined a classification system based on identification of clinically independent prognostic features such as extent of disease and post-orchiectomy levels of serum tumor markers. This classification system categorizes patients with pure seminoma and nonseminoma GCTs into good-, intermediate-, or poor-risk groups.[53] When determining a patient's risk classification, the relevant serum tumor marker value is the value on day 1 of cycle 1 of first-line chemotherapy. Definitions of stage and risk classification in these guidelines are done according to the IGCCCG classifications.

Pure Seminoma

If a pure seminoma is found, an abdominal/pelvic CT scan with contrast should be performed to assess the retroperitoneal lymph nodes. A chest x-ray is also recommended. A chest CT with contrast is indicated if the abdominal/pelvic CT or the chest x-ray shows evidence of metastatic disease.

Measurement of beta-hCG, LDH, and AFP levels should be repeated since TNM staging is based on marker levels at the time the patient starts post-orchiectomy therapy. Elevated levels should be followed with repeated measurement to allow for precise staging. Declining markers should be followed until normalization or plateau. Beta-hCG and LDH may be elevated in patients with seminoma; however, elevated LDH and beta-HCG alone should not be used to stage or risk stratify patients with pure seminoma. An elevated AFP indicates nonseminoma unless another cause of the elevated AFP (such as liver disease) is identified. Patients with seminoma arising from an extragonadal site, such as the mediastinum, are usually diagnosed via biopsy and treated with standard chemotherapy regimens according to risk classification. The NCCN Panel recommends performing a brain MRI if beta-hCG levels exceed 5000 IU/L or there is extensive metastatic disease in the lungs (as noted above, a beta-hCG >1000 IU/L is rare in seminoma and a value >5000 IU/L is generally indicative of a nonseminomatous GCT). Sperm banking should also be recommended to patients who will be undergoing chemotherapy, RT, or retroperitoneal lymph node dissection (RPLND), if clinically indicated.

Pure Seminoma Stages IA and IB

Primary Treatment for Pure Seminoma Stages IA and IB

Although most patients with stage I pure seminoma are cured by orchiectomy alone, 15% to 20% of patients relapse. The standard management options after initial orchiectomy include active surveillance (preferred), chemotherapy with one or two cycles of single-agent carboplatin, or RT (20 Gy, preferred or 25.5 Gy). Disease-specific survival for stage I disease is 99% irrespective of the management strategy used.[54]

Surveillance: Several prospective non-randomized studies on surveillance for stage I seminoma have been conducted.[55-58] The 5-year relapse rate seen in these studies have ranged from 15% to 20%, with most disease relapse detected in the infra-diaphragmatic lymph nodes.[56-58] The best established risk factor for relapse of pure seminoma is increased size of the primary tumor.[59] As the tumor size increases the risk of relapse also increases, but any cutoff point is arbitrary.[57,60,61,62-64] Additionally, some studies have reported that rete testis invasion is an independent risk factor for relapse in stage I pure seminoma while others have reported that it is not.[57,59-62,65] A recent systematic review determined that rete testis invasion

is significantly associated with risk of relapse in stage I seminoma patients managed by surveillance.[65] In contrast, another recent systematic review found rete testis invasion to be significantly associated with relapse in only 4 out of the 13 studies analyzed.[59] Due to these concerns, the NCCN Panel discourages risk-adapted management in stage I pure seminoma and instead recommends surveillance for all patients who find it acceptable and are able to adhere to the surveillance schedule.

A retrospective study analyzing 2483 patients with clinical stage I GCTs managed by active surveillance showed that 13% of patients with stage I seminoma relapsed. Median time to relapse was 14 months (range, 2–84 months) and 92% of relapses were observed within 3 years. The overall 5-year disease-specific survival rate was 99%.[66,67] Based on this and other similar studies, surveillance is the preferred option for patients with stage I seminoma. If surveillance is not applicable, alternative options are either adjuvant chemotherapy with carboplatin or adjuvant RT as described below. Each approach has distinct advantages and disadvantages that should be discussed with patients and their families in order to pick the best approach on an individual basis.

Adjuvant Chemotherapy: Oliver et al reported the initial results of a trial that randomized 1477 patients with stage I seminoma to receive either RT (n = 885) or 1 cycle of intravenous carboplatin (n = 560) at the dose AUC x 7 (ie based on the formula 7 x [glomerular filtration rate (GFR, mL/min) + 25 mg]).[68] At a follow-up time of 3 years, the relapse-free survival rates for both groups were similar (95.9% for the RT group and 94.8% for the carboplatin group), which established the noninferiority of carboplatin compared to RT.[68] The mature results of this trial confirmed the noninferiority of single-dose carboplatin versus RT in terms of relapse-free survival.[69] In an intent-to-treat analysis, the relapse-free survival rates at 5 years were 96% in the RT arm and 94.7% in the carboplatin arm (hazard ratio [HR], 1.25; P = 0.37). One seminoma-related death occurred after RT and none occurred after carboplatin. Additionally, patients given carboplatin were less lethargic and less likely to take time off work than patients receiving RT. Therefore, the authors concluded that a single dose of carboplatin is less toxic and as effective in preventing disease relapse as adjuvant RT in men with stage I pure seminoma after orchiectomy.[69] However, it should be noted that there are limited long-term follow-up data regarding the toxicity and efficacy of carboplatin.[61,70] A recent non-randomized population-based study of 897 patients with stage I seminoma suggested that patients with tumor size >4 cm, rete testis invasion, or both derive a smaller reduction in relapse rate with one cycle of carboplatin than previously reported.[57,61,70] After a median follow-up of 5.6 years, the relapse rate in patients with one or both risk factors was 15.5% for patients managed by surveillance versus 9.3% for patients who received one cycle of carboplatin.[61] An absolute reduction in the risk of relapse by only 6.2% may not be sufficient to justify the use of single-cycle adjuvant carboplatin.[70] Therefore, more data are needed to assess the value of one cycle of carboplatin in reducing the risk of relapse in patients with stage I seminoma.

Use of two cycles of adjuvant carboplatin in this setting has also been studied. The 2nd and 3rd Spanish Germ Cell Cancer Cooperative Group studies reported that two cycles of adjuvant carboplatin is effective in reducing the rate of relapse in high-risk stage I seminoma patients, with a 5-year relapse-free survival rate of 96.2% and a 5-year overall survival (OS) rate of 100%.[71,72] The efficacy of two cycles of adjuvant carboplatin was confirmed in a study by the Hellenic Cooperative Oncology Group, which reported a 5-year relapse-free survival rate of 96.8% among 138 stage I seminoma patients treated with this regimen.[73] A recent prospective study reported the treatment outcomes of 725 stage I seminoma patients managed by surveillance, one cycle of carboplatin, or two cycles of carboplatin.[74] Although disease-specific survival was 100% for all 3 strategies, crude relapse rates were significantly higher with the one-cycle regimen (5%) compared to the two-cycle regimen (1.5%) after a median follow-up of 30 months. The crude relapse rate for surveillance was 8.2%. Furthermore, one cycle of carboplatin demonstrated low efficacy to control large tumors. Regardless of the regimen used, performing abdominal/pelvic CT scan with contrast and chest x-ray or CT scan is recommended within 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scans were previously performed. Chest CT should be performed if either abdominal/pelvic CT or chest x-ray shows evidence of metastatic disease.

Adjuvant Radiation Therapy: Numerous studies have found an increased risk for secondary malignancies in seminoma patients treated with RT;

however, many of these patients were treated at a time when treatment fields were larger and radiation doses were higher than those currently used.[75,76] One population-based study reported that RT for stage I seminoma was associated with an 80% increase in the risk of death from secondary cancers.[77] Another study found that moderate-dose infradiaphragmatic RT for stage I seminoma was associated with an increased risk for secondary cancers in organs within the radiation field.[78] Additionally, one study reported that RT might increase the risk of a subsequent cardiac event,[79] but other analyses have not confirmed this risk.[77] Platinum-based chemotherapy has also been associated with an increased risk for secondary cancers and cardiac toxicity.[79,80] However, whether such long-term risks ensue from single-agent carboplatin as dosed for seminoma remains unknown.

The NCCN Panel prefers active surveillance to the routine use of adjuvant therapy for stage I seminoma patients, because the risk of relapse is low compared to the potential harms of adjuvant therapy. However, if adjuvant chemotherapy is given, the NCCN Panel recommends carboplatin (AUC x 7) for either 1 or 2 cycles for patients with stage IA or IB pure seminoma. If RT is delivered, the panel recommends a preferred total dose of 20 Gy administered in 10 fractions of 2.0 Gy each.[81] Alternatively, a total dose of 25.5 Gy can be given in 17 fractions of 1.5 Gy each.[82] Other RT dose schedules are listed in the *Principles of Radiotherapy for Pure Testicular Seminoma* in the algorithm (see Table 1 on TEST-C 2 of 5). Patients at higher risk for morbidity from RT, such as those with a history of inflammatory bowel disease or prior RT, are generally not given primary RT.

Nodal mapping studies suggest that treatment fields should target the retroperitoneal lymph nodes but not necessarily the ipsilateral renal hilar nodes.[83,84] Special circumstances, such as ipsilateral pelvic surgery, may alter the lymphatic drainage of the testis. Therefore, irradiation of the ipsilateral iliac and inguinal lymph nodes has been advocated even in stage I patients.[83,85,86] It should be noted that patients treated with para-aortic RT have a slightly higher rate of pelvic relapse compared with those treated with “dog-leg” RT.[86-89] Prophylaxis to the mediastinum is not provided, because relapse rarely occurs at this site. Sperm banking should be recommended beforehand, if clinically indicated, when patients are to receive either chemotherapy or RT.

Follow-up for Pure Seminoma Stages IA and IB After Primary Treatment

Follow-up strategies vary according to the treatment modality received by the patient (surveillance vs. adjuvant therapy). An analysis of >5000 stage I seminoma patients from various trials reported that the 5-year relapse rate was higher with surveillance (18.6%) compared to RT (4.8% with extended-field RT and 3.6% with para-aortic RT) or chemotherapy (6.1% with 1 cycle of carboplatin and 2.3% with 2 cycles of carboplatin).[88] An analysis of data from the National Cancer Database examined the survival outcomes of 33094 stage I seminoma patients who received surveillance, chemotherapy, or RT as primary treatment after orchiectomy.[90] Although OS was high for all strategies, results showed a small absolute survival advantage for adjuvant therapy (RT or chemotherapy) over active surveillance at 10 years (95% vs. 93.4%; HR, 0.58, $P < .0005$). Independent of the modality, the risk of relapse is highest in the first 2 years following treatment.[88] In the event of relapse, clinicians should keep in mind the potential for development of a second primary tumor in the contralateral testis.

Follow-up During Active Surveillance: Although no single follow-up plan is applicable to all patients, the NCCN Panel has provided guidance for the follow-up of patients with stage I seminoma managed with active surveillance after orchiectomy (see Table 1 on TEST-A 1 of 2 in the algorithm). The recommendations outlined may be individualized and extended beyond 5 years at the discretion of the physician. Follow-up for patients on surveillance includes a history and physical examination, with optional measurement of serum tumor markers (AFP, beta-hCG, and LDH), performed every 3 to 6 months for the first year, every 6 to 12 months for years 2 to 3, and annually for years 4 and 5.[72,91,92] The measurement of serum tumor markers is optional due to the rarity of marker-only relapse, since most patients with elevated markers will also have evidence of relapse on imaging. Additionally, in one of the largest prospectively maintained databases of stage I seminoma patients managed with surveillance, it was reported that routine measurement of serum tumor markers did not aid in the early diagnosis of relapse.[93] Therefore, routine

measurement of serum tumor markers can be safely omitted from stage I seminoma surveillance schedules.

There is controversy regarding how many imaging studies should be performed in patients on active surveillance. The NCCN Panel recommends an abdominal/pelvic CT scan with or without contrast at 3, 6, and 12 months during the first year, every 6 to 12 months for years 2 and 3, and then every 12 to 24 months for years 4 and 5. CT is not recommended beyond 5 years, unless clinically indicated. A clinical trial in the United Kingdom entitled TRISST (MRC TE24/TRial of Imaging and Schedule in Seminoma Testis) is currently investigating whether MRI or a reduced CT schedule could be used as a safe and effective alternative to standard CT-based surveillance in the management of stage I seminoma (Clinical Trial ID: NCT00589537).[94] The panel regards MRI as an appropriate option that can be considered to replace abdominal/pelvic CT in select circumstances. The MRI protocol should include visualization of all the nodes that need to be assessed, including the retroperitoneal and pelvic nodes, and should be performed in centers with experience in interpreting MRI results for testicular cancer. The same imaging modality (CT or MRI) should be used throughout surveillance. Several studies have suggested that relapses in the lung are rarely detected by chest x-ray alone in patients with stage I seminoma managed by active surveillance.[66,95,96] In a recent retrospective analysis of 886 stage I seminoma patients, 83 patients experienced relapse.[96] All relapses were detected by either rising tumor markers or follow-up CT scan; not a single relapse was detected by routine chest x-ray. Other studies have reported similar results, calling into question the value of chest x-rays in surveillance settings for stage I seminomatous GCTs.[66,95] Therefore, routine chest imaging, including chest x-ray and chest CT with contrast, should be reserved for patients with thoracic symptoms.

Follow-up After Adjuvant Treatment: Follow-up of patients treated with adjuvant therapy (chemotherapy or RT) is outlined in Table 2 on TEST-A 1 of 2 in the algorithm and includes a history and physical examination, with optional measurement of post-orchiectomy serum tumor markers (AFP, beta-hCG, and LDH) performed every 6 to 12 months for the first 2 years and annually for years 3, 4, and 5. A meta-analysis of 2466 patients reported that relapse rarely occurred >3 years after treatment with RT or carboplatin (0.2% of patients).[54] Since the rate of relapse beyond 3 years is very low for patients treated with chemotherapy or RT, the NCCN Panel recommends performing an abdominal/pelvic CT scan with or without contrast annually for 3 years. In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include visualization of the retroperitoneal and pelvic nodes and should be performed in centers with experience in interpreting MRI results for testicular cancer. The same imaging modality (CT or MRI) should be used throughout surveillance. Chest x-rays should be obtained only when clinically indicated and chest CT scans with contrast should be considered for symptomatic patients. CT is not recommended beyond 5 years, unless clinically indicated. Relapses are treated according to the stage at relapse.[54] However, patients should not be treated based upon an elevated LDH level alone.

Pure Seminoma Stage IS

Primary Treatment for Pure Seminoma Stage IS

Stage IS pure seminoma is very uncommon and requires persistent elevation of serum tumor markers following orchiectomy. However, physicians are cautioned against treating a patient based on minimally elevated LDH or beta-hCG alone, as other causes may be responsible for elevation of these markers. Persistent elevation of serum markers is usually evidence of metastatic disease, which will show up radiographically if doubt exists in the diagnosis.

Follow-up for Pure Seminoma Stage IS

The NCCN Panel recommends repeating measurements of serum tumor markers and performing imaging studies (chest/abdominal/pelvic CT with contrast) to determine the extent of disease.

Pure Seminoma Stages IIA and IIB

Primary Treatment for Pure Seminoma Stages IIA and IIB

Stage IIA pure seminoma is defined as metastatic disease to lymph nodes, with a lymph node mass measuring ≤2 cm in greatest diameter.[12] A lymph node mass measuring 2 to 5 cm in greatest diameter is classified as stage IIB disease.[12] To confirm staging before treatment in select cases of stage

IIA disease with borderline retroperitoneal lymph nodes, waiting 4 to 6 weeks after initial imaging assessment and repeating chest/abdominal/pelvic CT scans with contrast to confirm staging may be considered.

Options for the primary treatment of stage IIA and IIB seminomas include RT or chemotherapy with 3 cycles of bleomycin, etoposide, and cisplatin (BEP) or 4 cycles of etoposide and cisplatin (EP).[97-99] If chemotherapy is given, both EP and BEP are preferred regimens in this setting. However, a bleomycin-free regimen should be considered in patients with reduced or borderline GFR and in patients over the age of 50. Different studies have reported different outcomes with regard to whether chemotherapy or RT is more effective in this setting. Two recent studies utilized data from the National Cancer Database to assess survival outcomes according to treatment strategy in stage IIA/B seminoma patients. A retrospective study by Glaser et al compared RT with multi-agent chemotherapy in 1772 stage IIA-C seminoma patients treated with orchiectomy.[100] After a median follow-up of 65 months, 5-year OS was significantly higher with RT compared to chemotherapy in stage IIA patients (99% vs. 93%; HR, 0.28; 95% CI, 0.09–0.86; P = .027). However, no significant difference in 5-year OS was seen in stage IIB patients treated with post-orchiectomy RT or chemotherapy (95.2% vs. 92.4%). A similar study by Paly et al evaluated data from the same database during the same time period and reached similar conclusions. This retrospective, non-randomized study evaluated 1885 stage IIA/B seminoma patients selected to receive either adjuvant chemotherapy or adjuvant RT.[101] Receipt of adjuvant chemotherapy was associated with decreased 5-year OS in stage IIA patients (HR, 13.33; P < .01), but not in stage IIB patients (HR, 1.39; P = .45). These studies were not randomized trials and treatment decisions were based on the treating physician's clinical judgment, which presumably was influenced by the specific characteristics of each patient. Therefore, it is possible that patients with more extensive disease were selected for chemotherapy. Nevertheless, these studies provide some support for the use of RT over chemotherapy to treat stage IIA seminoma. In contrast, a study by Mortensen et al evaluating 363 patients with stage II-III seminoma reported that the relapse rate was 6% among patients treated with chemotherapy compared to 12.6% among those treated with RT. It should be noted that chemotherapy was used for more advanced stage disease than RT in this study.[64] This has led some physicians to prefer chemotherapy for stage II patients; however, these results must be interpreted with caution since this study was not a randomized trial and did not specifically compare the two treatment modalities for stage IIA disease. The NCCN Guidelines recommend either RT or chemotherapy as primary treatment for both stage IIA and IIB seminoma. However, chemotherapy is preferred for stage IIB seminoma,[99,102] with RT being reserved for select patients with non-bulky (≤3 cm) disease.[97]

The target fields for RT for stage IIA/B disease should include the retroperitoneal and proximal ipsilateral iliac lymph nodes. Treatment is delivered in two consecutive anteroposterior-posteroanterior (AP/PA) phases with no break in between. The initial phase consists of treatment of modified dog-leg fields at a dose of 20 Gy delivered in 10 fractions of 2.0 Gy each or 25.5 Gy delivered in 17 fractions of 1.5 Gy each. The panel prefers modified dog-leg fields as described by Classen et al.[97] The second phase (cone down) consists of daily 1.8- to 2-Gy fractions to a cumulative total dose of 30 Gy for stage IIA patients and 36 Gy for stage IIB patients.[97] Prophylactic mediastinal RT is not indicated for the management of stage II disease.[103] For details on field arrangement, see *Principles of Radiotherapy for Pure Testicular Seminoma* in the algorithm.

Follow-up for Pure Seminoma Stages IIA and Non-bulky IIB After Primary Treatment

The recommended follow-up schedule for patients with stage IIA and non-bulky stage IIB seminoma after RT or chemotherapy is outlined in Table 3 on TEST-A 2 of 2 in the algorithm and includes a history and physical examination with optional measurement of post-orchiectomy serum tumor markers (AFP, beta-hCG, and LDH), performed every 3 months for year 1 and then every 6 months for years 2 through 5.

An abdominal/pelvic CT scan with contrast is recommended at 3 months and 6 to 12 months for year 1; annually for years 2 and 3; and then as clinically indicated for years 4 and 5. In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include visualization of the retroperitoneal and pelvic nodes and should be performed in centers with experience in interpreting MRI results for

testicular cancer. The same imaging modality (CT or MRI) should be used throughout surveillance. CT is not recommended beyond 5 years, unless clinically indicated. Chest x-ray is recommended every 6 months for the first 2 years only.

Pure Seminoma Stages IIC and III

Primary Treatment for Pure Seminoma Stages IIC and III

Patients with stage IIC or stage III seminomas are classified as either good or intermediate risk. Intermediate risk in seminoma is based on metastases to organs other than the lungs. All stage IIC and stage III seminomas are considered good risk except for stage IIIC disease, which involves non-pulmonary visceral metastases (eg, bone, liver, brain) and is considered intermediate risk. Standard chemotherapy is used for both groups of patients. However, 3 cycles of BEP or 4 cycles of EP are recommended for patients with good-risk disease (both preferred),[104-106] while more intensive chemotherapy with 4 cycles of BEP (preferred) or 4 cycles of etoposide, mesna, ifosfamide, and cisplatin (VIP) is recommended for patients with intermediate-risk disease.[107-112] VIP should be reserved for patients with a contraindication to bleomycin. Additionally, a bleomycin-free regimen should also be considered in patients with reduced or borderline GFR and in patients over the age of 50. All of these chemotherapy options are category 1 recommendations except for VIP, which is a category 2A recommendation.

Management of Pure Seminoma Stages IIA, IIB, IIC, and III After Chemotherapy

After primary treatment with chemotherapy, patients with stage IIA, IIB, IIC, or III seminoma are evaluated by CT scan with contrast of the chest, abdomen, and pelvis as well as measurement of serum tumor markers. Patients are then classified according to the presence or absence of a residual mass and the status of serum tumor marker levels. Patients with normal serum AFP and beta-hCG levels and either no residual mass or a residual mass ≤3 cm should undergo surveillance as described in Table 3 on TEST-A 2 of 2 in the algorithm and discussed in the section above on *Follow-up for Pure Seminoma Stages IIA and Non-bulky IIB After Primary Treatment.*

Surveillance is also recommended for patients with a residual mass >3 cm and normal serum AFP and beta-hCG levels. Additionally, a PET/CT scan from skull base to mid-thigh can be considered to better delineate the presence of viable residual tumor since CT alone cannot discriminate between residual neoplastic lesions and necrotic or fibrotic tissue.[113-117] PET can provide useful metabolic information on these lesions, which may aid in the early detection of recurrent disease in patients with normal CT findings, since functional abnormalities usually precede morphologic ones.[117] However, testicular GCTs are typically slow-growing and have low uptake of 18-fluorodeoxyglucose (FDG) on PET scans, often resulting in unclear images of testicular lesions.[118] Additionally, the abdomen and retroperitoneal space are sites of non-specific FDG uptake, which can lead to false-positive results.[118] Possible sources of false-negative results include small malignant lesions (<3 cm) and lesions with low proliferative indices.[117] Therefore, accurate interpretation of PET scans is paramount and possible positive findings should be corroborated with the corresponding CT results. PET/CT is not indicated for residual masses ≤3 cm.

To reduce the incidence of false-positive results due to inflammation, the PET/CT scan should be performed at least 6 weeks after the completion of the last cycle of chemotherapy in patients with a residual mass >3 cm and normal serum tumor marker levels.[117,119] A negative PET/CT following chemotherapy is very reassuring. If the PET/CT is negative, surveillance is recommended as described in the next section on *Follow-up for Pure Seminoma Bulky Stage II and Stage III After Chemotherapy*. If the PET/CT is positive, resection or interventional radiology (IR)-guided biopsy of the residual mass should be considered. If the biopsy results show viable seminoma and the resection is complete, 2 cycles of adjuvant chemotherapy with the following regimens: EP, TIP (paclitaxel, ifosfamide, cisplatin),[120] VIP, or VeIP (vinblastine, mesna, ifosfamide, cisplatin) is recommended.[121,122] If the resection is incomplete or there is progressive disease (growing mass or rising markers), a full course of second-line chemotherapy (4 cycles of TIP or 4 cycles of VeIP; both preferred) is recommended.[120-123] Borderline PET/CT results require careful interpretation by experienced clinicians. If the PET/CT is borderline, consider surveillance and repeat PET/CT in 8 to 12 weeks to assess for changes. If the mass is persistently FDG-avid on PET/CT, then resection or biopsy is

recommended. Following adjuvant or second-line chemotherapy, patients should undergo follow-up as discussed in the next section. Patients should also adhere to this follow-up schedule if their biopsy results are negative for viable seminoma.

Follow-up for Pure Seminoma Bulky Stage II and Stage III After Chemotherapy

The recommended follow-up schedule for patients with bulky stage II or stage III seminoma after treatment with chemotherapy is outlined in Table 4 on TEST-A 2 of 2 in the algorithm and includes a history and physical examination as well as measurement of serum tumor marker levels every 2 months for year 1, every 3 months for year 2, every 6 months for years 3 and 4, and once during year 5. Abdominal/pelvic CT scans with contrast are recommended every 4 months for year 1, every 6 months for year 2, annually for years 3 and 4, and then as clinically indicated for year 5.[124] In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include visualization of the retroperitoneal and pelvic nodes and should be performed in centers with experience in interpreting MRI results for testicular cancer. The same imaging modality (CT or MRI) should be used throughout surveillance. Patients with residual masses may require more frequent imaging based on clinical judgment. However, CT is not recommended beyond 5 years unless clinically indicated. Chest x-ray is recommended every 2 months for year 1, every 3 months for year 2, and annually for years 3 through 5. While chest x-ray may be used for routine follow-up, chest CT with contrast is preferred for patients with thoracic symptoms. Since viable tumor cells have been found in tumors >3 cm with a negative post-chemotherapy PET scan,[125] the NCCN Panel recommends that patients with a residual mass measuring >3 cm and negative PET results after chemotherapy should undergo an abdominal/pelvic CT scan with contrast every 6 months for the first year and then annually for 5 years.

Nonseminoma

Nonseminomatous GCTs include nonseminoma tumors, mixed seminoma/nonseminoma tumors, and seminoma tumors in patients with elevated serum AFP levels. The post-diagnostic workup for nonseminoma includes CT scans with contrast of the chest, abdomen, and pelvis. PET/CT scan is not clinically indicated for nonseminoma.[126,127] Elevated levels of serum beta-hCG, LDH, or AFP should be followed up with repeated tests. Repeated measurement of serum tumor markers is important because TNM staging is based on post-orchiectomy values. The NCCN Panel emphasizes that mildly elevated AFP levels may not indicate the presence of a GCT. Therefore, decisions to treat should not be based on AFP levels <20 ng/mL. MRI of the brain, with and without contrast, should be performed if clinically indicated (ie, beta-hCG >5000 IU/L, extensive lung metastasis, choriocarcinoma, neurologic symptoms, non-pulmonary visceral metastasis, AFP >10000 ng/mL).

Sperm banking should be recommended to patients of reproductive age, if clinically indicated, before undergoing any therapeutic intervention that may compromise fertility, including surgery, RT, and chemotherapy.[29-32] If desired, sperm banking may be performed either before or after orchiectomy, but certainly prior to adjuvant therapy.

Stage-dependent treatment options after inguinal orchiectomy include surveillance, primary chemotherapy, and RPLND. Although the timing of RPLND may vary, most patients with nonseminoma will undergo 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-sparing dissection techniques preserve antegrade ejaculation in 90% of cases.[128] Therefore, nerve-sparing RPLND is recommended.

Nonseminoma Stage I Without Risk Factors

Primary Treatment for Nonseminoma Stage I Without Risk Factors

The NCCN Panel recommends treating stage I nonseminoma patients based on the presence or absence of risk factors known to be associated with an increased risk of relapse (LVI, invasion of the spermatic cord, or invasion of the scrotum).[36-44] Stage I nonseminoma patients with or without these risk factors are managed similarly after orchiectomy and can receive surveillance,[41,48,129,130] nerve-sparing RPLND, or chemotherapy (1 cycle of BEP)[131,132] as primary treatment. The major difference in the management of these two patient populations is that surveillance is preferred for patients with stage I nonseminoma without risk factors. The survival rate for stage I nonseminoma managed with surveillance or nerve-sparing RPLND exceeds 98%. However, the high survival rate associated with surveillance depends on adherence to periodic follow-up examinations and subsequent chemotherapy for the 20% to 30% of patients who relapse. Therefore, patients who choose surveillance should adhere to the follow-up schedule. When nerve-sparing RPLND is performed, it should be done within 4 weeks of a CT scan and within 7 to 10 days of repeat serum marker testing to ensure accurate presurgical staging.[133]

A phase III trial by Albers et al randomized stage I nonseminoma patients to undergo unilateral RPLND (n = 191) or 1 course of adjuvant BEP (n = 191) after orchiectomy.[131] After a median follow-up of 4.7 years, 2 relapses were reported in the BEP arm compared to 13 in the RPLND arm (P = .0011). This indicates that 1 course of BEP is active in stage I nonseminoma and could be an appropriate option for select patients.[131] In another prospective trial (SWENOTECA), stage I nonseminoma patients with or without LVI received 1 course of adjuvant BEP.[132] The relapse rate at 5 years was 3.2% for patients with LVI and 1.6% for patients without LVI. Five-year OS was 100% in both groups.[36] The results after a median follow-up of 7.9 years confirmed the low relapse rate with 1 course of adjuvant BEP, especially in patients with LVI.[36] In this setting, the NCCN Panel considers 1 cycle of BEP an appropriate option to reduce the risk of relapse. However, performing abdominal/pelvic CT scan and chest x-ray or CT scan is recommended within 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scans were done previously. Chest CT should be performed if either abdominal/pelvic CT or chest x-ray shows evidence of metastatic disease.

Follow-up for Nonseminoma Stage I Without Risk Factors

The long-term follow-up for stage I nonseminoma patients without risk factors includes a history and physical examination, serum tumor marker assessment, abdominal/pelvic CT scan, and chest x-ray. In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include visualization of the retroperitoneal and pelvic nodes and should be performed in centers with experience in interpreting MRI results for testicular cancer. The same imaging modality (CT or MRI) should be used throughout surveillance. All imaging in this setting is performed with contrast. The frequency of these tests varies with the primary treatment modality received by the patient (see Tables 5 and 7 on TEST-B in the algorithm). It should be noted that routine chest x-ray may have limited value for detecting relapse in stage I nonseminoma. In a recent retrospective study, a total of 76 relapses were detected among 561 stage I nonseminoma patients managed by active surveillance following orchiectomy.[96] All relapses were detected by either rising serum tumor markers or abnormal routine follow-up CT scans; not a single relapse was detected by chest x-ray alone. Similar results have been reported in other studies, calling into question the value of chest x-rays in surveillance settings for stage I nonseminomatous GCTs.[48,66,134] The current schedule for routine chest x-ray in the follow-up of stage I nonseminoma patients without risk factors is two chest x-rays in year 1 and one chest x-ray in years 2 through 5 in patients managed by surveillance. Chest x-ray is not indicated in years 3, 4, and 5 for stage I nonseminoma patients without risk factors treated with adjuvant BEP or primary RPLND.

Nonseminoma Stage I With Risk Factors

Primary Treatment for Nonseminoma Stage I With Risk Factors

Surveillance, adjuvant chemotherapy (1 cycle of BEP), or nerve-sparing RPLND are the recommended primary treatment options to reduce the risk of relapse in stage I nonseminoma patients with LVI, invasion of the spermatic cord, or invasion of the scrotum. In a prospective trial (SWENOTECA), stage I nonseminoma patients with or without LVI received

1 course of adjuvant BEP.[132] The relapse rate at 5 years was 3.2% for patients with LVI and 1.6% for patients without LVI. Five-year OS was 100% in both groups.[36] The results after a median follow-up of 7.9 years confirmed the low relapse rate with 1 course of adjuvant BEP, especially in patients with LVI.[36] Several other studies using two cycles of BEP as primary treatment for stage I nonseminoma have similarly reported relapse-free survival rates >95%.[130,135-139] However, late consequences of cisplatin-based chemotherapy, such as hearing damage and loss, cardiovascular conditions, hypertension, and neuropathy, have been reported during long-term follow-up.[79,140-146] Therefore, one cycle of BEP is recommended due to its lower toxicity. Surveillance is also a recommended primary treatment option for stage I nonseminoma patients with risk factors. However, it should be noted that LVI is a significant predictor of relapse when orchiectomy is followed by surveillance alone.[24]

Management of Nonseminoma Stage I After RPLND

If the resected lymph nodes are negative for malignancy (pN0) after nerve-sparing RPLND, the patient should undergo surveillance. For positive lymph nodes (pN1 to pN3), the decision whether to use adjuvant chemotherapy is based on the degree of nodal involvement. Surveillance is the preferred option for patients with pN1 disease, while chemotherapy is the preferred option for patients with pN2 disease. However, chemotherapy is the only option for patients with pN3 disease. Recommended chemotherapy regimens include two cycles of either EP (preferred) or BEP for patients with pN1 or pN2 disease[139,147] and 3 cycles of BEP or 4 cycles of EP (both preferred) for patients with pN3 disease.

Follow-up for Nonseminoma Stage I With Risk Factors

The long-term follow-up for stage I nonseminoma patients with risk factors includes a history and physical examination, serum tumor marker assessment, chest x-ray, and abdominal/pelvic CT scan. In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include visualization of the retroperitoneal and pelvic nodes and should be performed in centers with experience in interpreting MRI results for testicular cancer. The same imaging modality (CT or MRI) should be used throughout surveillance. All imaging in this setting is performed with contrast. The frequency of these tests varies with the primary treatment modality received by the patient (see Tables 6 and 7 on TEST-B in the algorithm).

Nonseminoma Stage IS

Patients with stage IS nonseminoma exhibit persistent elevation of serum tumor markers post-orchiectomy, but no radiographic evidence of disease. However, mildly elevated levels of AFP or beta-hCG after orchiectomy must be interpreted with caution, as the reason for marker elevation may be hepatobiliary disease, marijuana use, or hypogonadism. Mildly elevated AFP levels (<20 ng/mL) may not indicate the presence of a GCT and should not be used to guide treatment decisions. In addition, in very rare instances, heterophile antibodies can result in significant false-positive elevations of beta-hCG. Elevated beta-hCG due to metastatic disease typically rises steadily on serial measurements. In a patient with stable (ie, not rising) elevated beta-hCG and no other evidence of metastatic disease, repeating the test using a different assay should be considered. Furthermore, many different conditions can result in an elevation of LDH, including many benign conditions. Therefore, patients should not be treated with chemotherapy for systemic disease if the only evidence of systemic disease is an elevation of LDH.

Primary Treatment for Nonseminoma Stage IS

The NCCN Panel recommends that stage IS nonseminoma patients be treated with primary chemotherapy if the elevated marker is either AFP or beta-hCG. For the purposes of this guideline, the NCCN Panel assumes that patients with stage IS disease have markers in the S1 range. It would be extraordinarily rare for a patient to have an AFP >1000 ng/mL or a beta-hCG >5000 IU/L and yet have no evidence of metastatic disease on imaging studies. These guidelines cannot address every possible situation, and the management of those rare patients with T any, N0, M0, S2-3 disease should be individualized. The vast majority of stage IS patients have serum tumor markers in the S1 range, and they should receive primary chemotherapy for good-risk disease: either 3 cycles of BEP or 4 cycles of EP (both preferred). Both regimens are category 1 recommendations, and either is preferable to initial RPLND as these patients nearly always have disseminated disease.[148,149]

Management of Nonseminoma Stage IS After Primary Treatment

The management of patients with stage IS nonseminoma after primary treatment with chemotherapy is described below in *Advanced Metastatic Nonseminoma* (see *Management of Good, Intermediate, and Poor-Risk Nonseminoma After Chemotherapy*).

Nonseminoma Stage IIA

Primary Treatment for 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 beta-hCG, the NCCN Panel recommends either nerve-sparing RPLND or chemotherapy with 3 cycles of BEP or 4 cycles of EP as primary treatment options (both BEP and EP are preferred regimens).[150,151] Chemotherapy is considered particularly appropriate if the patient has multifocal disease. For stage IIA patients with persistently elevated AFP or beta-hCG levels, the NCCN Panel recommends primary chemotherapy with 3 cycles of BEP or 4 cycles of EP (both category 1; both preferred).[152,153] A bleomycin-free regimen should be considered in patients with reduced or borderline GFR and in patients over the age of 50. For select stage IIA nonseminoma patients with borderline retroperitoneal lymph nodes, repeating imaging (chest/abdominal/pelvic CT scan) after 4 to 6 weeks to confirm staging before the initiation of treatment can be considered.

Management of Nonseminoma Stage IIA After Primary Treatment

Treatment options following primary nerve-sparing RPLND include either surveillance or chemotherapy, depending on the number of positive lymph nodes identified. Since RPLND is likely a curative procedure in patients with pN0 disease, surveillance is recommended for this group. Surveillance is also the preferred option for patients with pN1 disease, although chemotherapy with 2 cycles of either EP or BEP can also be considered.[153,154] If chemotherapy is given, EP is the preferred regimen in this setting. The risk of relapse in stage IIA nonseminoma patients with pN2 or pN3 disease after RPLND is >50%.[153,155] This risk is reduced to <1% with 2 cycles of adjuvant cisplatin-based chemotherapy.[153,156,157] Therefore, the NCCN Panel prefers 2 cycles of adjuvant chemotherapy with EP (preferred) or BEP to surveillance for pN2 disease and recommends full-course chemotherapy (and not surveillance) for pN3 disease (either 3 cycles of BEP or 4 cycles of EP; both preferred).

Subsequent management after primary chemotherapy depends on the size of the residual mass on CT scan. Patients should thus undergo abdominal/pelvic CT scan with contrast after completing chemotherapy. Chest CT with contrast or chest x-ray may also be considered. If the residual mass is ≥1 cm after chemotherapy, nerve-sparing bilateral RPLND is recommended. 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.[158] Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy. Surveillance is recommended for patients with no residual mass or a residual mass <1 cm. Nerve-sparing bilateral RPLND is a category 2B recommendation in this setting and may be performed in selected cases.

Follow-up for Nonseminoma Stage IIA

The long-term follow-up for stage IIA nonseminoma patients includes a history and physical examination, serum tumor marker assessment, chest x-ray, and abdominal/pelvic CT scan. In select circumstances, an MRI can be considered to replace an abdominal/pelvic CT. The MRI protocol should include visualization of the retroperitoneal and pelvic nodes and should be performed in centers with experience in interpreting MRI results for testicular cancer. The same imaging modality (CT or MRI) should be used throughout surveillance. All imaging in this setting is performed with contrast. The frequency of these tests varies with the primary treatment modality and post-surgical management received by the patient (see Tables 8, 9, and 10 on TEST-B in the algorithm).

Nonseminoma Stage IIB

Primary Treatment for Nonseminoma Stage IIB

Treatment for patients with stage IIB nonseminoma depends on post-orchiectomy tumor marker levels and radiographic findings. When tumor marker levels are normal, the CT findings determine the proper course of treatment. If abnormal radiographic findings are limited to lymph node metastases within lymphatic drainage sites in the retroperitoneum (ie, the landing zone), patients should receive primary chemotherapy with either 3 cycles of BEP or 4 cycles of EP (both preferred). Primary treatment with nerve-sparing RPLND should be reserved for highly selected cases. Both options of primary chemotherapy or primary nerve-sparing RPLND are comparable in terms of outcome, but side effects and toxicity are different.[151] The reported relapse-free survival with either approach is close to 98%.[155-157,159,160] If metastatic disease (based on radiographic findings) is not confined to within the lymphatic drainage sites (ie, multifocal lymph node metastases with aberrant lymphatic drainage sites), primary chemotherapy is recommended with either 3 cycles of BEP or 4 cycles of EP (both preferred). For stage IIB nonseminoma patients with persistent marker elevation, the recommended treatment option is also primary chemotherapy with either 3 cycles of BEP or 4 cycles of EP (both category 1; both preferred). A bleomycin-free regimen should be considered in patients with reduced or borderline GFR and in patients over the age of 50.

Management of Nonseminoma Stage IIB After Primary Treatment

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

Follow-up for Nonseminoma Stage IIB

The long-term follow-up schedule for stage IIB nonseminoma patients is similar to the follow-up schedule outlined above for patients with stage IIA nonseminoma and is dependent upon the primary treatment modality and post-surgical management received by the patient (see *Follow-up for Nonseminoma Stage IIA* and Tables 8, 9, and 10 on TEST-B in the algorithm).

Advanced Metastatic Nonseminoma

The primary chemotherapy options for patients with advanced metastatic nonseminoma are based on the IGCCCG risk classification, which categorizes patients as good, intermediate, or poor risk.[53] When determining a patient's risk classification, the relevant serum tumor marker value is the value on day 1 of cycle 1 of first-line chemotherapy (see *Risk Classification for Advanced Disease* in the algorithm).[13] Patients with an extragonadal primary site, whether retroperitoneal or mediastinal, are also treated with primary chemotherapy. As previously mentioned, a bleomycin-free regimen should be considered in patients with reduced or borderline GFR and in patients over the age of 50.

Primary Treatment for Good-Risk Nonseminoma

The IGCCCG good-risk group includes patients with stages IS, IIA (S1), IIB (S1), IIC, and IIIA disease. Treatment for good-risk GCTs is designed to decrease toxicity while maintaining maximal efficacy. Presently, two regimens are recommended by the NCCN Panel: 3 cycles of BEP[104,106,161] or 4 cycles of EP[105,106,161] (both category 1; both preferred). Both regimens are well tolerated and cure approximately 90% of patients with good-risk disease.[161,162]

Primary Treatment for Intermediate-Risk (Stage IIIB) Nonseminoma

For patients with intermediate-risk disease, the cure rate is approximately 70% with the standard chemotherapy regimen of 4 cycles of BEP.[163,164] Therefore, the NCCN Panel recommends 4 cycles of BEP (preferred), or 4 cycles of VIP[163,165] for patients who may not tolerate bleomycin, for the treatment of intermediate-risk nonseminoma. Both regimens are category 1 recommendations. However, if intermediate-risk status is based on LDH levels 1.5 to 3 times the upper limit of normal, then 3 cycles of BEP can be considered.

Primary Treatment for Poor-Risk (Stage IIIC) Nonseminoma

The standard chemotherapy regimen for poor-risk disease is 4 cycles of BEP (preferred). Alternatively, 4 cycles of VIP can be used to treat select patients who may not tolerate bleomycin.[165] Both regimens are category 1 recommendations. However, between 20% and 30% of patients with poor-risk nonseminoma are not cured with conventional cisplatin-based chemotherapy and <50% experience a durable complete response to 4 cycles of BEP. Therefore, consultation with a high-volume center should be considered for these patients.[162]

Management of Good-, Intermediate-, and Poor-Risk Nonseminoma After Chemotherapy

At the conclusion of primary chemotherapy, chest/abdominal/pelvic CT scan with contrast and measurement of serum tumor marker levels are indicated to assess treatment response. If a complete response to chemotherapy is found by radiographic imaging and the tumor marker levels are normal, the NCCN Panel recommends surveillance. Nerve-sparing bilateral RPLND can be considered in select cases for patients who had retroperitoneal lymphadenopathy prior to chemotherapy (category 2B).[166] RPLND is recommended within 4 weeks of the CT scan and 7 to 10 days of marker measurement. Referral to high-volume centers should be considered for surgical resection of residual masses following chemotherapy.

If there is a partial response to chemotherapy and the tumor marker levels are normal, then surgical resection of all residual masses is recommended.[167-170] As previously stated, referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy. If only necrotic debris or mature teratoma is present in the resected tissue, the patient should be put under surveillance. If embryonal, yolk sac, choriocarcinoma, or seminoma elements are found in the residual mass, 2 cycles of chemotherapy (EP, TIP, VIP, or VeIP) should be administered. All regimens are preferred in this setting, though EP should be reserved for low-volume residual disease.

Patients who experience an incomplete response to chemotherapy with persistently elevated AFP and/or beta-hCG levels should be referred to a high-volume center experienced in the management of this disease. Management of these patients should include close surveillance. Surgical resection of residual masses, as described in the previous paragraph, can also be considered. Salvage chemotherapy should be reserved for patients with rising markers or other evidence of progressive disease.

Follow-up for Good-, Intermediate-, and Poor-Risk Nonseminoma

The recommended follow-up tests and their frequencies during surveillance of good-, intermediate-, and poor-risk nonseminoma after chemotherapy (with or without post-chemotherapy RPLND) are outlined in Table 8 on TEST-B 2 of 3 in the algorithm.

Second-Line and Subsequent Therapy for Metastatic Germ Cell Tumors

Second-Line Therapy

Patients with disease relapse following first-line therapy, or those who do not experience a durable complete response to first-line therapy, are divided into favorable or unfavorable prognostic groups based on prognostic factors.[171-173] Favorable prognostic factors include low levels of post-orchiectomy serum tumor markers, low-volume disease, complete response to first-line therapy, and the presence of a testicular primary tumor. Unfavorable prognostic features include an incomplete response to first-line therapy, high levels of serum tumor markers, high-volume disease, and the presence of an extratesticular primary tumor. Regardless of prognosis, sperm banking should be recommended to patients before the initiation of second-line therapy, if clinically indicated. Patients with recurrent disease who have not been treated with prior chemotherapy should be managed per their risk status, as described in the preceding sections. It is preferred by the panel that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease. Second-line therapy options for those with favorable or unfavorable prognosis include enrollment in a clinical trial (preferred), or conventional-dose or high-dose chemotherapy. If chemotherapy is given, both conventional-dose and high-dose regimens are preferred in this setting. The conventional-dose regimens are TIP or VeIP.[120,174-176] The high-dose regimens include high-dose carboplatin plus etoposide followed by

autologous stem cell transplant,[177] or paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide with stem cell support.[178] Alternatively, a surgical salvage may be considered in patients with an unfavorable prognosis if the relapse is in a solitary resectable site.[179]

It is not known whether high-dose chemotherapy is better than conventional-dose chemotherapy in the second-line setting for patients with relapsed disease. Therefore, the NCCN Panel recommends clinical trial enrollment as the preferred management option for these patients. An ongoing, randomized, international phase III trial (TIGER) will compare second-line standard-dose chemotherapy with high-dose chemotherapy in patients with relapsed GCTs, with OS as the primary endpoint.[180,181] Participation in this trial is highly encouraged (Clinical Trial ID: NCT02375204).

Late relapses (>2 years after completion of primary therapy) occur in 2% to 3% of testicular cancer survivors.[182,183] The NCCN Panel prefers surgical salvage for patients with late relapse, if technically feasible.[179] Conventional-dose and high-dose chemotherapy are also options for patients with late relapse.

Management of Metastatic Germ Cell Tumors After Second-Line Therapy

To assess response after second-line therapy, a CT scan with contrast of the chest, abdomen, pelvis, and any other sites of disease is recommended. Levels of serum tumor markers should also be measured. Patients experiencing a complete response to second-line therapy with normal marker levels should be put under surveillance. Alternatively, select patients may receive nerve-sparing bilateral RPLND (category 2B), followed by surveillance. For patients with a partial response to second-line therapy (as indicated by residual mass on CT scan) and normal marker levels, surgical resection of all residual masses is recommended, followed by surveillance. Patients with an incomplete response to second-line therapy and persistently elevated marker levels should be managed with either close surveillance or surgical resection of residual masses followed by surveillance. Referral to high-volume centers should be considered for surgical resection of residual masses following chemotherapy.

Patients who do not experience a complete response to second-line therapy should be managed according to the NCCN Panel's recommendations for third-line therapy, summarized below.

Third-Line Therapy

Participation in a clinical trial is the preferred treatment option for patients who experience relapse following first- and second-line therapy. Patients previously treated with conventional-dose chemotherapy should be considered for high-dose regimens. Alternative options for patients previously treated with high-dose regimens include conventional-dose salvage chemotherapy, surgical salvage (if solitary site of relapse), and microsatellite instability/mismatch repair (MSI/MMR) testing (if disease progresses after high-dose chemotherapy or third-line therapy).

The preferred treatment option for patients who experience a late relapse (>2 years after completion of second-line therapy) is surgical salvage, if the recurrent mass is resectable. Conventional-dose or high-dose chemotherapy (if not previously given), are also options for patients with late relapse.

In order to maintain optimal efficacy and limit treatment-related toxicities, the chemotherapy regimens previously received by the patient should be taken into account when deciding on third-line chemotherapy options. High-dose chemotherapy is the preferred third-line option if it has not been previously received. High-dose chemotherapy is also preferred if VIP or TIP was received as second-line therapy. If high-dose chemotherapy was previously received by the patient, then palliative chemotherapy is the preferred third-line treatment option. Additionally, the panel considers pembrolizumab immunotherapy to be useful in certain circumstances (ie, in patients with MSI-high/deficient MMR [MSI-H/dMMR] testicular GCTs).

The recommended third-line palliative chemotherapy options for patients with intensively pretreated, cisplatin-resistant, or refractory GCTs are combinations of gemcitabine with paclitaxel and/or oxaliplatin,[184-190] or oral etoposide.[191] The recommendation for gemcitabine and oxaliplatin (GEMOX) is based on data from phase II studies investigating the efficacy and toxicity of GEMOX in patients with relapsed or cisplatin-resistant

GCTs.[185,187,189] These studies showed that GEMOX is safe for patients with cisplatin-resistant testicular GCTs and may offer a chance of long-term survival.[185,187,189] Gemcitabine and paclitaxel is another option that has shown promising results in a phase II study.[186] Follow-up results showed long-term disease-free survival in patients who progressed after high-dose chemotherapy and had not received prior paclitaxel or gemcitabine.[188] A phase II study of patients with treatment-resistant GCTs found the combination of gemcitabine, oxaliplatin, and paclitaxel to be effective with acceptable toxicity.[184] The overall response rate was 51% with 5% of patients achieving a complete response. A second study reported similar results.[190] Additionally, high-dose single-agent oral etoposide was shown to be effective in a phase II study involving patients who had previous treatment with cisplatin/etoposide combination regimens.[191]

Pembrolizumab, a PD-1 antibody, was recently approved by the FDA for the treatment of patients with unresectable or metastatic MSI-H/dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[192] This first-ever tissue- and site-agnostic indication was based on phase II clinical trials that demonstrated the efficacy of pembrolizumab in MSI-H/dMMR solid tumors.[193,194] In the first ever phase II trial investigating the efficacy of immunotherapy in testicular cancer, 12 patients with nonseminoma GCTs who progressed after first-line cisplatin-based chemotherapy and at least 1 salvage regimen (high-dose or conventional-dose chemotherapy) were treated with pembrolizumab.[195] Two patients achieved stable disease for 28 and 19 weeks, respectively, but no partial or complete responses were observed. There were 6 grade 3 adverse events, but no immune-related adverse events were reported. Therefore, pembrolizumab was well tolerated but appears to have limited single-agent activity in refractory GCTs. However, larger phase II and phase III trials of pembrolizumab in patients with metastatic or refractory testicular cancers are needed to fully assess the value of this therapy, especially in treating MSI-H/dMMR testicular GCTs.

Treatment of Brain Metastases

Brain metastases from testicular GCTs are relatively rare and occur almost exclusively in patients with nonseminoma histology.[196] The development of brain metastases may be more common in patients with a higher burden of systemic disease; lung, liver, and/or bone metastases; high levels of serum beta-HCG (>5000 IU/L); and in those who experience relapse after cisplatin-based chemotherapy. The prognosis of patients with brain metastases from testicular GCTs is poor, with >50% of patients dying within 1 year of diagnosis.[196,197] Patients with additional adverse prognostic factors, especially those with metachronous brain metastases, have even worse outcomes.[196,198,199]

In a recent retrospective analysis, Loriot et al reported on the pattern of relapse among patients with poor-risk nonseminoma GCTs previously treated with chemotherapy.[200] After a median follow-up of 4.1 years, 32% were found to have radiographic evidence of brain metastases. The brain was the only site of progression in 54% of these patients and 19% experienced progression in the brain as the first progression event. Furthermore, involvement of the brain was more common among patients who were previously treated with dose-dense chemotherapy (29%) compared to BEP (12%). These data suggest that brain metastases from testicular GCTs may occur more frequently than previously thought, often as the only site of progression, and may be more likely to occur in poor-risk patients previously treated with dose-dense chemotherapy versus BEP. However, it is unknown whether this reduced efficacy is due to lower cerebral drug penetrance used in the dose-dense regimen.

The optimal management of brain metastases from testicular GCTs is controversial, with a lack of evidence from prospective trials to guide treatment decisions.[196,198] Therefore, management decisions are usually based on institutional preferences, which may in part explain the large variation in treatment modalities received by these patients. The NCCN Guidelines recommend primary treatment with cisplatin-based chemotherapy for patients with brain metastases. The addition of RT to chemotherapy regimens can also be considered.[201] Surgical resection of metastatic brain lesions should be performed if clinically indicated and feasible.

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