National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Testicular Cancer

Version 2.2018 — February 16, 2018

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Testicular Cancer

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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/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2018 of the NCCN Guidelines for Testicular Cancer from Version 1.2018 include:

- **The Discussion has been updated to reflect the changes in the algorithm. (MS-1)**

Updates in Version 1.2018 of the NCCN Guidelines for Testicular Cancer from Version 2.2017 include:

Global changes

- **AJCC Cancer Staging tables (7th edition) for Testis Cancer: The following statement was added, "*Both the AJCC Staging for Testis Cancer 7th and 8th editions are included for reference and documentation.*" (ST-1 and ST-2)**
- **The AJCC Cancer Staging tables (8th edition) for Testis Cancer were added (ST-3, ST-4, ST-5).**

TEST-1

- **Primary Treatment; Third bullet**
  - ◊ **First sub-bullet: Revised to "~~Suspicious~~ Ultrasound *showing* ~~with~~ intratesticular ~~abnormalities~~ *mass concerning for testicular cancer*."**
  - ◊ **New sub-bullet added "*Suspicious mass*"**
- **Pathologic Diagnosis: Top pathway revised to "Pure seminoma (pure seminoma histology and AFP ~~negative~~ *normal*; may..." (Also for TEST-2)**
- **Footnote "b" revised: "...when a patient presents with rapidly increasing beta-hCG *or AFP* and symptoms..."**
- **Footnote "c" is new: "*Biopsies are not recommended for microcalcifications*."Pure Seminoma**

TEST-2

- **Postdiagnostic workup: Last bullet revised to "~~Discuss~~ *Recommend* sperm banking, if clinically indicated."**
- **Footnote "g" revised: "...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)*."**
- **Footnote "i" revised: " Eg, ~~high~~ beta-hCG *>5000 IU/L*, or extensive lung metastasis, ~~*or choriocarcinoma*~~."**
- **Footnote "j" regarding Clinical Stage IA, IB is new: "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)**
- **Footnote "k" revised: "...(chest/abdomen/pelvic CT *with contrast*)..."**

TEST-3

- **Stage IS; Follow-up: Revised to "Repeat elevated serum tumor marker *measurement* and assess with *chest*/abdominal/pelvic CT (*with contrast) to* scan for evaluable disease."**
- **Footnote "q" is new: "*Elevated tumor markers increase the risk of disease outside of the retroperitoneum. Therefore, systemic therapy should be encouraged*."**
- **Footnote "m" is new: "Recommend chest/abdomen/pelvic CT scan within the 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scan was done previously."**
- **Footnote "r" is new: "*Patients should not be treated based upon an elevated LDH alone*."**

TEST-4

- **Stage IIA; Primary Treatment: Revised to "Primary chemotherapy: BEP for 3 cycles or EP for 4 cycles ~~for multiple positive lymph nodes~~"**
- **Footnote "u" is new: "*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 patients with a serum bHCG above 1000 IU/L are also generally presumed to have a nonseminoma. LDH should not be used to stage or risk stratify patients with pure seminoma*."**
- **Footnote "w" is new: "*Patients should not be treated based only upon an elevated LDH*."**

TEST-5

- **Top pathway revised: "No residual mass or residual mass ≤3 cm and normal ~~markers~~ *serum AFP and beta-hCG*"**
- **Middle pathway**
  - ▸ **Revised "Residual mass (>3 cm) and normal ~~markers~~ *serum AFP and beta-hCG*"**
  - ▸ **"Surveillance" added as an option and imaging recommendation revised: "*Consider* PET/CT scan *from skull base to mid-thigh* (6 wks...)."**
- **Footnote "y" revised: "...If resection incomplete, ~~consider~~ full course of second-line therapy *is recommended (see TEST-12). If a biopsy is performed and is positive, consider surgery if complete resection is possible or full course of second-line chemotherapy.*"**

Continued

Nonseminoma

TEST-6
- Postdiagnostic Workup; Second bullet: Revised "Repeat beta-hCG, LDH, AFP ~~since~~ *because* TNM staging..."
- Footnote "j" regarding Clinical Stage IA, IB is new: "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-7)
- Footnote "i" revised: "Eg, ~~high~~ beta-hCG *>5000 IU/L*, extensive lung metastasis, ~~or~~ choriocarcinoma, *neurologic symptoms, non-pulmonary visceral metastasis, or AFP >10,000 ng/mL*."
- Footnote "z" is new: "*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.*" (Also for TEST-7, 8)

TEST-7
- Primary Treatment options for Stage IB revised:
  - "Primary chemotherapy: BEP for ~~1–2~~ *1* cycle"
  - "Surveillance ~~for T2 or T3~~ (category 2B)"
- Footnote "m" is new: "*Recommend chest/abdomen/pelvic CT scan within the 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scan was done previously.*"

TEST-11
- Primary treatment for Intermediate risk Stage IIIB: Revised "VIP for 4 cycles *(category 1)*"
- After "Complete response, negative markers": Revised, "If original stage, ~~Stage IIA, S1 Stage IIB, S1 Stage IIC Stage IIIA~~ *T any N1-3, M0-1*"
- Third column: Revised to include "Incomplete response *with persistently elevated AFP and/or beta-hCG levels*" along with a new post-chemotherapy management section for these patients.
- Footnote "hh" is new: "*If Intermediate risk is based on LDH 1.5–3 (U/L), then BEP for 3 cycles can be considered.*"
- Footnote "jj" is new: "*Salvage chemotherapy should be reserved for patients with rising AFP, beta-hCG, or other evidence of progressive disease.*"
- Footnote regarding incomplete response removed: "There is limited predictive value for PET/CT scan for residual masses."

TEST-12
- Prior chemotherapy; Second-Line Therapy: "Recommend sperm banking if clinically indicated" added to all three pathways.
- No prior chemotherapy; Second-Line Therapy: Revised, "~~Discuss~~ *Recommend* sperm banking if clinically indicated"
- Footnote ll: References revised.

TEST-13
- New pathway added with treatment options for recurrence for patients who had prior second-line therapy.

TEST-14
- New pathway added with treatment options for recurrence for patients who had prior chemotherapy. Includes recommendations for third-line therapy.

TEST-A 1 of 2 Follow-up for Seminoma
- Footnote 3 revised: "*With or* without contrast."
- Footnote "4" is new: "*CT is not recommended beyond 5 years unless clinically indicated.*"

TEST-A 2 of 2 Follow-up for Seminoma
- Table 4
  - Title revised: "Bulky Clinical Stage IIB, IIC, and Stage III Seminoma: Surveillance Post-Chemotherapy ~~with No Residual Mass or Residual Mass <3 cm and Normal Tumor Markers~~"
  - Imaging time interval recommendations for "Abdominal/Pelvic CT" revised for all years.
- Footnote "4" is new: "*CT is not recommended beyond 5 years unless clinically indicated.*"
- Footnote "9" is new: "*Patients with residual masses may require more frequent imaging based on clinical judgment.*"
- Footnote "10" is new: "*PET/CT scan skull base to mid-thigh as clinically indicated.*"

Continued

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TEST-B 1 of 3 Follow-up for Nonseminoma
- Footnote "1" is new: "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)."

TEST-B 2 of 3 Follow-up for Nonseminoma
- Table 7: Title revised, "Clinical Stage ~~IB~~ *IA/B* NSGCT: Treated with ~~1–2~~ 1 Cycle of Adjuvant BEP Chemotherapy"
- Table 8: "Abdominal ± Pelvic CT" intervals revised
  - Year 2: "~~Annually~~ *Every 6–12 mo*"
  - Year 3: *Annually* added.

TEST-B 3 of 3 Follow-up for Nonseminoma
- Table 9; "Abdominal ± Pelvic CT" interval revised:
  - Year 1: "*4 mo* after RPLND"

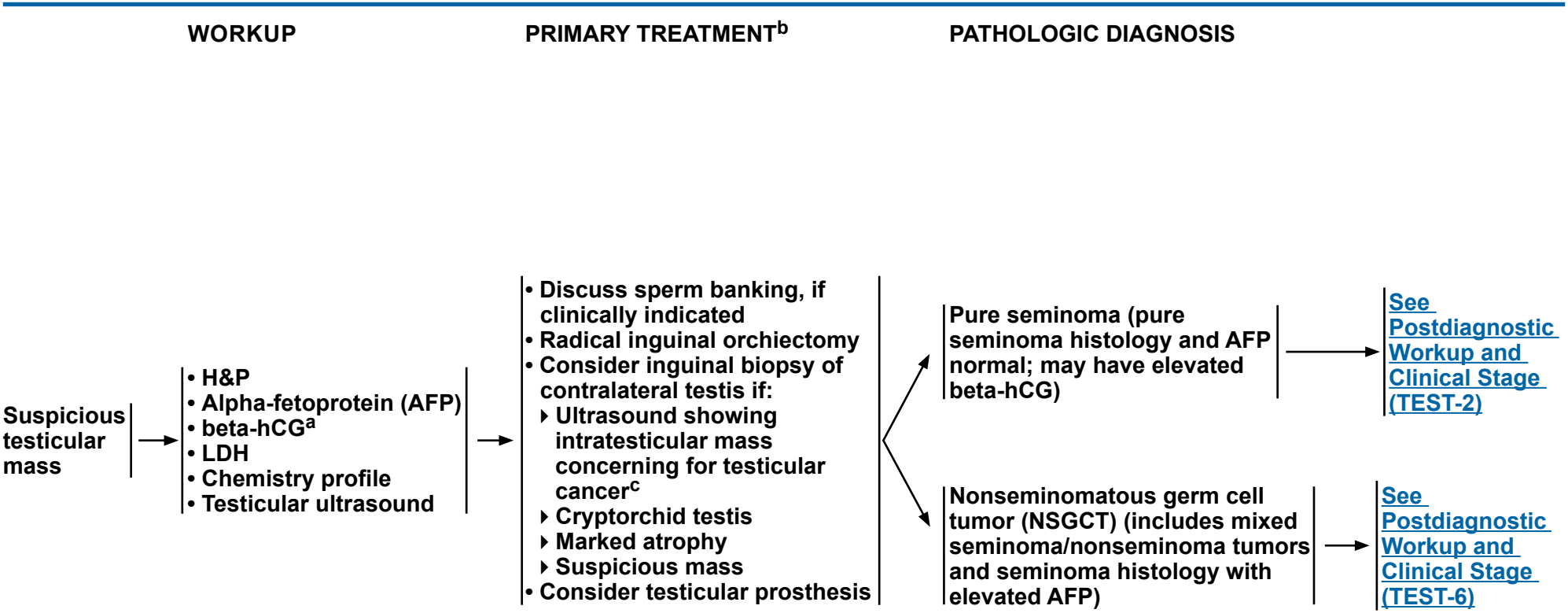
TEST-C 4 of 5 Principles of Radiotherapy for Pure Testicular Seminoma
- Figure titles added.

TEST-E Primary Chemotherapy Regimens for Germ Cell Tumors
- EP: Added "*(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)*"
- VIP
  - Added "*(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)*"
  - Mesna dose revised.
- New footnote "3" added for 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).*"

TEST-F Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors
- Mesna dose revised for VeIP and TIP.

TEST-G Third-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors
- Page title revised: "~~Subsequent~~ *Third-Line* Chemotherapy Regimens For Metastatic Germ Cell Tumors"
- Palliative Chemotherapy Regimens: "*Pembrolizumab (for MSI-H/dMMR tumors)*" added as an option. Supporting references also added.
- New footnote "2" added: "*For high-dose regimens, See Second-Line Therapies (TEST-F)*"

TEST-H Principles of Surgery for Germ Cell Tumors
- First bullet revised, "... and post-chemotherapy setting. *Referral to high-volume centers with experience in performing RPLNDs should be considered.*"



[a]Quantitative analysis of beta subunit.
[b]Though rare, when a patient presents with rapidly increasing beta-hCG or AFP and symptoms 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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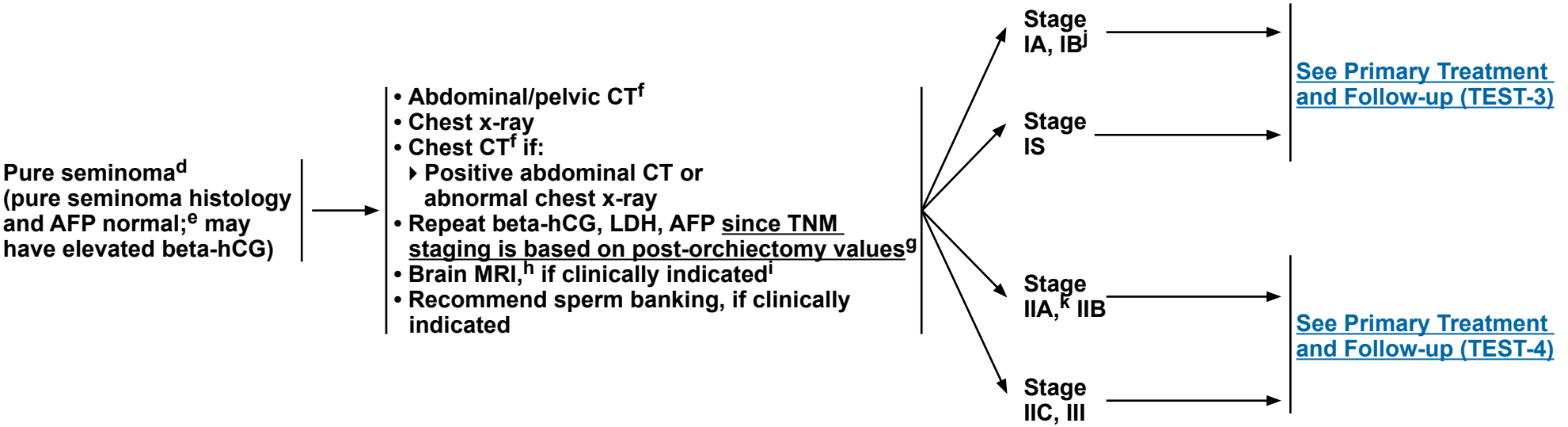

[d]Mediastinal primary seminoma should be treated by risk status used for gonadal seminomas with etoposide/cisplatin for 4 cycles or bleomycin/etoposide/cisplatin for 3 cycles.
[e]If AFP positive, treat as nonseminoma.
[f]With contrast.
[g]Elevated values should be followed after orchiectomy with repeated 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]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)
[k]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.

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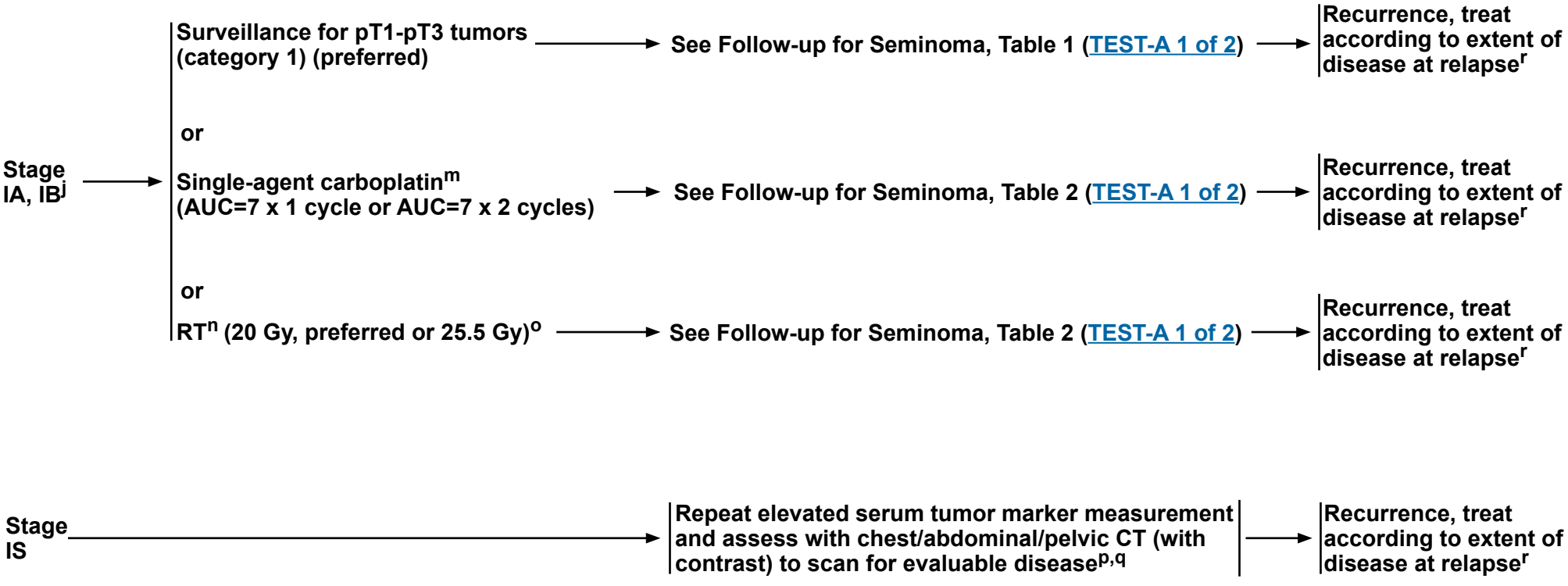

[j]The panel recommends using the AJCC Staging 7th edition for subclassifying and making treatment decisions about stage I tumors. (See ST-1 and ST-2)
[l]Discuss sperm banking prior to chemotherapy or radiation treatment.
[m]Recommend chest/abdomen/pelvic CT scan within the 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scan was done previously.
[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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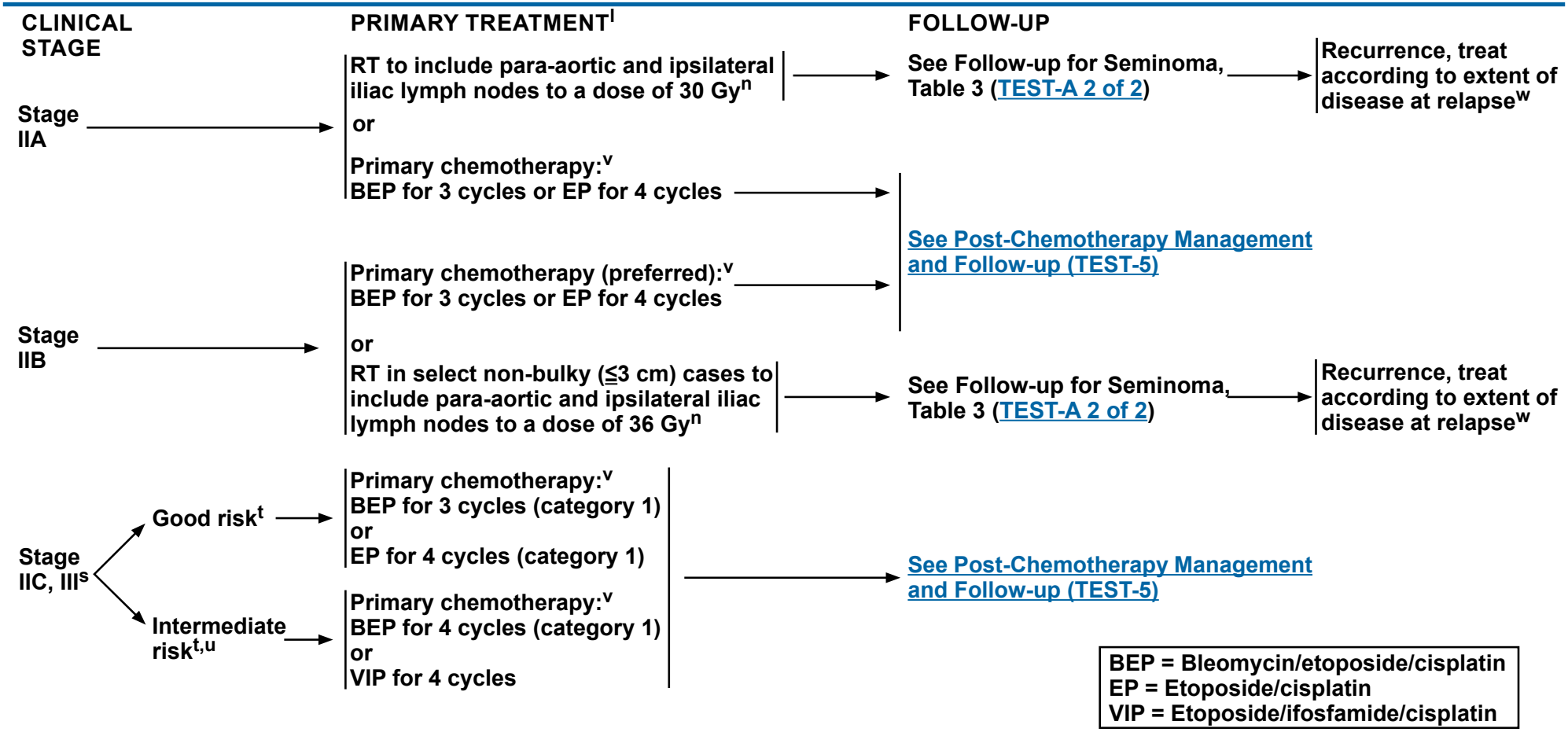

[l]Discuss sperm banking prior to chemotherapy or radiation treatment.
[n]See Principles of Radiotherapy for Pure Testicular Seminoma (TEST-C).
[s]All stage IIC and stage III seminomas are considered good-risk disease except for stage III disease with non-pulmonary visceral metastases (eg, bone, liver, 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 and patients with a serum bHCG above 1000 IU/L are also generally presumed to have a nonseminoma. LDH 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]Patients should not be treated based only upon an elevated LDH.

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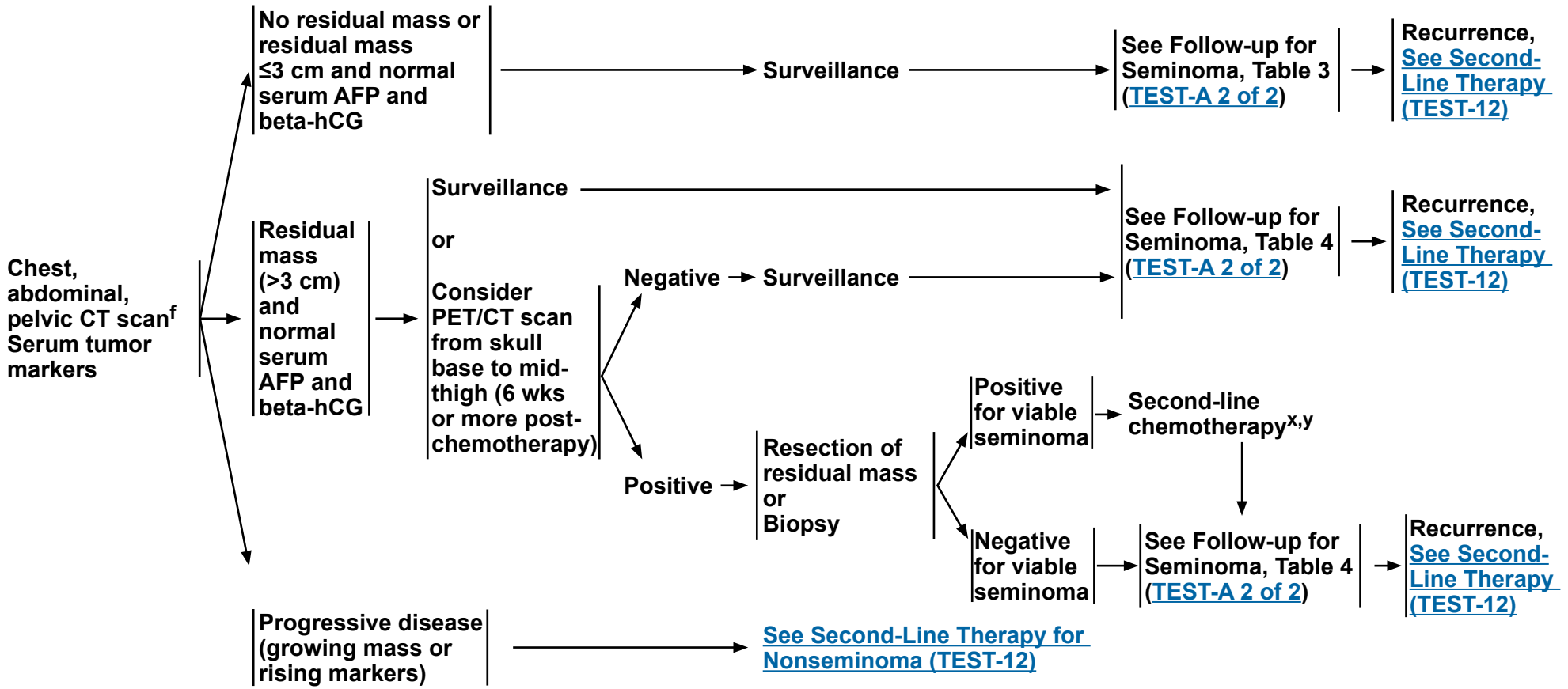

[f]With contrast.

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

[y]If complete resection of all residual disease, consider chemotherapy for 2 cycles (EP or TIP or VIP/VeIP). If resection incomplete, full course of second-line therapy is recommended (see TEST-12). If a biopsy is performed and is positive, consider surgery if complete resection is possible or full course of second-line chemotherapy.

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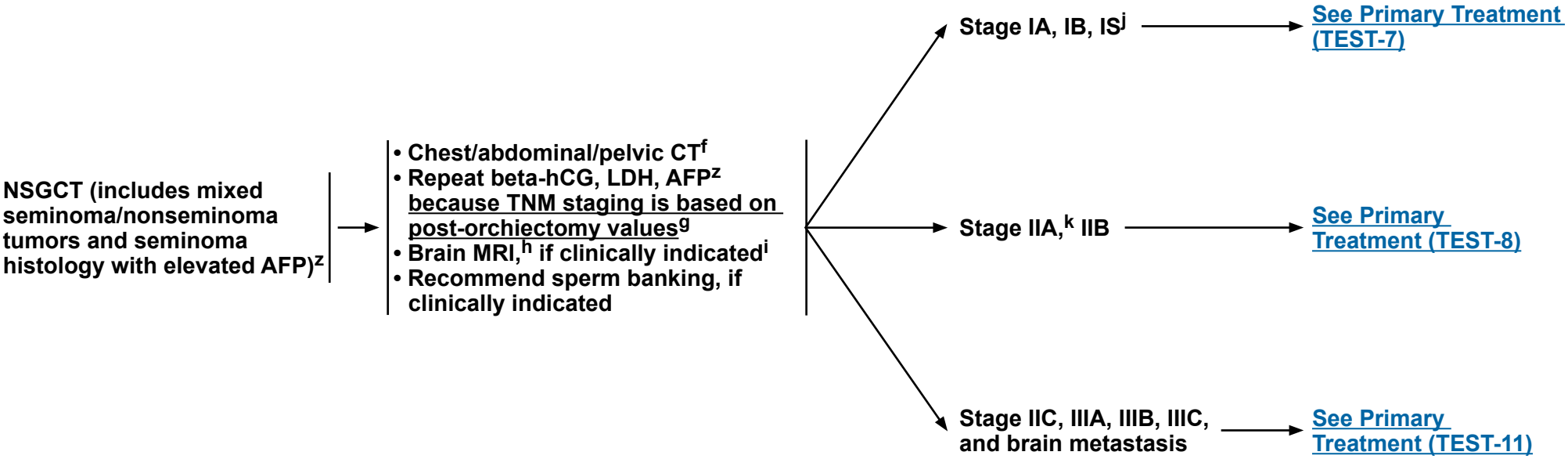
PATHOLOGIC DIAGNOSIS | **POSTDIAGNOSTIC WORKUP[aa]** | **CLINICAL STAGE[g]**



[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, extensive lung metastasis, choriocarcinoma, neurologic symptoms, non-pulmonary visceral metastasis, or AFP >10,000 ng/mL, choriocarcinoma, neurologic symptoms, non-pulmonary visceral metastasis, or AFP >10,000 ng/mL.
[j]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)
[k]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.
[z]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.
[aa]PET/CT scan is not clinically indicated for nonseminoma.

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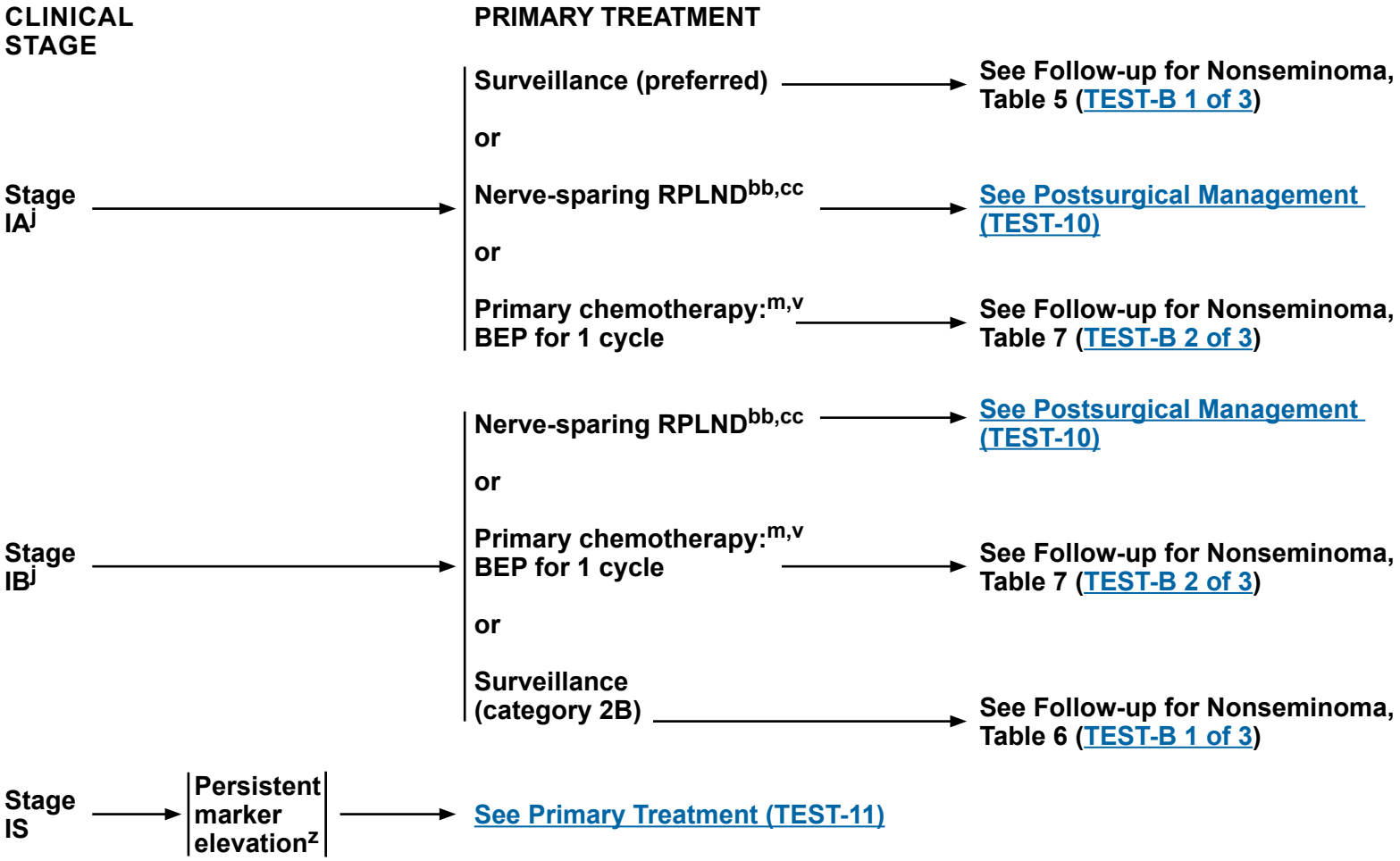

[j]The panel recommends using the AJCC Staging 7th edition for subclassifying and making treatment decisions about stage I tumors. (See ST-1 and ST-2)
[m]Recommend chest/abdomen/pelvic CT scan within the 4 weeks prior to the initiation of chemotherapy to confirm staging, even if scan was done previously.
[v]See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[z]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.
[bb]Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.
[cc]See Principles of Surgery for Germ Cell Tumors (TEST-H).

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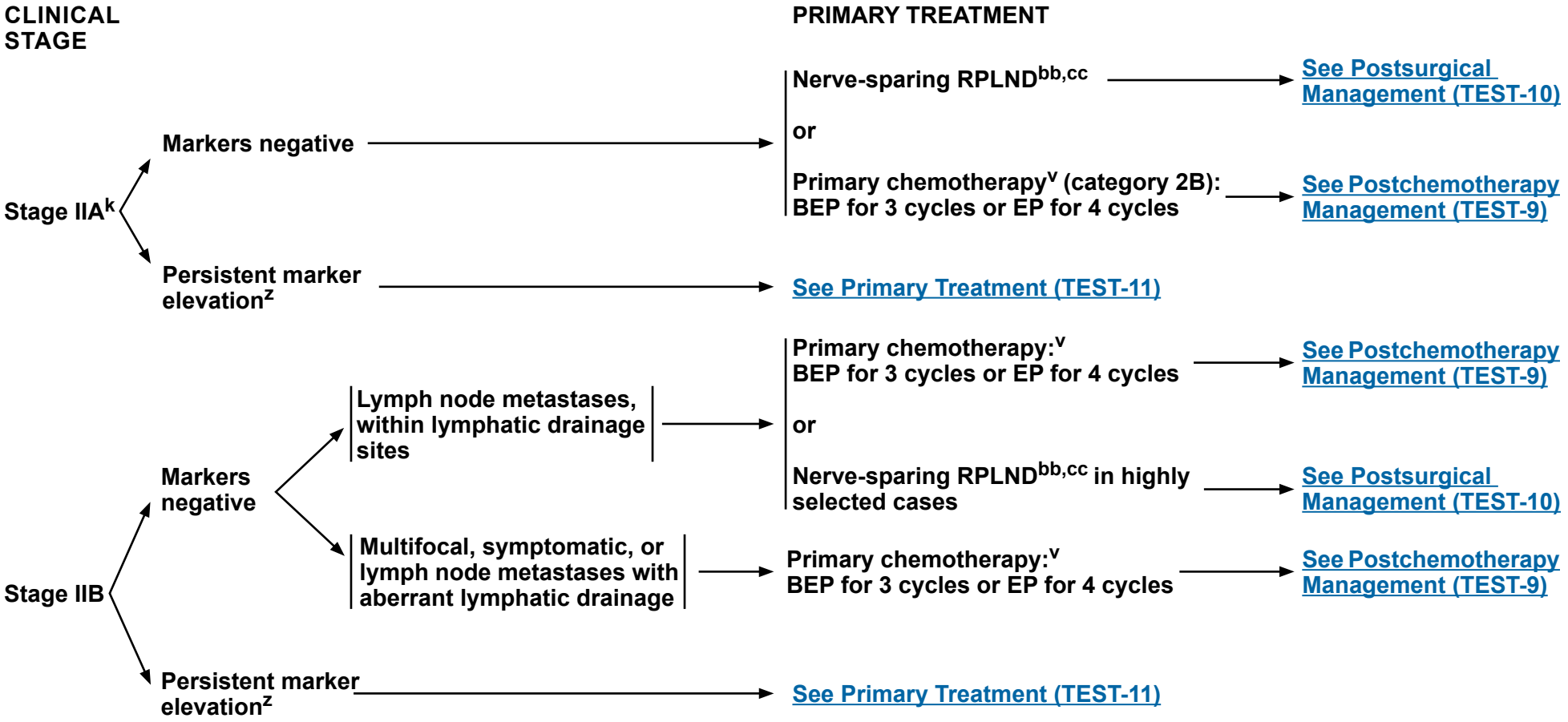

BEP = Bleomycin/etoposide/cisplatin
EP = Etoposide/cisplatin

[k]For select cases of clinical stage IIA disease with borderline retroperitoneal lymph nodes, waiting 4–6 weeks and repeating imaging (chest/abdomen/pelvic CT) to confirm staging before initiating treatment can be considered.
[v]See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[z]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.
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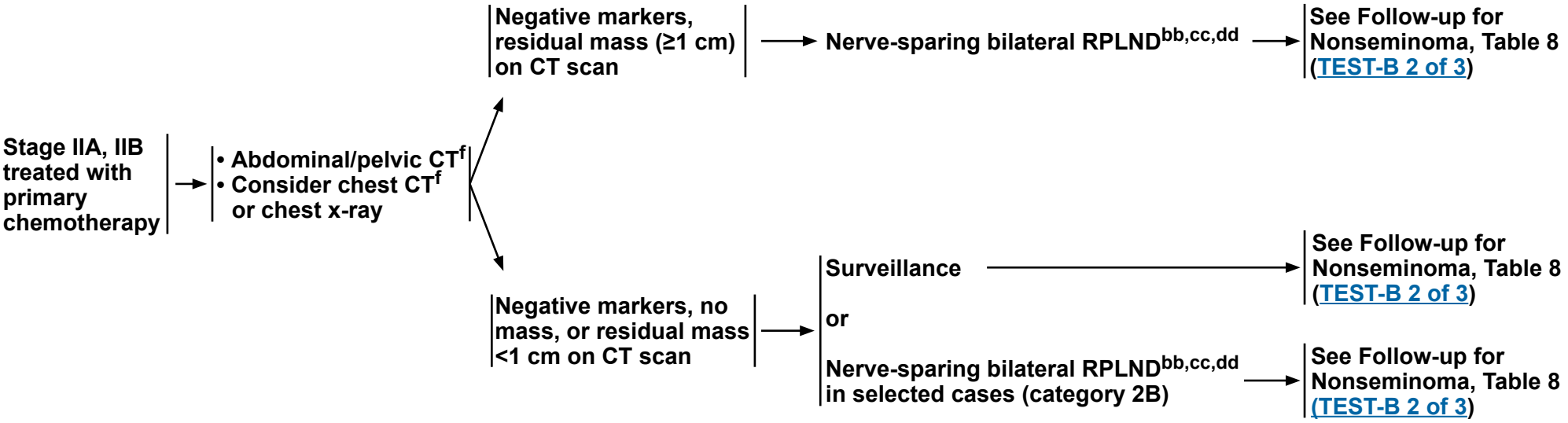
POSTCHEMOTHERAPY MANAGEMENT



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

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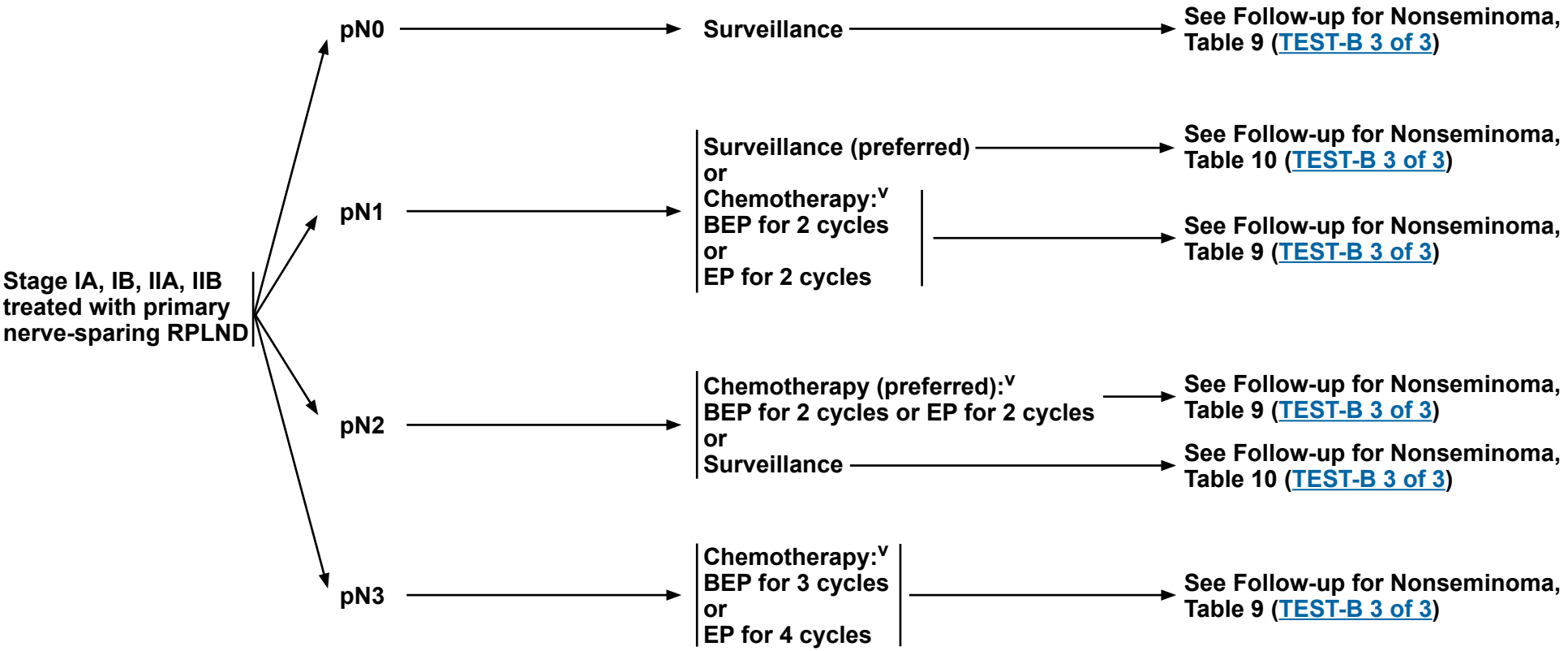
POSTSURGICAL MANAGEMENT



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

vSee Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).

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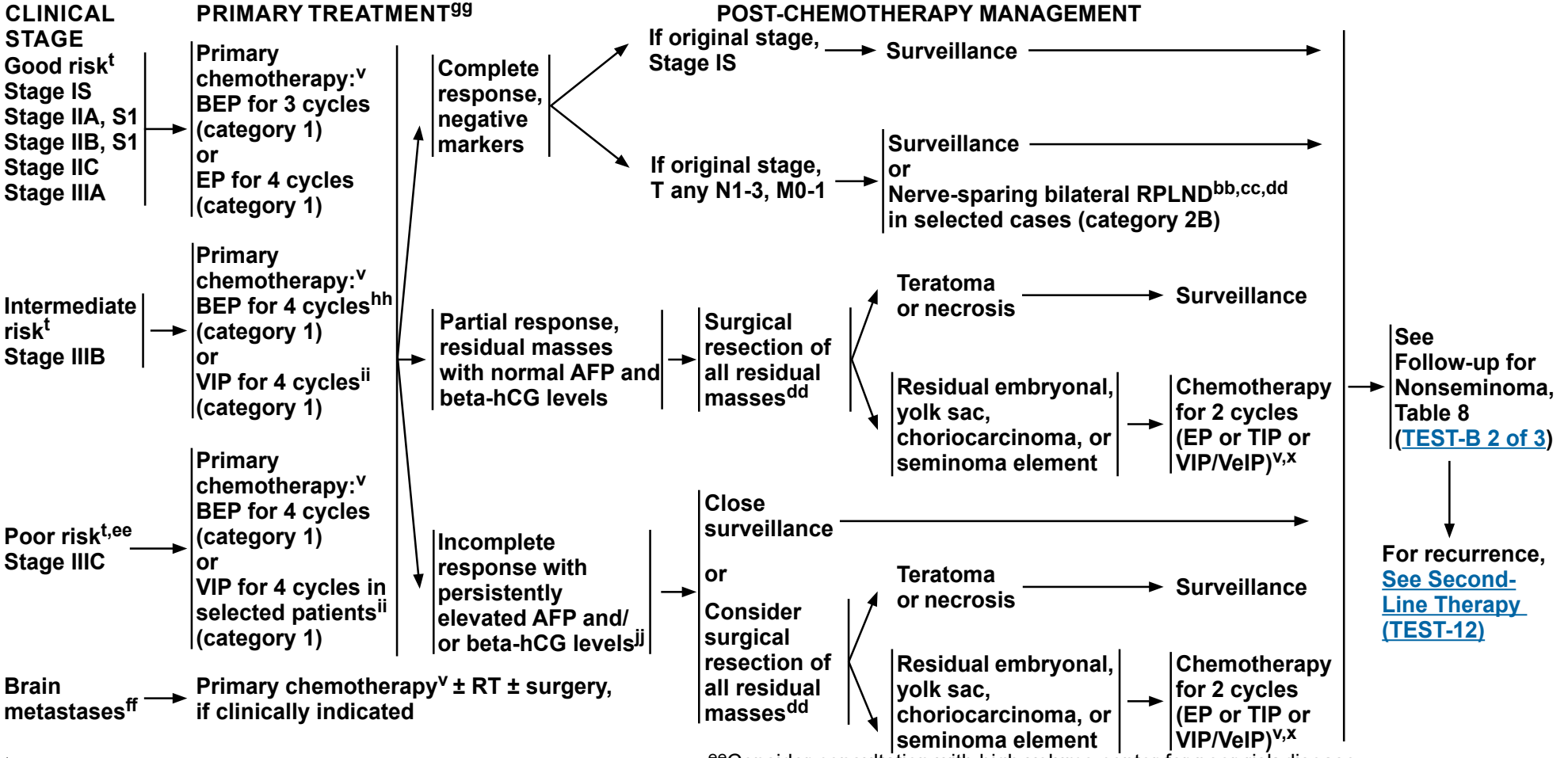

[t] See Risk Classification for Advanced Disease (TEST-D).
[v] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[x] See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).
[bb] Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan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

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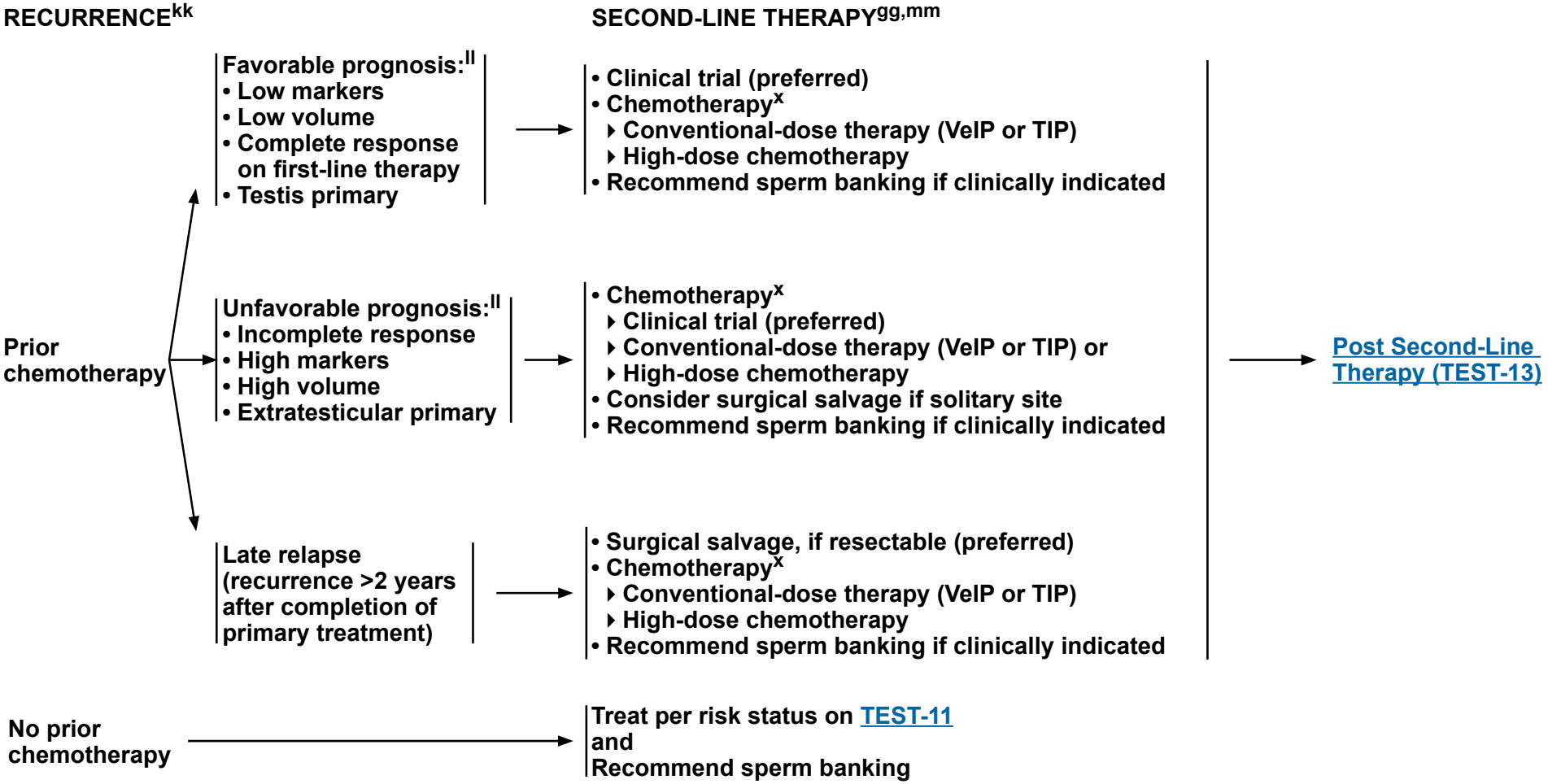

[x] See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).

[gg] To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.

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

[ll] Examples of systems used to estimate prognosis are: 1) Fossa SD, Cvancarova, 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.

[mm] Includes best supportive care.

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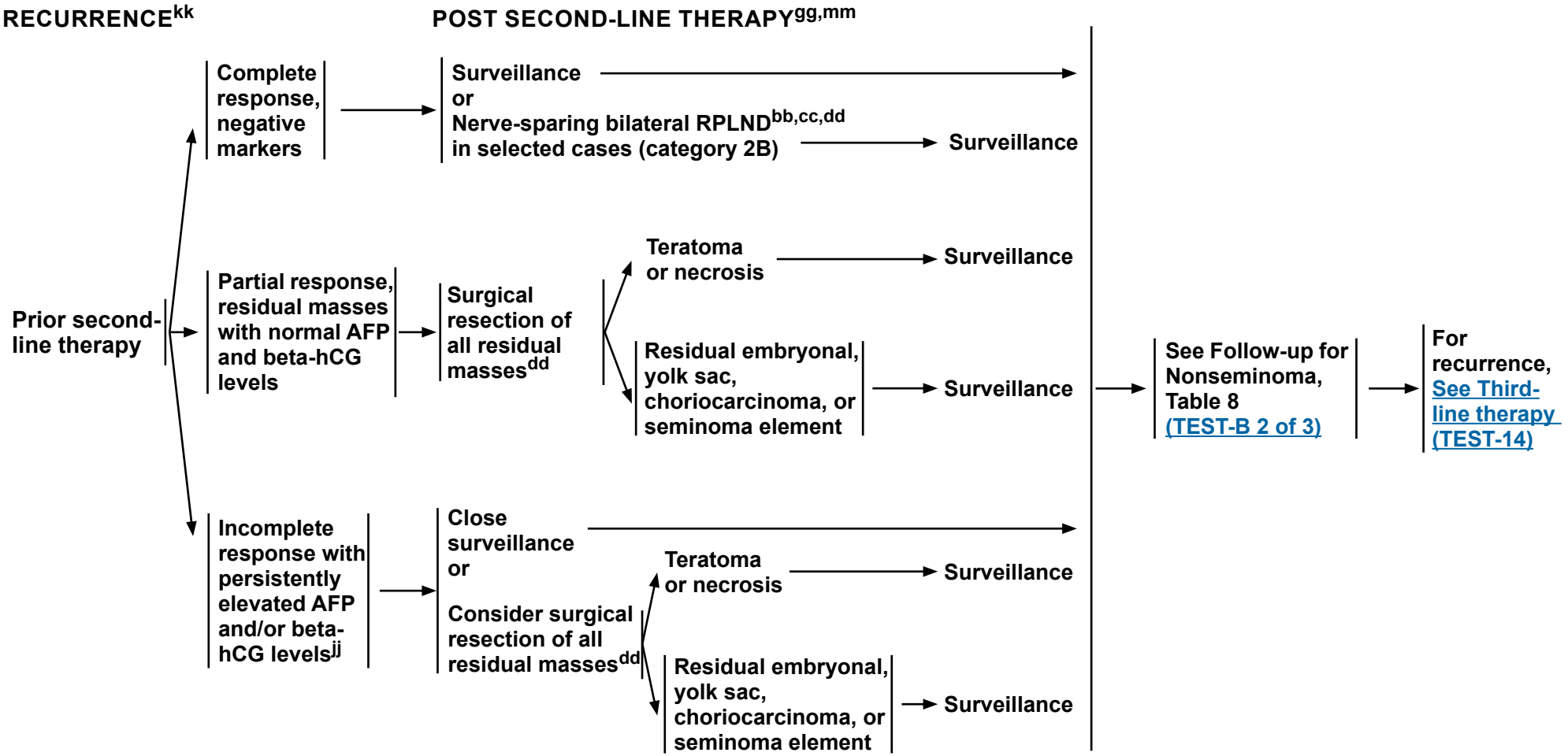


[bb]Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.

[cc]See Principles of Surgery for Germ Cell Tumors (TEST-H).

[dd]Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy.

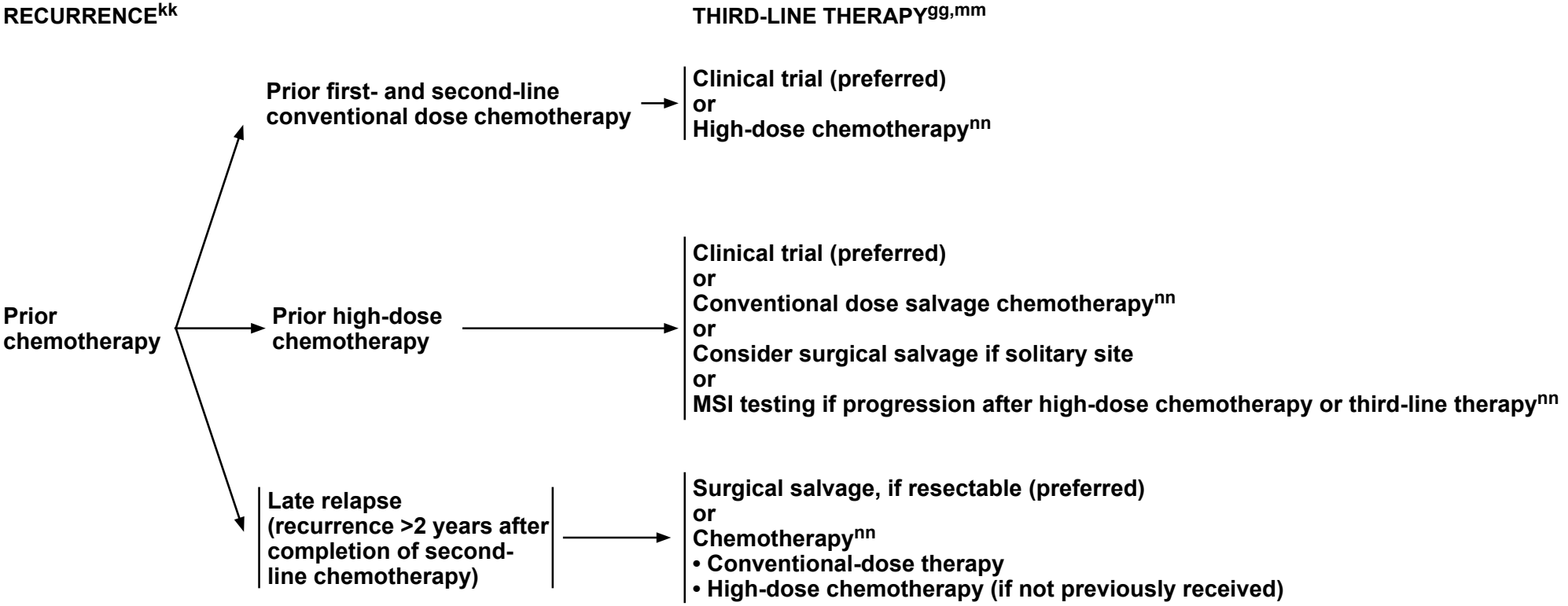
[gg]To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.

[jj]Salvage chemotherapy should be reserved for patients with rising AFP, beta-hCG, or other evidence of progressive disease.

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

[mm]Includes best supportive care.

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.



[gg]To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.
[kk]It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.
[mm]Includes best supportive care.
[nn]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[4]
H&P[1,2]	Every 3–6 mo	Every 6–12 mo	Every 6–12 mo	Annually	Annually
Abdominal ± Pelvic CT[3]	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[4]
H&P[1,2]	Every 6–12 mo	Every 6–12 mo	Annually	Annually	Annually
Abdominal ± Pelvic CT[3]	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

[1]Serum tumor markers are optional.
[2]Testicular ultrasound for any equivocal exam.
[3]With or without contrast.
[4]CT is not recommended beyond 5 years unless clinically indicated.

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 SEMINOMA

Table 3 Clinical Stage IIA and Non-Bulky IIB Seminoma: Surveillance After Radiotherapy or Post-Chemotherapy[5]

	Year (at month intervals)				
	1	2	3	4	5[4]
H&P[1,2]	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal ± Pelvic CT[6]	At 3 mo, then at 6–12 mo	Annually	Annually	As clinically indicated	
Chest x-ray[7]	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[4]
H&P and markers[2]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT[6,8-10]	Every 4 mo	Every 6 mo	Annually	Annually	As clinically indicated
Chest x-ray[7]	Every 2 mo[11]	Every 3 mo[11]	Annually	Annually	Annually

If Recurrence, see TEST-12.

[1]Serum tumor markers are optional.
[2]Testicular ultrasound for any equivocal exam.
[4]CT is not recommended beyond 5 years unless clinically indicated.
[5]Assuming no residual mass or residual mass <3 cm and normal tumor markers.
[6]With contrast.
[7]Chest x-ray may be used for routine follow-up, but chest CT with contrast is preferred in the presence of thoracic symptoms.
[8]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.
[9]Patients with residual masses may require more frequent imaging based on clinical judgment.
[10]PET/CT scan skull base to mid-thigh as clinically indicated.
[11]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 IA,[1] NSGCT: Active Surveillance

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

If Recurrence, see TEST-12.

Table 6 Clinical Stage IB,[1] NSGCT: Active Surveillance

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

If Recurrence, see TEST-12.

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

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

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

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

If Recurrence, see TEST-12.

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

	Year (at month intervals)				
	1	2	3	4	5
H&P and marker[2]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal ± Pelvic CT[3,5]	Every 6 mo	Every 6–12 mo	Annually	---	---
Chest x-ray[4,6]	Every 6 mo	Every 6 mo	Annually[7]	Annually[7]	---

If Recurrence, see TEST-12.

[2]Testicular ultrasound for any equivocal exam.
[3]With contrast.
[4]Chest x-ray may be used for routine follow-up but chest CT with contrast is preferred in the presence of thoracic symptoms.
[5]Patients who undergo RPLND and are found to have pN0 disease (no tumor or teratoma) need only 1 CT scan at postoperative month 4.
[6]Chest CT with contrast if supradiaphragmatic disease at baseline.
[7]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[2]	Every 6 mo	Every 6 mo	Annually	Annually	Annually
Abdominal/ Pelvic CT[3]	4 mo after RPLND	As clinically indicated			
Chest x-ray[4]	Every 6 mo	Annually	Annually	Annually	Annually

If Recurrence, see TEST-12.

Table 10 Pathologic Stage IIA/B NSGCT: Post-Primary RPLND and NOT Treated with Adjuvant Chemotherapy[8]

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[2]	Every 2 mo	Every 3 mo	Every 4 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT[3]	At 3–4 mo[9]	As clinically indicated			
Chest x-ray[4]	Every 2–4 mo	Every 3–6 mo	Annually	Annually	Annually

If Recurrence, see TEST-12.

[2]Testicular ultrasound for any equivocal exam.
[3]With contrast.
[4]Chest x-ray may be used for routine follow-up but chest CT with contrast is preferred in the presence of thoracic symptoms.
[8]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).
[9]This schedule assumes a complete resection has taken place.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

General Principles

- Modern radiotherapy involves smaller fields and lower doses than were used in the past. References are provided to support current recommended management.
- Risk-adapted management using tumor size >4 cm and rete testis invasion for stage I seminoma is discouraged. This is based on a validation study in 2010, which revealed that tumor size >4 cm and rete testis invasion were not predictors of relapse.[1,2]
- Linear accelerators with >6 MV photons should be used when possible.
- The mean dose (Dmean) and dose delivered to 50% of the volume (D50%) of the kidneys, liver, and bowel are lower with CT-based anteroposterior-posteroanterior (AP-PA) three-dimensional conformal radiation therapy (3D-CRT) than intensity-modulated radiation therapy (IMRT).[3] As a result, the risk of second cancers arising in the kidneys, liver, or bowel may be lower with 3D-CRT than IMRT, and IMRT is not recommended.[4]
- Timing of Radiotherapy:
  - Radiotherapy should start once the orchiectomy wound has fully healed.
  - Patients should be treated 5 days per week.
  - Patients who miss a fraction should be treated 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.[5,6] If sperm banking is desired, it should be performed prior to imaging and the delivery of adjuvant therapy.

Treatment Planning Principles

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

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

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Stage I

- Dose: For stages IA, IB, a total dose of 20.0 Gy (midplane) in 10 fractions (preferred) or 25.5 Gy in 1.5 Gy fractions.
  - For 20.0 Gy dose, daily 2.0 Gy is recommended for the minority of patients who prefer adjuvant treatment, realizing that there is a high likelihood of salvage should a relapse occur during surveillance.[9]
- Para-aortic (PA)-Strip Fields[10] - Field Arrangement:
  - In patients with no history of pelvic or scrotal surgery, para-aortic strip irradiation may be delivered with opposed AP-PA fields. The weights of the fields may be equal.
    - ◊ Recent nodal mapping studies suggest that fields should target the retroperitoneal lymph nodes but not necessarily the ipsilateral renal hilar nodes (see Lateral borders).[11,12]
    - ◊ Superior and inferior borders: Borders may be determined by bony anatomy.
      - – The superior border should be placed at the bottom of vertebral body T-11.[13]
      - – The inferior border should be placed at the inferior border of vertebral body L-5.[10,14]
    - ◊ Lateral borders:
      - – Conventionally, PA-strip fields are approximately 10 cm wide, encompassing the tips of the transverse processes of the PA vertebrae.
      - – The location of the kidneys within the PA-strip fields varies from patient to patient.
        - ▪ For patients whose kidneys are relatively medial, small renal blocks may be added at the level of T-12. The right and left kidney D50% should be ≤8 Gy (ie, no more than 50% of each kidney can receive 8 Gy or higher).[3] If only one kidney is present, the kidney D15% should be ≤20 Gy (ie, no more than 15% of the volume of the kidney can receive 20 Gy or higher).[3]
        - ▪ An alternative 3D-CRT planning technique is to base the lateral borders on vascular structures on a treatment planning CT scan without contrast. The aorta and inferior vena cava (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.[11,15] The planning target volume is then established by uniformly expanding the clinical target volume by 0.5 cm in all directions to account for treatment setup errors.[16] A uniform 0.7-cm margin should be provided on the planning target volume to the block edge to take beam penumbra into account (Figure 1, see TEST-C 4 of 5).[3]

Special Considerations:

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

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

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Stage IIA-IIB

- Patients should not receive primary RT if they have a horseshoe (pelvic) kidney, inflammatory bowel disease, or a history of RT.
- For clinical stage IIA-B patients, treatment is delivered in two consecutive AP-PA phases (modified dog-leg fields and cone down). There is no break between the 2 phases.
- Modified Dog-Leg Fields:
  - Dose: The initial phase consists of treatment of modified dog-leg fields to 20.0 Gy (midplane) in 10 fractions; daily 2.0 Gy.[17]
  - Target: The fields should include the retroperitoneal and proximal ipsilateral iliac lymph nodes.
    - ◊ Modified dog-leg fields as described by Classen et al are preferred.[18]
      - – Care should be taken to ensure coverage of the ipsilateral common, external, and proximal internal iliac lymph nodes down to the top of the acetabulum.
      - – The fields can be set up using bony landmarks or by contouring the vascular structures, as for stage I.
        - ▪ The superior border should be placed at the bottom of vertebral body T-11.[19]
        - ▪ The inferior border should be placed at the top of the acetabulum.[18]
        - ▪ The medial border for the lower aspect of the modified dog-leg fields extends from the tip of the contralateral transverse process of the fifth lumbar vertebra toward the medial border of the ipsilateral obturator foramen.
        - ▪ The lateral border for the lower aspect of the modified dog-leg fields is defined by a line from the tip of the ipsilateral transverse process of the fifth lumbar vertebra to the superolateral border of the ipsilateral acetabulum.
        - ▪ Preferably, one should contour the aorta and IVC from the bottom of the T-11 vertebra inferiorly and ipsilateral iliac arteries and veins down to the top of the acetabulum. One should provide a 1.2- to 1.9-cm margin on these vascular structures for the clinical target volume.[11,15] The planning target volume is then established by uniformly expanding the clinical target volume by 0.5 cm in all directions to account for treatment setup errors.[16] A uniform 0.7-cm margin should be provided on the planning target volume to the block edge to take beam penumbra into account (Figure 2, see TEST-C 4 of 5).[3]
        - ▪ It is not necessary to include the ipsilateral inguinal nodes or the inguinal scar in the AP-PA fields unless the patient has a history of ipsilateral pelvic surgery (eg, inguinal herniorrhaphy or orchiopexy).
- Cone Down:
  - Dose: The second phase (cone down) of the radiotherapy consists of daily 2 Gy fractions to a cumulative total dose of approximately 30 Gy for stage IIA and 36 Gy for stage IIB.[18]
  - Target: The nodal mass (gross tumor volume) must be contoured. A uniform, 2-cm margin from the gross tumor volume to block edge should be provided for the AP-PA cone down fields (Figure 3, see TEST-C 4 of 5).

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

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Figure 1:
Template for Stage I RT Field

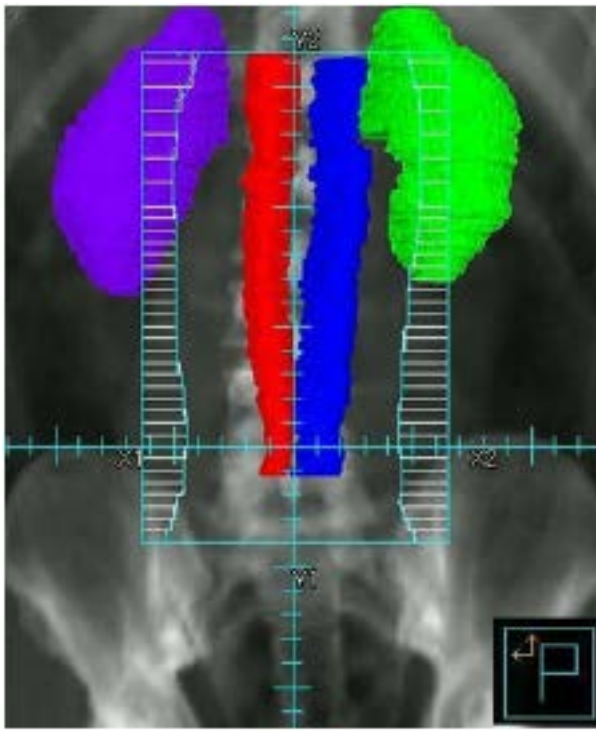


Figure 2:
Template for Stage II RT Large field

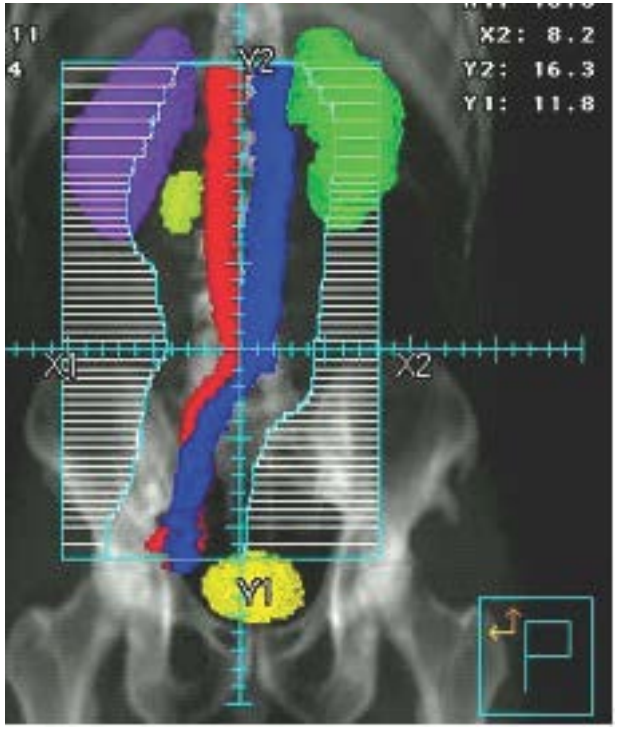
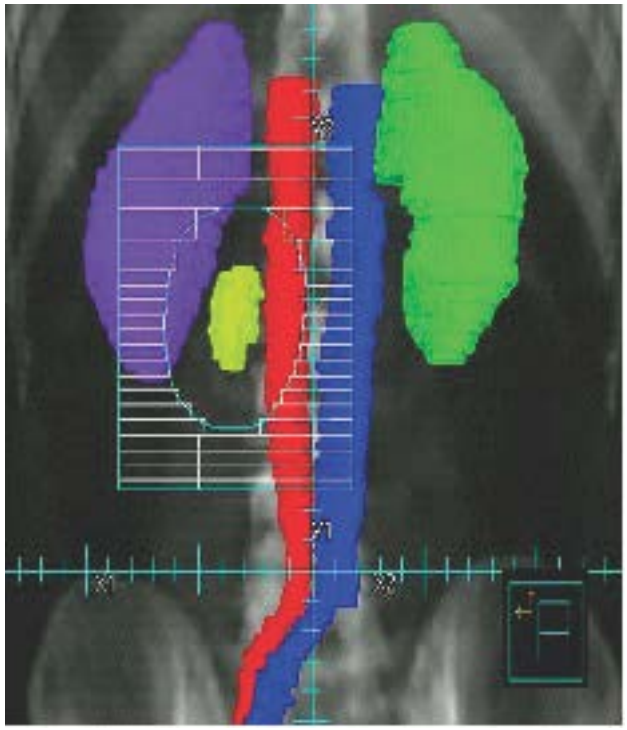


Figure 3:
Template for Stage II Cone-down Field



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

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA
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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.

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

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

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

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

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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.

PRIMARY CHEMOTHERAPY REGIMENS FOR GERM CELL TUMORS

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/m² IV on Days 1–5
Cisplatin 20 mg/m² IV on Days 1–5
Repeat every 21 days[1]

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

VIP[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/m² IV on Days 1–5
Mesna 240 mg/m² 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/m² on Days 1–5
Cisplatin 20 mg/m² IV on Days 1–5
Repeat every 21 days[4]

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[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.

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.

SECOND-LINE CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

Conventional-Dose Chemotherapy Regimens

VeIP[1]

Vinblastine 0.11 mg/kg IV Push on Days 1–2
Mesna 240 mg/m² 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/m² IV on Days 1–5
Cisplatin 20 mg/m² IV on Days 1–5
Repeat every 21 days[2]

TIP[1]

Paclitaxel 250 mg/m² IV on Day 1
Ifosfamide 1500 mg/m² IV on Days 2–5
Mesna 300 mg/m² 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/m² IV on Days 2–5
Repeat every 21 days[3]

High-Dose Chemotherapy Regimens

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

Paclitaxel 200 mg/m² IV over 24 hours on Day 1
Ifosfamide 2000 mg/m² over 4 hours with mesna protection on Days 2–4
Repeat every 14 days for 2 cycles followed by
Carboplatin AUC 7–8 IV over 60 minutes on Days 1–3
Etoposide 400 mg/m² 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

Palliative Chemotherapy Regimens[1,2]

- **Gemcitabine/oxaliplatin**
- **Gemcitabine/paclitaxel**
- **Gemcitabine/paclitaxel/oxaliplatin**
- **Etoposide (oral)**
- **Pembrolizumab (for MSI-H/dMMR tumors)**

[1]See references below for dosing.
[2]For high-dose regimens, See Second-Line Therapies (TEST-F)

Etoposide (oral)
- Miller JC, Einhorn LH. Phase II study of daily oral etoposide in refractory germ cell tumors. Semin Oncol 1990;17:36-39.

Gemcitabine/oxaliplatin
- 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.
- 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.
- De Giorgi U, Rosti G, Aieta M, et al. Phase II study of oxaliplatin and gemcitabine salvage chemotherapy in patients with cisplatin-refractory nonseminomatous germ cell tumor. Eur Urol 2006;50:893-894.

Gemcitabine/paclitaxel
- 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.
- Mulherin BP, Brames MJ, Einhorn LH. Long-term survival with paclitaxel and gemcitabine for germ cell tumors after progression following high-dose chemotherapy with tandem transplant. Am J Clin Oncol 2015;38:373-376.

Gemcitabine/oxaliplatin/paclitaxel
- 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.

Pembrolizumab
- Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-413.
- 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).**

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.

Table 1 **Both the AJCC Staging for Testis Cancer 7th and 8th editions are included for reference and documentation.**

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

Primary Tumor (T)*

The extent of primary tumor is usually classified after radical orchiectomy, and for this reason, a pathologic stage is assigned.

pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g. histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/ lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/ lymphatic invasion

*Note: Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Pathologic (pN)

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

Distant Metastasis (M)

M0	Regional lymph nodes cannot be assessed
M1	No distant metastasis
M1a	Distant metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lung

Continued

Table 1 **(continued)** **Both the AJCC Staging for Testis Cancer 7th and 8th editions are included for reference and documentation.**

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

Anatomic Stage/Prognostic Groups

Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

Serum Tumor Markers (S)

SX Marker studies not available or not performed

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

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

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Table 2
American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Testis Cancer (8th ed., 2016)

Definition of Primary Tumor (T)
Clinical T (cT)

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 confi rmed 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 (pT)

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.

Continued

Table 2 **(continued)**
American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Testis Cancer (8th ed., 2016)

Definition of Regional Lymph Node (N)

Clinical N (cN)

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 (pN)

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

Definition of Distant Metastasis (M)

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

Definition of Serum Markers (S)

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

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

Continued

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2016) published by Springer Science+Business Media. (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Table 2 **(continued)**
American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Testis Cancer (8th ed., 2016)

Prognostic Stage Groups

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

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2016) published by Springer Science+Business Media. (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

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.

Table of Contents

Overview

An estimated 9310 new cases of testicular cancer will be diagnosed in the United States in 2018.[1] Germ cell tumors (GCTs) comprise 95% of malignant tumors arising in the testes. These tumors may also occasionally occur in extragonadal primary sites (usually the retroperitoneum or anterior mediastinum), but are managed similarly to testicular GCTs with regard to systemic therapy and management of residual masses.[2] Orchiectomy is reserved for testicular cancers. In addition, it is important to note that prepubertal testis cancers and other pediatric GCTs are managed differently from adult GCTs. Testicular GCTs are relatively uncommon tumors and account for 1% of all male tumors.[1] However, testicular GCTs constitute the most common solid tumor in men between the ages of 20 and 34 years,[3] and the incidence of testicular GCTs has been increasing for over 60 years.[4-7] Less than 5% of testicular tumors develop in the stroma (supportive and hormone-producing tissues) and are therefore not covered in these guidelines.

Several risk factors for testis cancer development have been identified, including prior history of testis cancer, positive family history, cryptorchidism, and Klinefelter's syndrome.[2,8,9]

GCTs are classified as seminoma or nonseminoma. Seminomas are more common. Nonseminomatous tumors tend to grow faster, and often include multiple cell types. The four main types of nonseminomas are embryonal carcinoma, choriocarcinoma, yolk sac tumor, and teratoma. Teratomas are sometimes classified as either mature or immature, but this distinction is of no clear significance in testicular GCTs 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 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.[10] It should be checked on the first day of the first cycle of first-line chemotherapy in these patients. It can also be used to monitor for relapse, but is nonspecific and there is 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 early signs of relapse.

Beta-hCG is the most commonly elevated tumor marker in testicular cancer. Although elevated serum concentrations of beta-hCG may be present with both seminomatous and nonseminomatous tumors, patients with beta-hCG levels above 1000 IU/L are generally presumed to have a nonseminoma. Patients with a post-orchiectomy beta-hCG >5000 IU/L are at increased risk of having brain metastases and a brain MRI should be performed in these patients. It is also 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.[11-13] Similarly, heterophile antibodies have been reported to result in substantially elevated false-positive beta-hCG results (above 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.[14,15]

Elevated serum AFP is associated with nonseminomatous GCTs, particularly embryonal or yolk sac carcinomas, and may be seen at any disease stage. When patients with a histologically "pure" testicular seminoma have an elevated level of AFP, it is generally assumed that an undetected nonseminoma is present.[10,16,17] In addition, a small number of people have a chronically elevated serum AFP 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.[10]

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 a normal serum concentration of AFP.

The 5-year survival rate for testicular cancer is 95%.[3] Standard care has been established for management of all disease stages and should be closely followed to ensure the potential for cure and to avoid unnecessary side effects, complications, and late effects.

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.[18]

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. In addition, a complete blood count (CBC), and levels of creatinine, electrolytes, and liver enzymes should be obtained. Serum tumor markers, including LDH, AFP, and beta-hCG, need to be assessed as they are used for diagnosis, prognosis, and staging.[19] 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 ultrasound serves to confirm the presence of a testicular mass, determine whether a mass is intra- or extratesticular, and to explore the contralateral testis.[20] Testicular cancers 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.[21] 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 should be considered if an ambiguous suspicious mass is identified in the contralateral testis on ultrasound. An open inguinal biopsy of the contralateral testis may also be considered when that testis is undescended or shows marked atrophy.[22] However, biopsies are not recommended for microcalcifications.

The extent of the primary tumor is classified after orchiectomy, and therefore pathologic (p) staging is assigned to the primary tumor (T). Concurrent insertion of testicular prosthesis may be considered during radical inguinal orchiectomy if desired by the patient.[23-25]

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), and chemotherapy.[26-30] 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

The AJCC TNM staging system is based on post-orchiectomy serum levels of beta-hCG, LDH, and AFP. 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 ordered to stage GCTs. In select patients, brain MRI should also be performed; these patients include those with neurologic symptoms concerning for brain metastasis, post-orchiectomy serum beta-hCG >5000 IU/L, or extensive lung metastases. In patients who had elevated tumor markers prior to orchiectomy, it is important to obtain the half-life kinetics of serum tumor markers after orchiectomy if the markers are declining because a slower-than-expected decline often indicates the presence of metastatic disease.

The NCCN Panel recommends using the AJCC Cancer Staging Manual, 7th Edition for testis cancer to subclassify stage I disease for the purpose of clinical decision-making. The prognostic variables used in the 7th edition have been clinically validated to predict recurrence in stage I patients. In contrast, the prognostic variables introduced in the 8th edition predict a higher disease stage at the time of diagnosis and have not been validated for clinical decision-making. It is the opinion of the panel that the treatment of stage I testicular cancer should be based upon the risk of recurrence. Therefore, the 7th edition of the AJCC staging system should be used to guide treatment for stage I testicular cancer and the 8th edition should be used for documentation purposes only.

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 non-seminoma GCTs into good-, intermediate-, or poor-risk groups.[31]

Definitions of stage and risk classification in these guidelines are done according to the AJCC and 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.[32] 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 abnormal results.[33]

The NCCN Panel recommends performing a brain MRI with and without contrast if beta-hCG levels exceed 5000 IU/L or there is extensive metastatic disease in the lungs. Sperm banking should also be recommended to patients who will be undergoing chemotherapy, RT, or retroperitoneal lymph node dissection (RPLND), if clinically indicated.

Measurement of beta-hCG, LDH, or AFP levels should be repeated because TNM staging is based on post-orchiectomy values. Serum concentrations of beta-hCG and LDH may be elevated in patients with seminoma, while an elevated AFP level 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.

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 for pT1-pT3 tumors (preferred), chemotherapy with 1 or 2 cycles of single-agent carboplatin, or RT at 20 Gy (preferred) or 25.5 Gy. Disease-specific survival for stage I disease is 99% irrespective of the management strategy used.[34]

Surveillance: A number of prospective non-randomized studies on surveillance for stage I seminoma have been conducted.[35-38] The 5-year recurrence rate seen in these studies ranged from 15% to 20%, with most disease recurrence detected in the infra-diaphragmatic lymph nodes.[36-38] The best established risk factor for relapse is increased size of the primary tumor. As the tumor size increases the risk of relapse also increases, but any cutoff point is arbitrary.[37,39-42,43-45] Some studies have reported that rete testis invasion and lymphovascular invasion are independent risk factors for relapse while others have reported that they are not. Therefore, the NCCN Panel discourages risk-adapted management in stage I pure seminoma and instead recommends surveillance as the preferred option for all patients who find it acceptable and are able to adhere to the surveillance testing schedule.

A retrospective study analyzed 2483 patients with clinical stage I GCTs managed with active surveillance. Analyses showed that 13% of patients with stage I seminoma relapsed. Median time to relapse was 14 months (range, 2–84 months) and 92% of recurrences were observed within 3 years. The overall 5-year disease-specific survival rate was 99%.[46,47] Based on this and other similar studies, surveillance is the preferred option for patients with pT1-pT3 tumors in the NCCN Guidelines.

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 Therapy: 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 a dose based on the formula 7 x [glomerular filtration rate (GFR, mL/min) + 25 mg].[48] 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.[48] The mature results of this trial confirmed the non-inferiority of single-dose carboplatin versus RT in terms of relapse-free survival and established a significant reduction in the risk of developing a second GCT with the use of carboplatin.[49] 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). There were 2 cases of GCTs in the contralateral testis in patients treated with carboplatin versus 15 in patients treated with RT. 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 recurrence as adjuvant RT in men with stage I pure seminoma after orchiectomy.[49]

Two cycles of adjuvant carboplatin have also been reported to reduce the rate of recurrence of stage I pure seminomas. The 2nd and 3rd Spanish Germ Cell Cancer Cooperative Group studies reported that 2 cycles of adjuvant carboplatin is effective in reducing the rate of

recurrence in stage I seminoma patients, with a 5-year recurrence-free survival rate of 93.4% and a 5-year overall survival (OS) rate of 100%.[50,51] The efficacy of 2 cycles of adjuvant carboplatin was confirmed in a study by the Hellenic Cooperative Oncology Group, which reported a 5-year recurrence-free survival rate of 96.8% among 138 stage I seminoma patients treated with this regimen.[52] A recent prospective study reported the treatment outcomes of 725 stage I seminoma patients managed by surveillance, 1 cycle of carboplatin, or 2 cycles of carboplatin.[53] Although disease-specific survival was 100% for all 3 strategies, crude relapse rates were significantly higher with the 1-cycle regimen (5%) compared to the 2-cycle regimen (1.5%) after a median follow-up time of 30 months. The crude relapse rate for surveillance was 8.2%. Furthermore, 1 cycle of carboplatin demonstrated low efficacy to control large tumors. Regardless of the regimen used, repeating chest/abdominal/pelvic CT scan is recommended within 4 weeks prior to the initiation of chemotherapy to confirm staging.

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.[54,55] 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.[56] Another study found that moderate-dose infradiaphragmatic RT for stage I seminoma was associated with increased risks for secondary cancers in organs within the radiation field.[57] Additionally, one study reported that RT might increase the risk of a subsequent cardiac event,[58] but other analyses have not confirmed this risk.[56] Platinum-based chemotherapy has also been associated with an increased risk for secondary cancers and heart disease.[58,59] However, whether such risks ensue from single-agent carboplatin as dosed for seminoma remains unknown.[60]

The NCCN Panel prefers active surveillance to the routine use of adjuvant therapy for stage I seminoma patients, because the risk of recurrence 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 (midplane) administered in 10 daily 2.0 Gy fractions[61] delivered to an infradiaphragmatic area, including para-aortic lymph nodes; in special circumstances, this may include the ipsilateral ilioinguinal nodes.[62-65] Alternatively, a total dose of 25.5 Gy can be given in 1.5 or 1.7 Gy fractions.[66] Patients at higher risk for morbidity from RT, such as those with a history of inflammatory bowel disease or pelvic surgery, are generally not given RT. 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 chemotherapy or RT.

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

Follow-up strategies should vary according to the treatment modality received by the patient (surveillance vs. adjuvant therapy). An analysis of over 5000 stage I seminoma patients from various trials reported that the 5-year recurrence rate was higher with surveillance (18.6 %) compared to either 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).[67] An analysis of data from the National Cancer Database examined the survival outcomes of 33,094 stage I seminoma patients who received either surveillance,

chemotherapy, or RT as primary treatment after orchiectomy. [68] Although OS was high for all 3 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 recurrence is highest in the first 2 years following treatment.[67] 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 follow-up of patients with stage I seminoma on active surveillance (see Table 1 on TEST-A 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 post-orchiectomy 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.[51,69,70] The measurement of serum tumor markers is regarded as optional by the panel 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, Vesprini et al reported that routine measurement of serum tumor markers did not aid in the early diagnosis of relapse.[71] 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 CT scan with or without a pelvic CT scan 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. The abdominal and pelvic CT scans are administered with or without contrast. CT is not recommended beyond 5 years, unless clinically indicated. No initial isolated relapses in the lung have been reported in studies of patients with stage I seminoma managed by active surveillance; therefore, routine chest imaging, including chest x-ray and chest CT with contrast, is only indicated for patients with thoracic symptoms.[72]

A clinical trial in the United Kingdom entitled TRISST (MRC TE24/TRial of Imaging and Schedule in Seminoma Testis) is currently investigating whether a reduced CT schedule or MRI could be used as a safe and effective alternative to standard CT-based surveillance in the management of stage I seminoma.[73]

Follow-up After Adjuvant Treatment: Follow-up of patients treated with adjuvant therapy (chemotherapy or RT) is outlined in Table 2 on TEST-A 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. Patients treated with para-aortic RT have a slightly higher rate of pelvic relapse compared with those treated with “dog-leg’’ RT.[63,67,74,75]

In a meta-analysis of 2466 patients, Mead et al reported that recurrence rarely occurred >3 years after treatment with RT or carboplatin (0.2% of patients).[34] Since the rate of recurrence beyond 3 years is very low for patients treated with chemotherapy and RT, the NCCN Panel recommends performing an abdominal CT scan with or without a pelvic CT scan annually for 3 years in patients treated with RT or carboplatin. The abdominal and pelvic CT scans are also administered with or without contrast in this setting. Chest x-rays should be obtained only when clinically indicated and chest CT scans with contrast should be

considered only in symptomatic patients. CT is not recommended beyond 5 years, unless clinically indicated. Recurrences are treated according to the stage at relapse.[34]

Pure Seminoma Stage IS

Primary Treatment for Pure Seminoma Stage IS

Per the AJCC definition, stage IS pure seminoma requires persistent elevation of serum tumor markers (LDH, AFP, and beta-hCG) following orchiectomy. Stage IS pure seminoma is very uncommon. 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. Since persistent elevation of markers increases the risk of disease outside the retroperitoneum, systemic therapy is encouraged. Chemotherapy given in this circumstance is similar to that given for nonseminoma (see *Nonseminoma* below).

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. A lymph node mass measuring 2 to 5 cm in greatest diameter is classified as stage IIB disease. 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 treatment of stage IIA and stage IIB seminomas include RT and chemotherapy with 3 cycles of bleomycin, etoposide, and cisplatin (BEP) or 4 cycles of etoposide and cisplatin (EP).[76-79] Different studies have reported different outcomes with regard to which treatment modality is more effective. 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.[80] 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 evaluated data from the same database during the same time period as the study by Glaser and reached similar conclusions. This retrospective, non-randomized study evaluated 1885 stage IIA/B seminoma patients selected by their treating physician to receive either adjuvant chemotherapy or adjuvant RT.[81] 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. It is possible that patients with more extensive disease were selected for chemotherapy. These papers 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.[45] This has led some physicians to prefer chemotherapy for stage II patients; however, these results must be taken with caution since this study was not a randomized trial and did not specifically compare the two treatment modalities for stage IIA disease.

In contrast, chemotherapy is the preferred treatment for stage IIB seminoma,[79,82] with RT being reserved for select patients with non-bulky (≤3 cm) disease.[76]

For RT for stage IIA/B disease, the standard radiation field is extended from the para-aortic region to include an ipsilateral iliac field in two consecutive anteroposterior-posteroanterior phases with no break in between. The initial phase consists of radiation to modified dog-leg fields at a dose of 20 Gy (midplane) in 10 daily 2.0 Gy fractions[62] or 25.5 Gy in 15 daily 1.7 Gy fractions.[66] The panel prefers modified dog-leg fields as described by Classen et al.[76] The second phase (cone down) consists of daily 2.0 Gy fractions to a cumulative total dose of 30 Gy for stage IIA patients and 36 Gy for stage IIB patients. Prophylactic mediastinal RT is not indicated for the management of stage II disease.[83] 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 of 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.

Chest x-ray is recommended every 6 months for the first 2 years. An abdominal CT scan with or without a pelvic CT scan is recommended at 3 months, 6 months, and 12 months in year 1; annually for years 2 and 3; and then as clinically indicated thereafter. The abdominal and pelvic CT scans are administered with contrast in this setting. CT is not recommended beyond 5 years, unless clinically indicated.

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 disease except for stage IIIC disease with non-pulmonary visceral metastases (eg, bone, liver, brain), which 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,[84-89] while more intensive chemotherapy with 4 cycles of BEP or 4 cycles of etoposide, mesna, ifosfamide, and cisplatin (VIP) is recommended for patients with intermediate-risk disease.[90-95] VIP should be reserved for patients with a contraindication to bleomycin. 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 chemotherapy, patients with stages 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 (AFP and beta-hCG). 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 discussed in the section below on *Follow-up for Pure Seminoma Bulky Stage II and Stage III After Chemotherapy.*

Surveillance is also recommended for patients with a residual tumor >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 assess whether there is a residual viable tumor in these patients.[96-101] To reduce the incidence of false-positive results, the PET/CT scan should be performed at least 6 weeks after the completion of chemotherapy.[102] If the PET scan is negative, surveillance is recommended.[103] If the PET scan is positive, resection and/or biopsy of the residual mass should be considered. If the resection is complete and the biopsy results show viable seminoma, consider 2 cycles of second-line chemotherapy with the following regimens: EP, TIP (paclitaxel, ifosfamide, cisplatin),[104] VIP, or VeIP (vinblastine, mesna, ifosfamide, cisplatin).[105,106] If the resection is incomplete, a full course of second-line chemotherapy (4 cycles of TIP or 4 cycles of VeIP) is recommended.[104-107] If a biopsy is performed and is positive, consider surgery if complete resection is possible. If complete resection is not possible, a full course of second-line chemotherapy should be given. Surveillance is recommended if the results of the biopsy 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 in the algorithm and includes a history and physical examination as well as measurement of post-orchiectomy serum tumor markers 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 and pelvic CT scans with contrast are recommended every 4 months during year 1, every 6 months for year 2, annually for years 3 and 4, and then as clinically indicated thereafter.[108] 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 during year 1, every 3 months during year 2, and annually during 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 even with a negative post-chemotherapy PET scan,[109,110] the NCCN Panel recommends that patients with a residual mass measuring >3 cm and negative PET results after chemotherapy should undergo an abdominal and pelvic CT scan 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 with elevated serum AFP levels. The post-diagnostic workup for nonseminoma includes CT scans with contrast of the chest, abdomen, and pelvis. Elevated levels of serum beta-hCG, LDH, or AFP should be followed up with repeated tests. 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.

Repeated measurement of serum tumor markers is important because TNM staging is based on post-orchiectomy values.

MRI of the brain, with and without contrast, should be performed if clinically indicated (ie, beta-hCG levels >5,000 IU/L, extensive lung metastasis, or neurologic signs or symptoms). Routine PET scanning is not recommended for nonseminoma patients.[111,112]

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.[26-30] 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, chemotherapy, and RPLND. Although the timing of the RPLND may vary, most patients with nonseminoma will undergo an RPLND for either diagnostic or therapeutic purposes at some point during treatment. The major morbidity associated with bilateral dissection is retrograde ejaculation, resulting in infertility. Nerve-sparing dissection techniques preserve antegrade ejaculation in 90% of cases.[113]

Nonseminoma Stage IA

Primary Treatment for Nonseminoma Stage IA

According to the NCCN Panel, three treatment options exist for patients with stage IA nonseminoma after orchiectomy: 1) surveillance (preferred);[114-119] 2) nerve-sparing RPLND; and 3) primary chemotherapy (1 cycle of BEP).[120,121]

The survival rate for 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 experience 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.[122,123]

A phase III trial by Albers et al randomized stage I nonseminoma patients after orchiectomy to undergo unilateral RPLND (n = 191) or 1 adjuvant course of BEP (n = 191).[120] After a median follow-up of 4.7 years, 2 relapses were reported in the BEP arm compared to 13 relapses in the RPLND arm (P = .0011). This study indicates that 1 course of BEP is active in nonseminoma and could be an option for select patients.[120] In another prospective trial (SWENOTECA), stage I nonseminoma patients with or without lymphovascular invasion received 1 course of adjuvant BEP.[121] The relapse rate at 5 years was 3.2% for patients with lymphovascular invasion and 1.6% for patients without lymphovascular invasion. Five-year OS was 100% in both groups.[124] 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 lymphovascular invasion.[124] In this setting, the NCCN Panel considers 1 cycle of BEP an option to reduce the risk of relapse. However, repeating chest/abdominal/pelvic CT scan is recommended within 4 weeks prior to the initiation of chemotherapy to confirm staging.

Management of Nonseminoma Stage IA 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 2 cycles of either EP or BEP for patients with pN1 or pN2 disease[125-131] and 3 cycles of BEP or 4 cycles of EP for patients with pN3 disease.

Follow-up for Nonseminoma Stage IA

The long-term follow-up tests for stage IA nonseminoma patients include a history and physical examination, serum marker assessment, chest x-ray, and an abdominal CT scan with or without a pelvic CT scan. All imaging in this setting is performed with contrast. The frequency of these tests is outlined in Table 5 on TEST-B in the algorithm (see *Follow-up for Nonseminoma* in the algorithm).

Nonseminoma Stage IB

Primary Treatment for Nonseminoma Stage IB

Post-orchiectomy nerve-sparing RPLND or adjuvant chemotherapy (1 cycle of BEP) are options to reduce the risk of relapse in patients with stage IB disease. Several studies using 2 cycles of BEP as primary treatment for stage IB nonseminoma have reported relapse-free survival rates >95%.[118,125,127,128,130-132] However, late consequences of cisplatin-based chemotherapy have been reported during long-term follow-up.[58,133-137] Therefore, 1 cycle of BEP is preferred due to its lower toxicity.

Surveillance alone is a category 2B recommendation for patients with stage IB nonseminoma. Vascular invasion is a significant predictor of relapse when orchiectomy is followed by surveillance alone.[21] Therefore, surveillance is generally not recommended for stage IB disease with vascular invasion due to the 50% chance of recurrence.

Management of Nonseminoma Stage IB After Primary Treatment

The management of stage IB disease following nerve-sparing RPLND is similar to that for stage IA (see *Management of Nonseminoma Stage IA After RPLND)*.

Follow-up for Nonseminoma Stage IB

The long-term follow-up tests for patients with stage IB disease include a history and physical examination, serum marker assessment, chest x-ray, and an abdominal CT scan with or without a pelvic CT scan. 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 and beta-hCG after orchiectomy must be interpreted with caution, as the reason for marker elevation may be hepatobiliary disease, marijuana use, or hypogonadism. 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. 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 chemotherapy for good-risk disseminated testis cancer: either 3 cycles of BEP or 4 cycles of EP. Both regimens are category 1 recommendations, and either is preferable to initial RPLND as these patients nearly always have disseminated disease.[138,139]

Management of Nonseminoma Stage IS After Primary Treatment

The management of patients with stage IS nonseminoma after primary treatment with chemotherapy is described in *Advanced Metastatic Nonseminoma* below.

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 (category 2B) as primary treatment options.[140-144] 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 (3 cycles of BEP or 4 cycles of EP).[145,146] 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 the only option given 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 given in this setting. [146-148] The risk of relapse in patients with pN2 or pN3 disease after RPLND is >50%.[146,147,149] This risk is reduced to <1% with 2 cycles of adjuvant cisplatin-based chemotherapy.[146,150,151] Therefore, the NCCN Panel prefers 2 cycles of adjuvant chemotherapy with EP or BEP to surveillance for pN2 disease[152] and recommends full course chemotherapy (not surveillance) for pN3 disease (either 3 cycles of BEP or 4 cycles of EP).

Subsequent management after primary chemotherapy depends on marker levels and the size of residual mass on CT scan. If the serum AFP and beta-hCG are normal, then the standard of care is to resect all residual enlarged lymph nodes after chemotherapy. Patients should thus undergo abdominal/pelvic CT scans with contrast after completing chemotherapy in order to look for residual adenopathy. Chest CT scans with contrast or chest x-rays may also be considered. The NCCN Panel considers nerve-sparing bilateral RPLND a category 2A

recommendation for patients with a residual mass ≥1 cm and a category 2B recommendation if the residual mass is <1 cm. A bilateral RPLND involves removal of lymphatic tissue between both ureters, spanning from the diaphragmatic crus to the bifurcation of the common iliac arteries. The rationale for this extended region of dissection is the greater likelihood of bilateral disease with greater tumor burden.[153] Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy. Surveillance is a category 2A option for patients with negative markers and no residual mass or with a residual mass <1 cm.

Nonseminoma Stage IIB

Primary Treatment for Nonseminoma Stage IIB

Treatment for patients with stage IIB nonseminoma also 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 the lymphatic drainage sites within the retroperitoneum (ie, the landing zone), patients should receive primary chemotherapy with either 3 cycles of BEP or 4 cycles of EP. 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.[141] The reported relapse-free survival with either approach is close to 98%.[147,152,154-158] 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.

For stage IIB nonseminoma patients with persistent marker elevation, the recommended treatment option is primary chemotherapy with either 3 cycles of BEP or 4 cycles of EP (both category 1).

Management of Nonseminoma Stage IIB After Primary Treatment

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

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.[31] Also, patients with an extragonadal primary site, whether retroperitoneal or mediastinal, are treated with initial chemotherapy. 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.[10]

Primary Treatment for Good-Risk Nonseminoma

The IGCCCG good-risk group includes patients with stages IS, IIA, IIB, IIC, and IIIA disease receiving chemotherapy as primary treatment. Treatment for good-risk GCTs was designed to decrease toxicity while maintaining maximal efficacy.[159-161] Presently, two regimens are recommended by the NCCN Panel: 3 cycles of BEP[85,88,162,163] or 4 cycles of EP[89] (both category 1). Either regimen is well tolerated and cures approximately 90% of patients with good-risk disease.[164]

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.[91,165] Therefore, the NCCN Panel recommends 4 cycles of BEP, or 4 cycles of VIP[91,166] 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 should be considered. If LDH is >3 times the upper limit of normal, then the patient should receive 4 cycles of either BEP or VIP.

Primary Treatment for Poor-Risk (Stage IIIC) Nonseminoma

The standard chemotherapy regimen for poor-risk patients is 4 cycles of BEP. Alternatively, 4 cycles of VIP can be used to treat patients who may not tolerate bleomycin.[166] 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 high-volume centers and participation in a clinical trial should be considered when treating poor-risk nonseminoma patients.[164]

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

At the conclusion of primary chemotherapy, CT scans with contrast of the chest, abdomen, and pelvis are indicated to assess treatment response. Measurement of serum tumor marker levels should also be performed. If a complete response to chemotherapy is found by radiographic imaging and the tumor marker levels are normal, the NCCN Panel recommends surveillance. For patients who had retroperitoneal adenopathy prior to chemotherapy, nerve-sparing bilateral RPLND can be considered in selected cases (category 2B).[167] 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. The recommended follow-up tests and their frequencies during surveillance of stage II to III nonseminoma after complete response to chemotherapy (with or without post-chemotherapy RPLND) are outlined in Table 8 on TEST-B in the algorithm.

If there is a partial response to chemotherapy (as indicated by the detection of a residual mass on imaging) and the serum tumor markers have normalized, then surgical resection of all residual masses is recommended.[168-170] 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 encountered in the resected tissue, patients should be put under surveillance. If embryonal, yolk sac, choriocarcinoma, or seminoma elements are found in the residual mass, 2 cycles of chemotherapy (EP, VelP, VIP, or TIP) should be administered.

Patients who experience an incomplete response to chemotherapy with persistently elevated AFP and beta-hCG levels are treated with either close surveillance or surgical resection of residual masses, as described in the previous paragraph. Chemotherapy should be reserved for select patients with rising marker levels or other evidence of progressive disease. The NCCN Panel recommends that patients with recurrent nonseminoma be treated at high-volume centers with expertise in the management of this disease.

Second-Line and Subsequent Therapy for Metastatic Germ Cell Tumors

Second-line Therapy

Patients with disease recurrence 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 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.

Second-line therapy options for those with favorable or unfavorable prognosis include conventional-dose or high-dose chemotherapy. The conventional-dose regimen consists of either VeIP or TIP.[174] The high-dose regimens include high-dose carboplatin plus etoposide followed by autologous stem cell transplant,[175,176] or paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide with stem cell support.[177] Patients with an unfavorable prognosis are usually considered for high-dose regimens. Alternatively, a surgical salvage may be considered if the recurrence is in a solitary resectable site.[178,179]

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 option for these patients. An ongoing, prospective, randomized, international phase III trial (TIGER) will compare second-line standard-dose chemotherapy with high-dose chemotherapy in patients with relapsed GCTs.[180] 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.[181-183] The NCCN Panel prefers surgical salvage for patients with late relapse, if technically feasible.[178,184,185] Conventional-dose or high-dose chemotherapy, participation in a clinical trial, and palliative therapy are also options for patients with late relapse.

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

Post 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 active 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 and normal marker levels, surgical resection of all residual masses is recommended. Patients with an incomplete response and persistently elevated marker levels should be managed with either close surveillance or surgical resection of residual masses followed by surveillance.

Third-line Therapy

Participation in a clinical trial is the preferred treatment option for patients who experience recurrence following first- and second-line conventional-dose or high-dose chemotherapy. Alternatively, patients previously treated with conventional-dose chemotherapy can be considered for high-dose regimens. Alternative options for patients previously treated with high-dose chemotherapy include conventional-dose salvage chemotherapy, surgical salvage (if solitary site of recurrence), and microsatellite instability (MSI) testing (if disease progresses after high-dose chemotherapy or third-line therapy). Patients with MSI-high (MSI-H) tumors may be candidates for pembrolizumab immunotherapy (see below).

The preferred treatment option for patients who experience a late relapse is surgical salvage, if the recurrent mass is resectable. Conventional-dose or high-dose chemotherapy, if not previously given, and palliative therapy are also options for patients with late relapse.

Palliative Therapy

All patients with treatment-resistant or refractory disease should be considered for palliative therapy. The palliative chemotherapy options for patients with intensively pretreated, cisplatin-resistant, or refractory GCTs are combinations of gemcitabine with paclitaxel and/or oxaliplatin,[186-192] oral etoposide,[193]or pembrolizumab.[194]

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-refractory GCTs.[187,189,191] These studies showed that GEMOX is safe for patients with cisplatin-refractory testicular GCTs and may offer a chance of long-term survival.[187,189,191] Gemcitabine and paclitaxel is another option that has shown promising results in a phase II study.[188] 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.[190]

A phase II study of patients with treatment-resistant GCTs found the combination of gemcitabine, oxaliplatin, and paclitaxel to be effective with acceptable toxicity.[186] A second study reported similar results.[192] 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.[193]

Pembrolizumab, a PD-1 antibody, was recently approved by the FDA for the treatment of patients with unresectable or metastatic MSI-H or mismatch repair-deficient (dMMR) solid tumors that have progressed following prior treatment and for which there are no satisfactory alternative treatment options.[195] This first-ever tissue- and site-agnostic indication was based on several phase IB and phase II clinical trials that demonstrated the efficacy of pembrolizumab in MSI-H/dMMR solid tumors.[196,197] In the first phase 2 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.[194] 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 is well tolerated but does not appear to have significantly meaningful single-agent activity in refractory GCTs. However, larger phase II and phase III trials of pembrolizumab in patients with metastatic refractory testicular cancers are needed to fully

assess the value of this therapy, especially in treating MSI-H/dMMR GCTs.

Treatment of Brain Metastases

The prognosis of patients with brain metastasis is poor.[198,199] Primary cisplatin-based chemotherapy is indicated for patients in whom brain metastases are detected. Additionally, there are data supporting the addition of RT to chemotherapy regimens in the treatment of patients with GCTs and brain metastases.[200,201] Surgical resection of metastatic brain lesions should also be performed if clinically indicated and feasible.

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