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Testicular Cancer, Version 2.2015

Clinical Practice Guidelines in Oncology

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Overview

An estimated 8,430 new cases of testicular cancer will be diagnosed in the United States in 2015.[1] Germ cell tumors (GCTs) comprise 95% of malignant tumors arising in the testes. These tumors also occur occasionally in extragonadal primary sites, but they are still managed the same as testicular GCTs. 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,[2] and the incidence of testicular GCTs has been increasing in the past 2 decades.[3–6]

Abstract

Germ cell tumors (GCTs) account for 95% of testicular cancers. Testicular GCTs constitute the most common solid tumor in men between the ages of 20 and 34 years, and the incidence of testicular GCTs has been increasing in the past 2 decades. Testicular GCTs are classified into 2 broad groups—pure seminoma and nonseminoma—which are treated differently. Pure seminomas, unlike nonseminomas, are more likely to be localized to the testis at presentation. Nonseminoma is the more clinically aggressive tumor associated with elevated serum concentrations of alphafetoprotein (AFP). The diagnosis of a seminoma is restricted to pure seminoma histology and a normal serum concentration of AFP. When both seminoma and elements of a nonseminoma are present, management follows that for a nonseminoma. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Testicular Cancer outline the diagnosis, workup, risk assessment, treatment, and follow-up schedules for patients with both pure seminoma and nonseminoma. (J Natl Compr Canc Netw 2015;13:772–799)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Testicular Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Testicular Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Testicular Cancer Panel members can be found on page 799. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

Several risk factors for GCT development have been identified, including prior history of a GCT, positive family history, cryptorchidism, testicular dysgenesis, and Klinefelter's syndrome.[7–9]

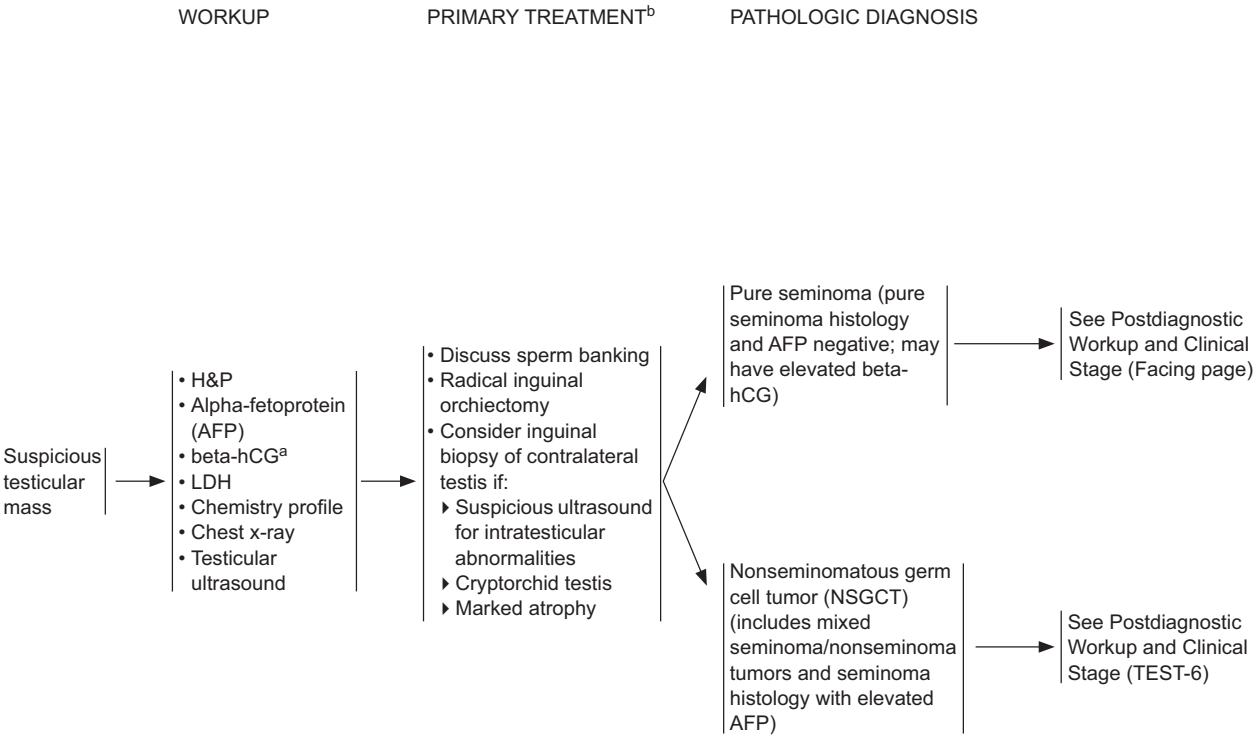
GCTs are classified as seminoma or nonseminoma. Nonseminomatous tumors often include multiple cell types, including embryonal cell carcinoma, choriocarcinoma, yolk sac tumor, and teratoma. Teratomas are considered to be either mature or immature, depending on whether adult-type differential cell types or partial somatic differentiation, similar to that present in the fetus, is found. Rarely, a teratoma histologically resembles a somatic cancer, such as sarcoma or adenocarcinoma. This is then referred to as a "teratoma with malignant transformation."

The serum tumor markers alphafetoprotein (AFP), lactate dehydrogenase (LDH), and beta-human chorionic gonadotropin (beta-hCG) are critical in diagnosing GCTs, determining prognosis, and assessing treatment outcomes.

Serum tumor markers should be determined before and after treatment and throughout the follow-up period. Serum tumor markers are very useful for monitoring all stages of nonseminomas. They are also useful in monitoring metastatic seminomas, because elevated marker levels are the early signs of relapse.

LDH is a less-specific marker compared with AFP and hCG. AFP is a serum tumor marker produced by nonseminomatous cells (ie, embryonal carcinoma, yolk sac tumor) and may be seen at any

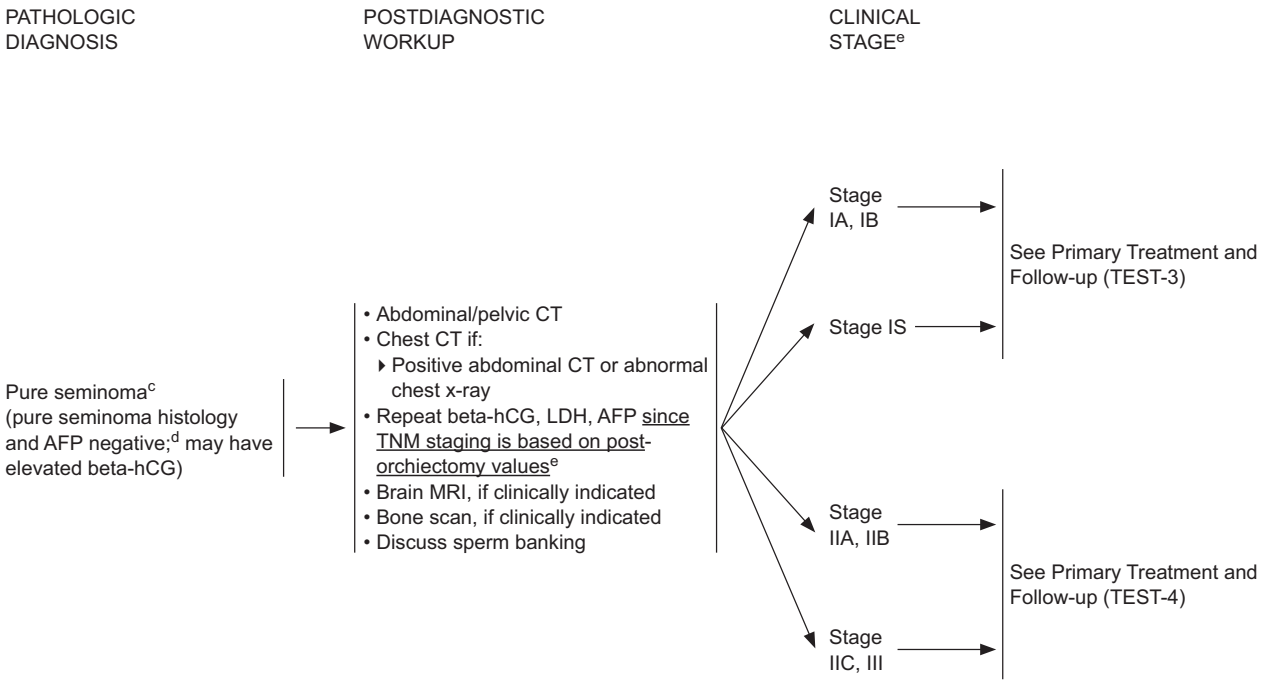
Text cont. on page 786.



[a]Quantitative analysis of beta subunit.

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

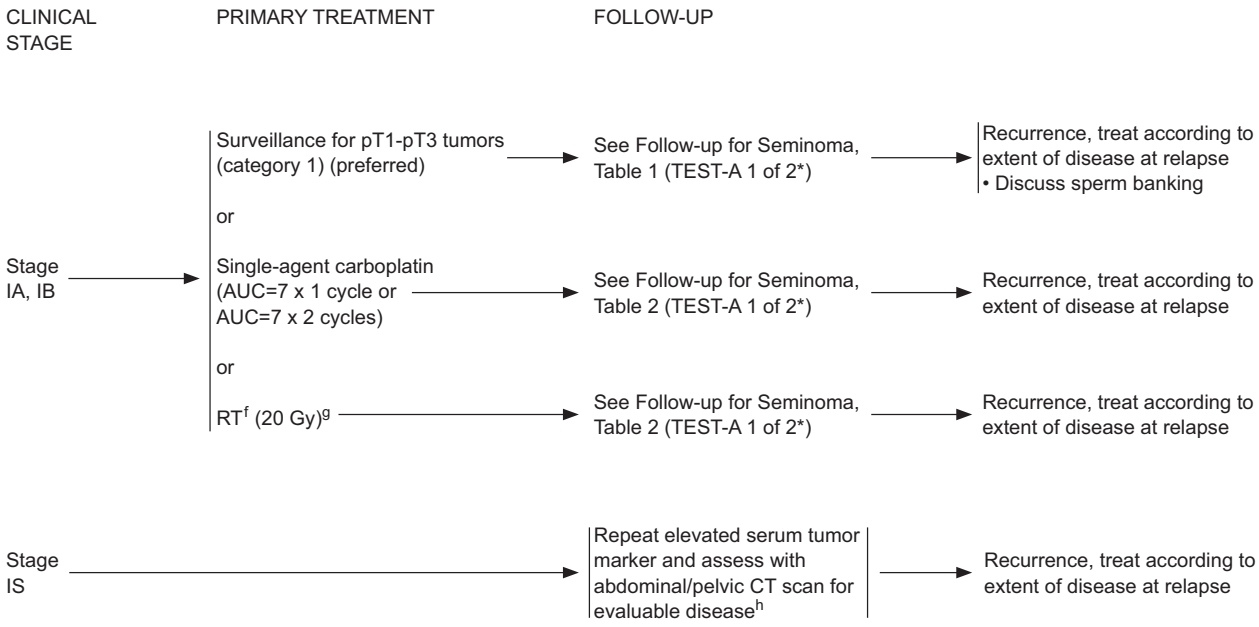
TEST-1



[c]Mediastinal primary seminoma should be treated by risk status used for gonadal seminomas with etoposide/cisplatin for 4 cycles or bleomycin/etoposide/cisplatin for 3 cycles.

[d]If AFP positive, treat as nonseminoma.

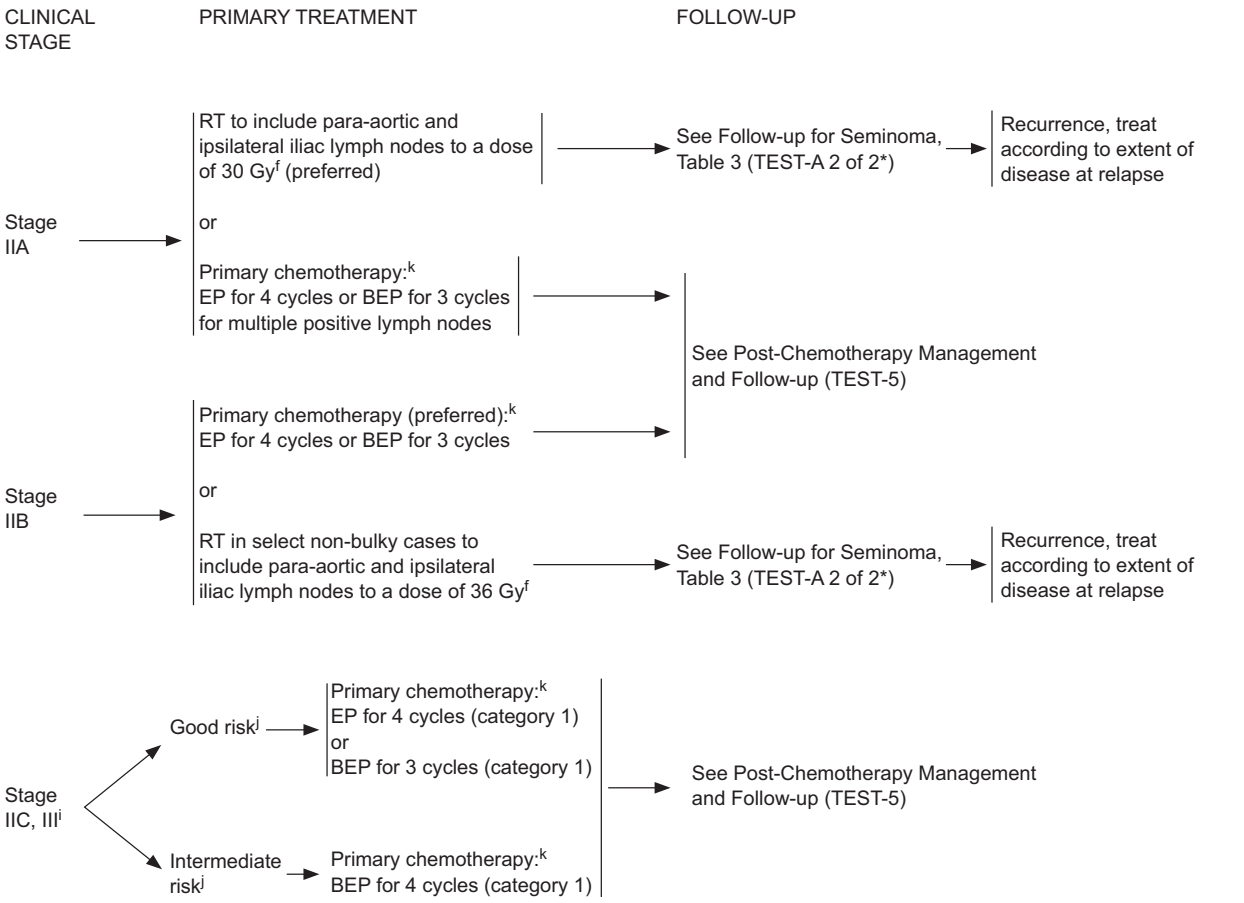
[e]Elevated values should be followed after orchiectomy with repeated determination to allow precise staging.



*Available online, in these guidelines, at NCCN.org.

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

TEST-3



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

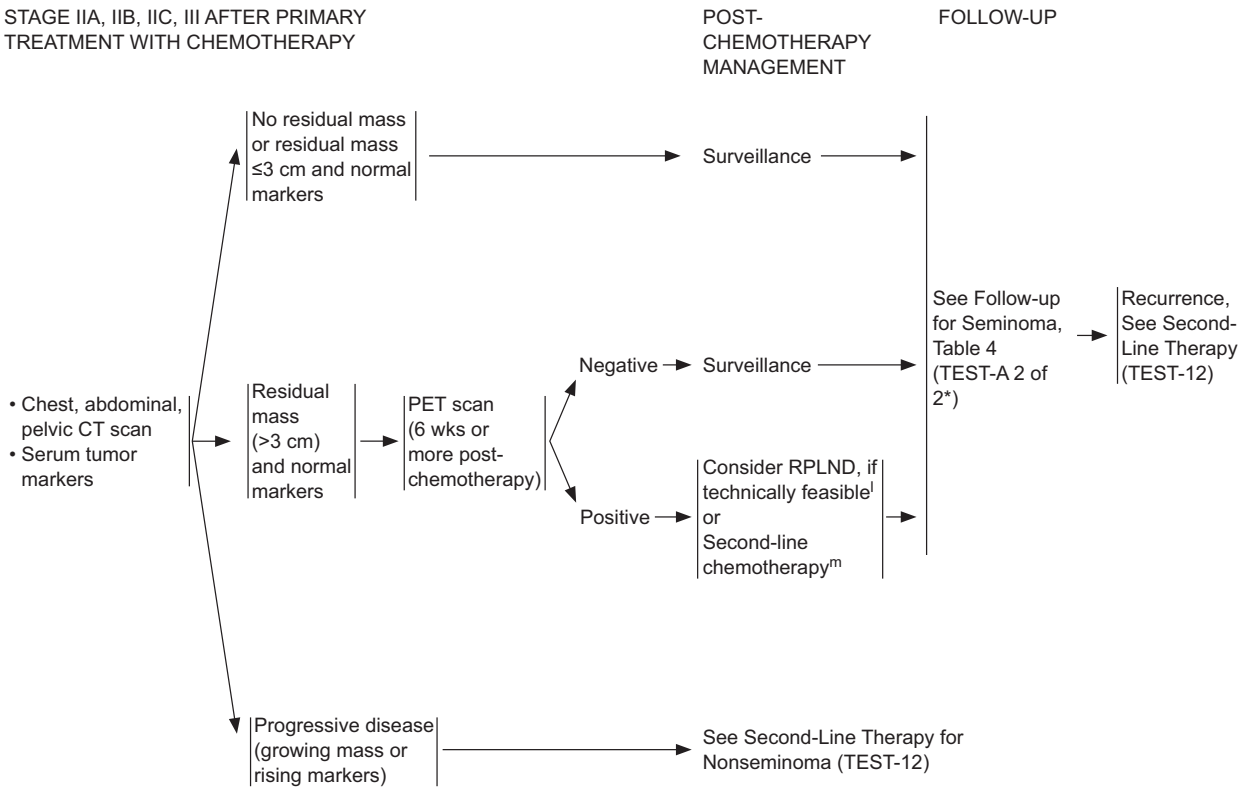
*Available online, in these guidelines, at NCCN.org.

[f]See Principles of Radiotherapy for Pure Testicular Seminoma (TEST-C*).

[i]All stage IIC and stage III seminoma is considered good-risk disease except for stage III disease with non-pulmonary visceral metastases (eg, bone, liver, or brain), which is considered intermediate risk.

[j]See Risk Classification for Advanced Disease (TEST-D*).

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

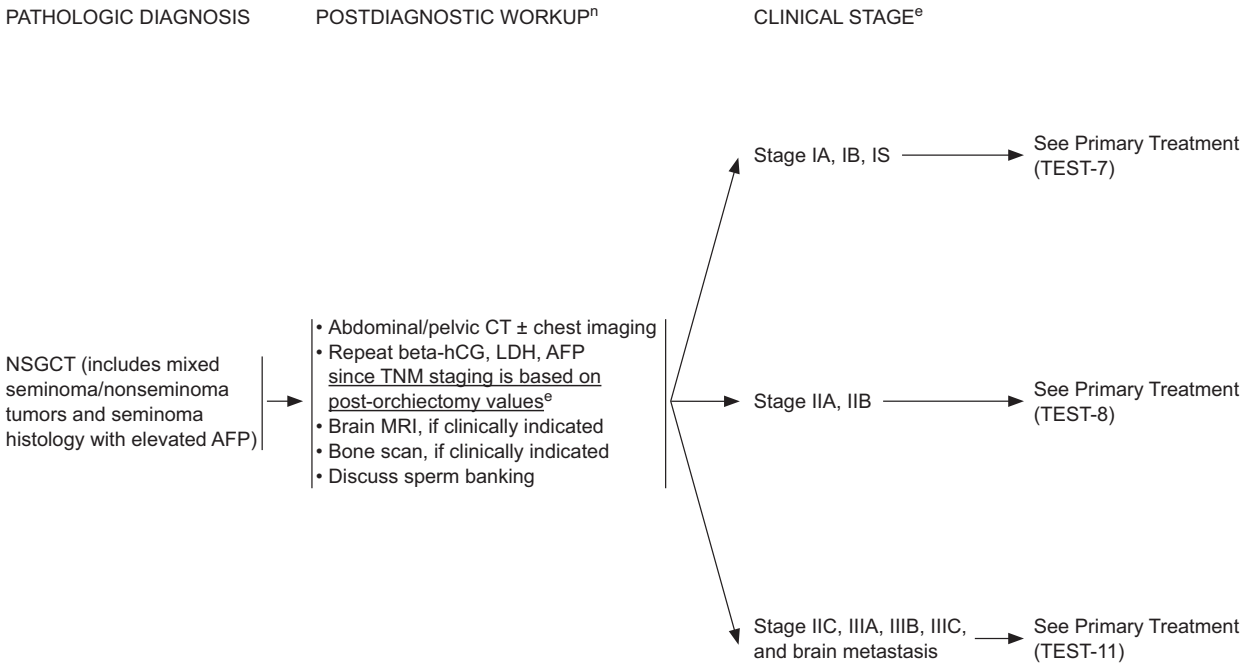


*Available online, in these guidelines, at NCCN.org.

[l]If viable seminoma found by retroperitoneal lymph node dissection (RPLND), see TEST-11 (residual embryonal, yolk sac, choriocarcinoma, or seminoma elements).

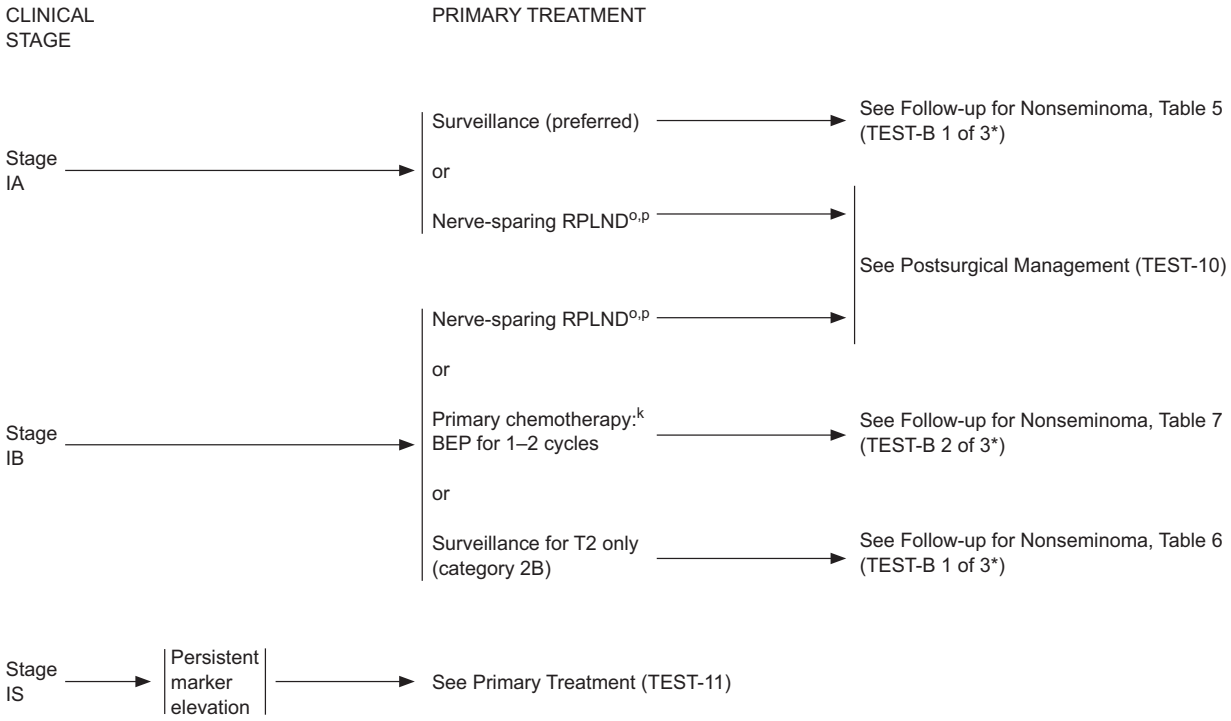
[m]See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F*).

TEST-5



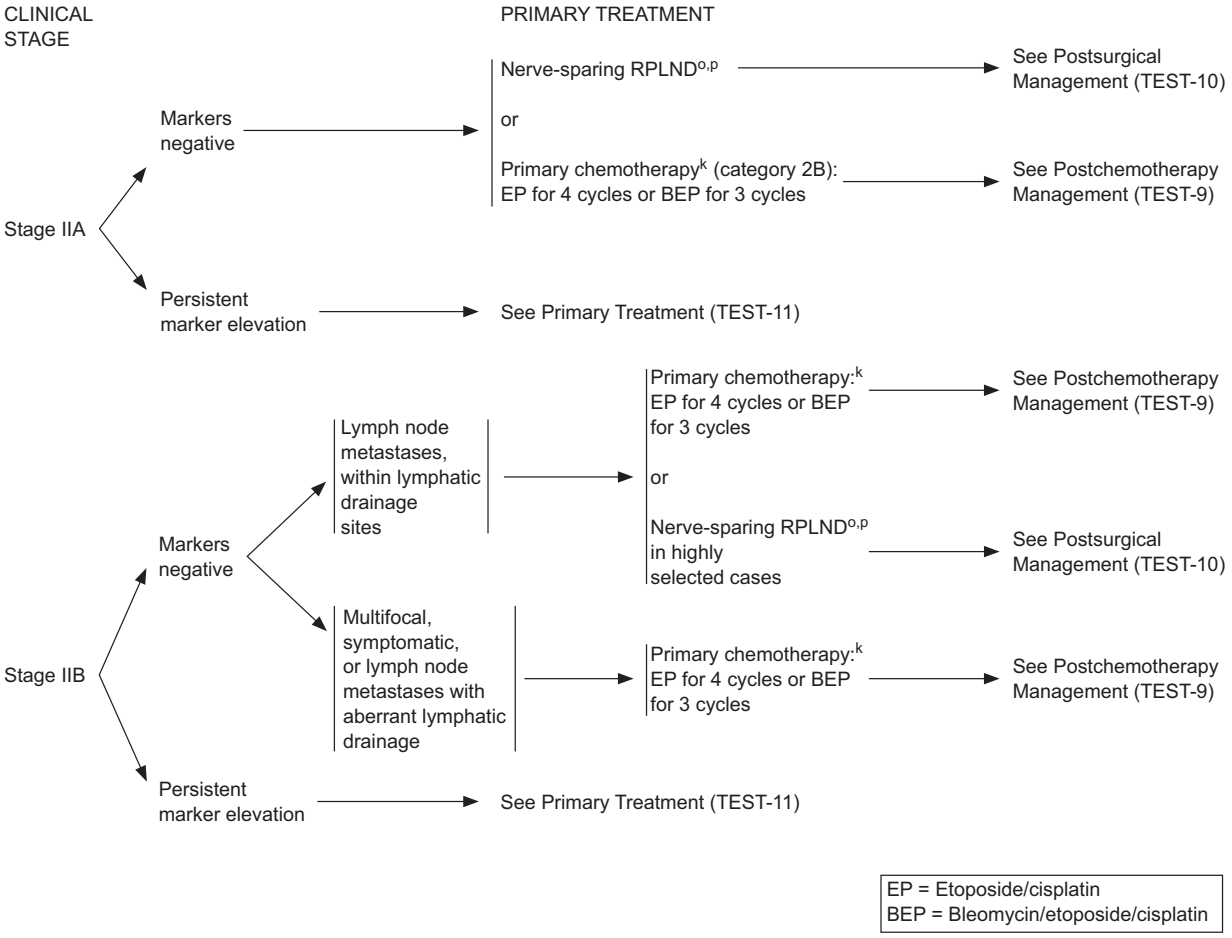
[e]Elevated values should be followed after orchiectomy with repeated determination to allow precise staging.
[n]PET scan is not clinically indicated for nonseminoma.

TEST-6



*Available online, in these guidelines, at NCCN.org.

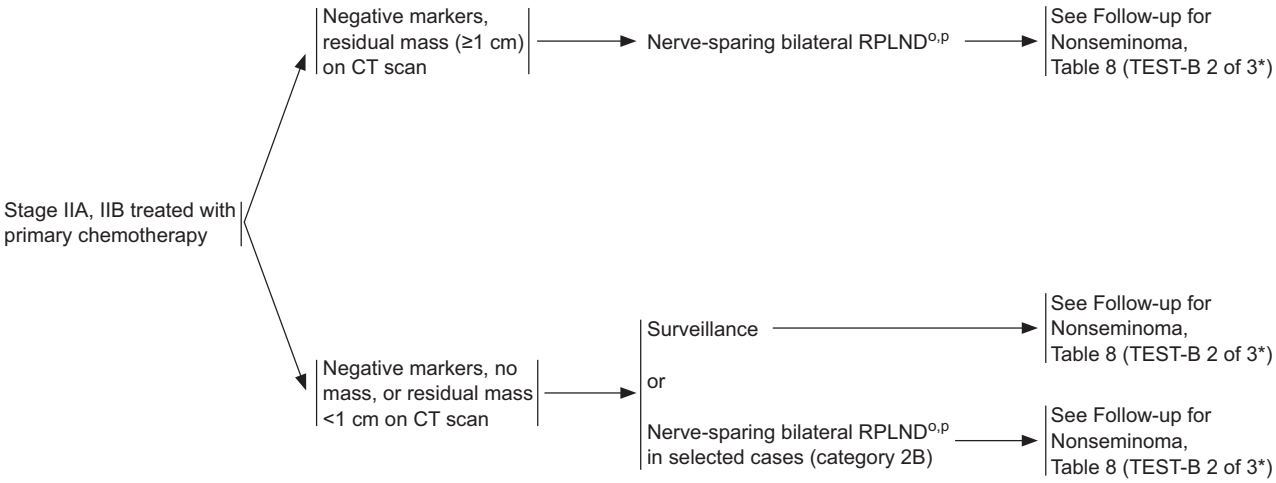
[k]See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E*).
[o]Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.
[p]See Principles of Surgery for Germ Cell Tumors (TEST-H*).



*Available online, in these guidelines, at NCCN.org.

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

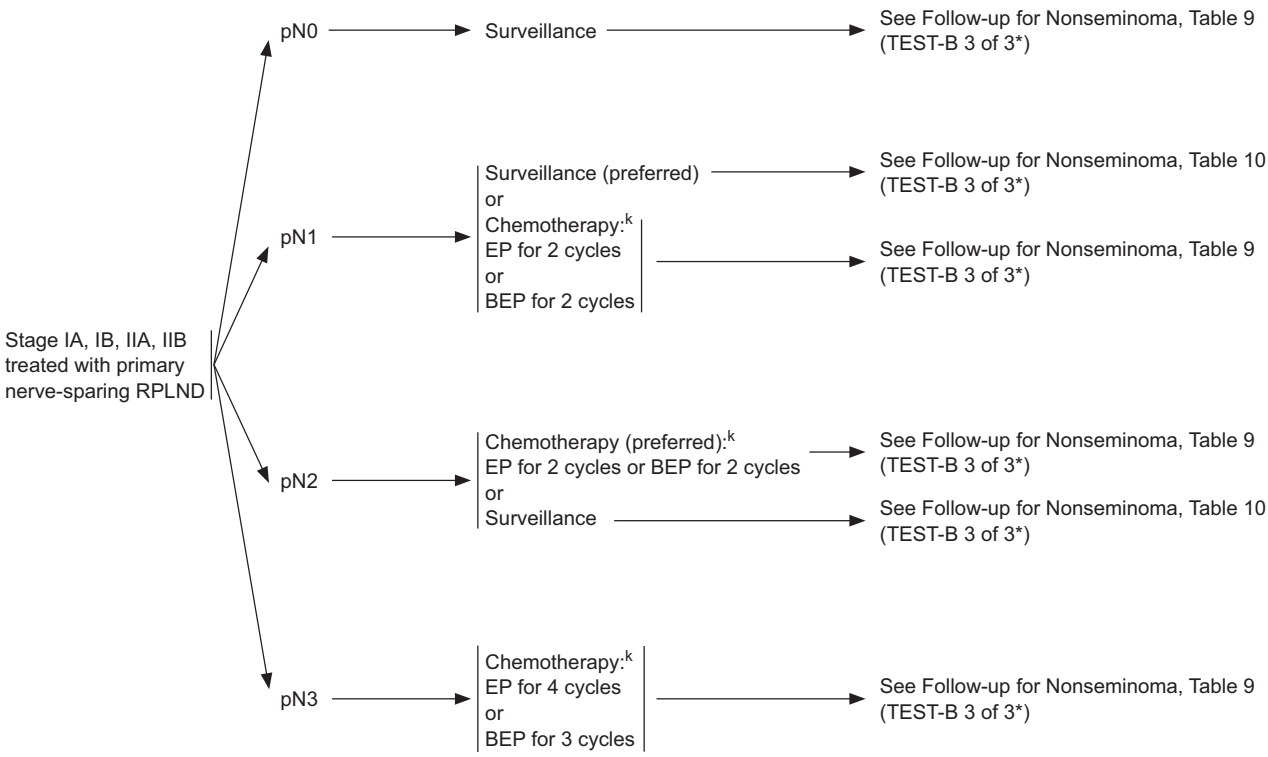
POSTCHEMOTHERAPY MANAGEMENT



*Available online, in these guidelines, at NCCN.org.

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

POSTSURGICAL MANAGEMENT



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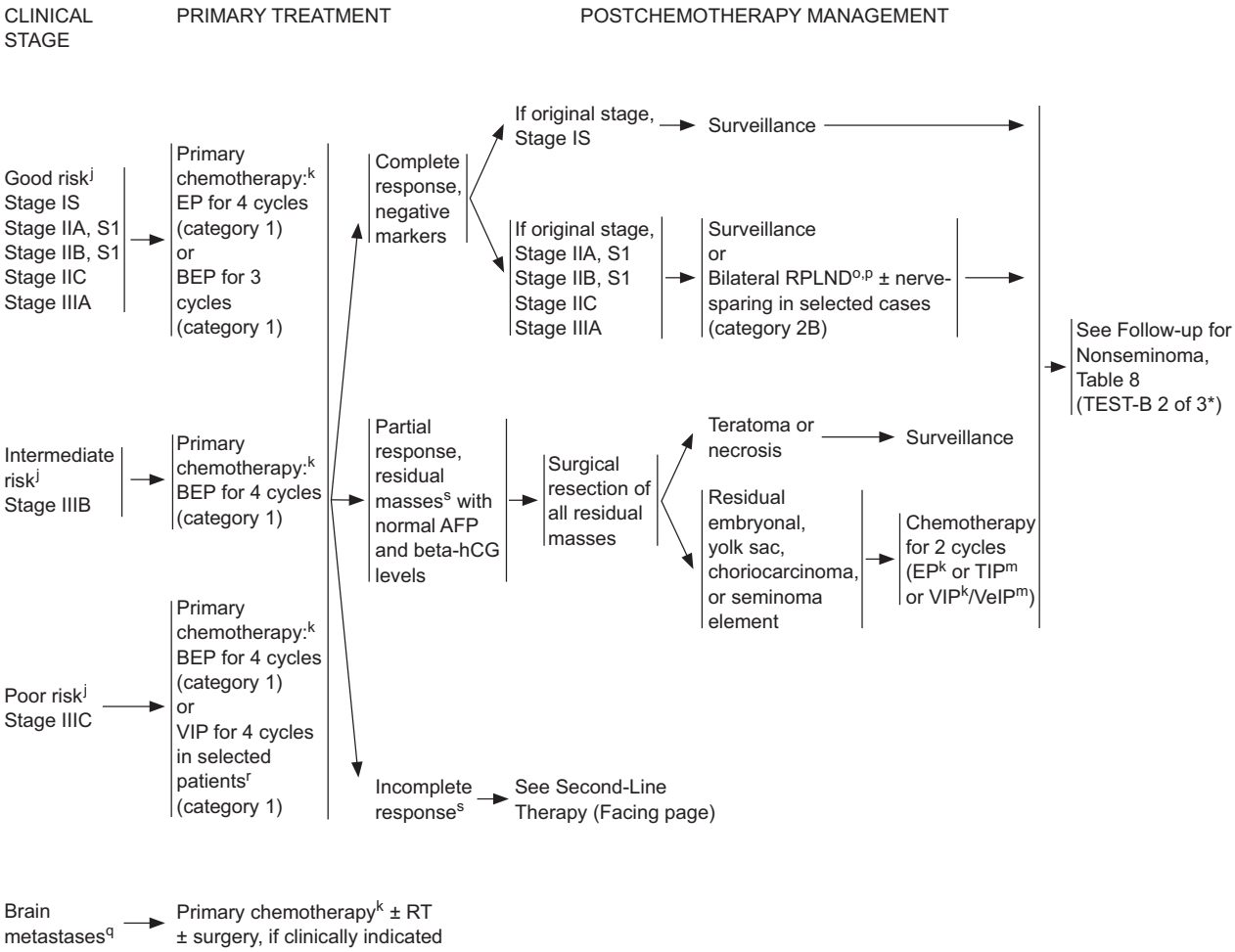
*Available online, in these guidelines, at NCCN.org.

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



*Available online, in these guidelines, at NCCN.org.

[j]See Risk Classification for Advanced Disease (TEST-D*).

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

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

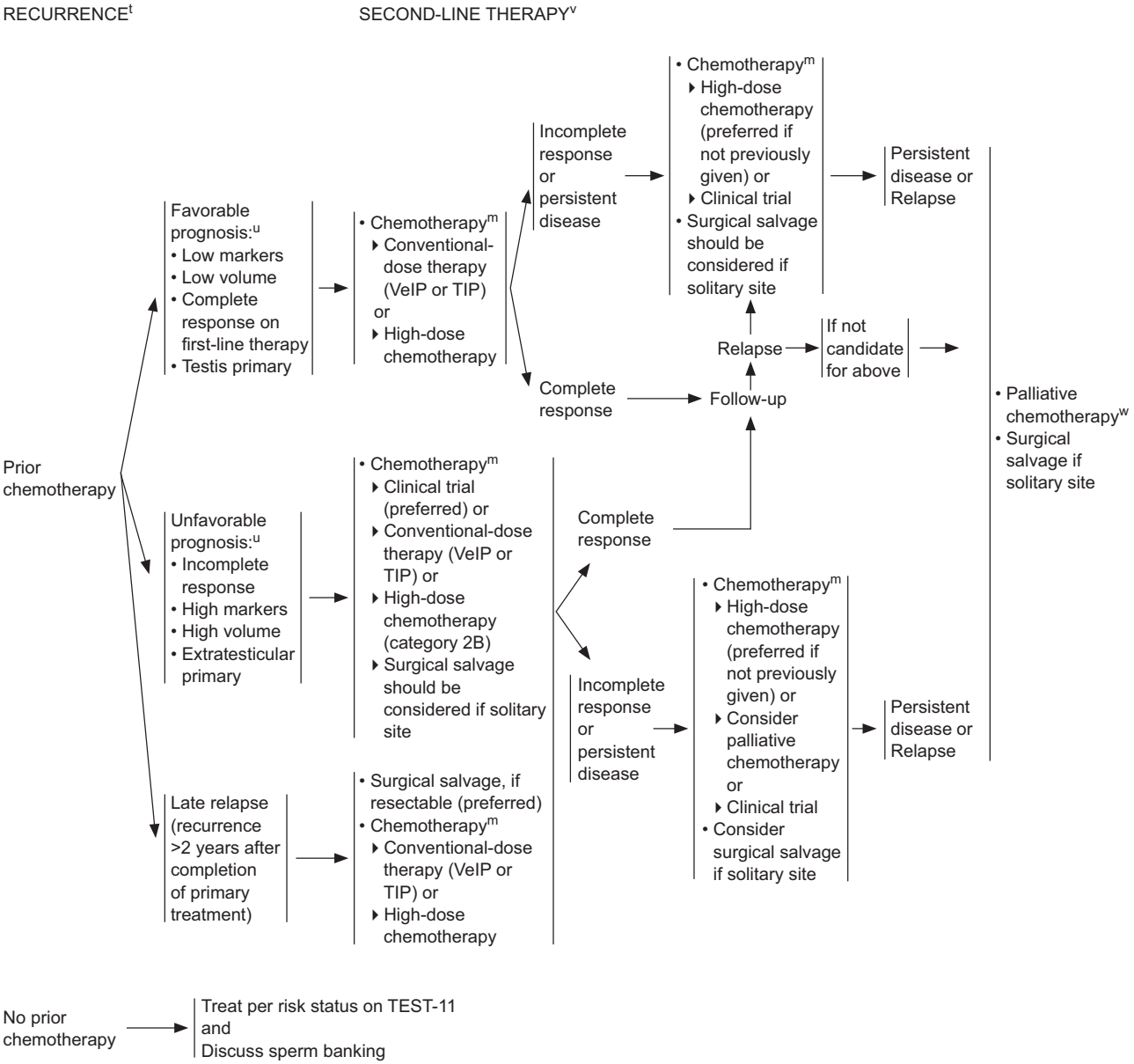
[o]Retroperitoneal lymph node dissection (RPLND) is recommended within 4 weeks of CT scan and 7–10 days of markers.

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

[q]Patients should receive adequate treatment for brain metastases, in addition to cisplatin-based chemotherapy.

[r]Patients who may not tolerate bleomycin.

[s]There is limited predictive value for PET scan for residual masses.



*Available online, in these guidelines, at NCCN.org.

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

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

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

[v]Includes best supportive care.

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

Text cont. from page 773.

stage. The approximate half-life of AFP is 5 to 7 days. A nonseminoma, therefore, is associated with elevated serum concentrations of AFP. When patients with a histologically "pure" testicular seminoma have an elevated level of AFP, it is generally assumed that an undetected focus of nonseminoma is present.[10,11] An elevated serum concentration of beta-hCG, which has a halflife of approximately 1 to 3 days, may also be present with seminomatous and nonseminomatous tumors. The elevations of beta-hCG need to be interpreted with caution because hypogonadism and marijuana use may cause benign serum elevations of beta-HCG.

Nonseminoma is the more clinically aggressive tumor. When both seminoma and elements of a nonseminoma are present, management follows that for a nonseminoma. Therefore, the diagnosis of a seminoma is restricted to pure seminoma histology and a normal serum concentration of AFP.

The 5-year survival for testis cancer is 98%.[2] A delay in diagnosis correlates with a higher stage at presentation. Standard therapy has been established at essentially all stages of management and must be closely followed to ensure the potential for cure.

Clinical Presentation

A painless solid testicular mass is pathognomonic for testicular tumor. More often, patients present with testicular discomfort or swelling suggestive of epididymitis or orchitis. A trial of antibiotics may be given in this circumstance, but persistent tenderness, swelling, or any palpable abnormality warrants further evaluation.

Diagnosis and Workup and Risk Assessment

Imaging and Blood Tests

If an intratesticular mass is identified, complete blood count, creatinine, electrolytes, and liver enzymes should be obtained. Testicular ultrasound serves to confirm the presence of a testicular mass and to explore the contralateral testis. It is sensitive and has an important role in determining whether a mass is intra- or extratesticular.[12]

Further evaluation includes measurement of the serum tumor markers and a chest radiograph. Serum tumor markers are critical in the assignment of prognosis and management during treatment as well. Serum tumor markers are prognostic factors and contribute to diagnosis and staging.[13] Markers are assessed before orchiectomy, and assessment is repeated after orchiectomy. Elevated values of beta-hCG, LDH, or AFP should be followed up with repeated tests to allow precise staging.

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

In patients of reproductive age, sperm banking must be discussed[14,15] before the patient undergoes any therapeutic intervention that may compromise fertility, including surgery, radiation therapy (RT), and chemotherapy.[16–18] If sperm banking is desired, it may be performed either before or after orchiectomy but certainly before subsequent therapy.

Primary Treatment

Inguinal orchiectomy is considered the primary treatment for most patients who present with a suspicious testicular mass.[19] An open inguinal biopsy of the contralateral testis is not routinely performed but can be considered when a cryptorchid testis or marked atrophy is present.[20] The extent of primary tumor is classified after orchiectomy, and therefore pathologic stage is assigned to the primary tumor.

Further management is dictated by histology, a diagnosis of pure seminoma or nonseminoma (includes mixed seminoma tumors and seminoma histology with elevated AFP), and stage. Though rare, when a patient presents with rapidly increasing beta-hCG, symptoms related to disseminated disease, and a testicular mass, chemotherapy can be started immediately without waiting for a biopsy diagnosis.

Staging

TNM staging is based on postorchiectomy beta-HCG, LDH, and AFP values. To assess for metastatic disease, important steps include obtaining the half-life kinetics of serum tumor markers after orchiectomy; determining the status of retroperitoneal lymph nodes; determining the presence of lung metastasis; and determining the presence of brain or bone metastasis if suspicious clinical symptoms are present.

Risk Classification for Advanced Disease

In 1997, the International Germ Cell Cancer Consensus Group (IGCCCG) defined a prognostic

factor–based classification system that used identification of some clinically independent prognostic features such as extent of disease and levels of serum tumor markers after orchiectomy. Postorchiectomy markers are used to make the IGCCCG risk classification. This classification categorizes patients with pure seminoma and nonseminoma GCT into good-, intermediate-, or poor-risk groups.[21]

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

Pure Seminoma

If a GCT is found, an abdominopelvic CT scan is performed. Abdominopelvic CT scanning is used to assess the retroperitoneal nodes.[22]

A chest CT is indicated if the abdominopelvic CT shows retroperitoneal adenopathy or the chest radiograph shows abnormal results. A chest CT scan is a sensitive way to evaluate the thorax and mediastinal nodes.[23] The NCCN Panel for testicular cancer recommends a brain MRI or bone scan only in cases with suspicion of metastases to these organs.

Elevated values of beta-HCG, LDH, or AFP should be followed with repeated tests. Serum concentrations of beta-hCG and LDH may be elevated in patients with seminoma. An elevated AFP level indicates nonseminoma, and the patient should be managed accordingly. Initial management of pure seminoma involves a radical inguinal orchiectomy. Orchiectomy is both diagnostic and therapeutic. Patients with seminoma arising from an extragonadal site, such as the mediastinum, are treated with standard chemotherapy regimens according to risk status.

Pure Seminoma Stages IA and IB

Primary Treatment for Pure Seminoma Stages IA and IB: Most patients with stage I seminoma are cured by orchiectomy alone. A small percentage of patients experience relapse. To prevent relapse in patients with stages IA and IB pure seminoma, the standard management options after initial orchiectomy include active surveillance, RT, or chemotherapy with 1 or 2 cycles of carboplatin. The disease-specific survival for stage I disease is 99% irrespective of the management strategy used.[24]

Surveillance: A number of prospective nonrandomized studies of surveillance have been conducted.[25–28] The relapse rate seen in these studies is 15% to 20% at 5 years, and most of the relapses are first detected in infradiaphragmatic lymph nodes.[26–28] Some studies report tumor size greater than 4 cm and rete testis invasion as a risk factor in predicting relapse in patients.[27,29,30] A validation study by Chung et al[31] revealed that tumor size greater than cm and rete testis invasion were not predictors of relapse.[32] Therefore, the panel discourages risk-adapted management using tumor size larger than 4 cm and rete testis invasion for stage I pure seminoma.

A retrospective study analyzed data from a total of 2,483 patients with clinical stage I GCT managed with active surveillance. The analyses showed that 173 of 1,344 (13%) patients with stage 1 seminoma had relapse. Median time to relapse was 14 months (range, 2–84 months). Of the recurrences, 92%were seen within 3 years. The overall 5-year disease-specific survival was 99.0%.[33,34] Surveillance is listed as the preferred option (category 1) for patients with pT1 to pT3 tumors by the NCCN Guidelines for Testicular Cancer.

If surveillance is not applicable, alternatives are either adjuvant carboplatin or adjuvant radiotherapy as described subsequently. Each approach has distinct advantages and disadvantages. The physicians should discuss these with patients and families and pick the best approach on a case-by-case basis.

Adjuvant Therapy: Oliver et al[35] reported on the results of a trial that randomized 1477 patients with stage 1 testicular cancer to undergo either radiotherapy or one injection of carboplatin. In the study, carboplatin (area under the curve [AUC] X 7) was administered intravenously. The dose was calculated by the formula 7 X (glomerular filtration rate [GFR, mL/min] + 25 mg). With a median followup of 4 years, the relapse-free survival rates for both groups were similar.[35]

Late relapses and secondary GCTs can occur beyond 5 and 10 years. Therefore, the investigators continued to follow-up with these patients. The updated results reported noninferiority of single-dose carboplatin versus RT.[36] In an intent-to-treat analysis, the relapse-free rates at 5 years were 94.7% for the carboplatin arm and 96% for the RT arm (hazard ratio, 1.25; P=.37). Two cases of contralateral GCTs were seen on carboplatin versus 15 on RT, with a hazard ratio of 0.22; the contralateral GCT-free rates at 5 years were 99.8% and 98.8%, respectively. The

authors concluded that a single dose of carboplatin is less toxic and as effective in preventing disease recurrence as adjuvant RT in men with stage I pure seminoma after orchiectomy.[36] Two courses of adjuvant carboplatin have also been reported to reduce the relapse rate.[37]

The NCCN Guidelines do not note a preference for routine use of adjuvant therapy for stage I seminoma patients, because the risk of recurrence is low compared with the potential harms of adjuvant therapy. Studies have suggested that RT might increase the risk of a subsequent cardiac event,[38] but other recent analyses have not confirmed this risk.[39]

Another study found that moderate-dose infradiaphragmatic RT for stage I seminoma was associated with increased risks of second cancers (nontesticular germ cell) to organs in the radiation field. As with RT, platinum-based chemotherapy has been associated with an increased risk of cancer and heart disease.

However, if adjuvant chemotherapy is chosen, the NCCN Guidelines for Testicular Cancer recommend carboplatin AUC X 7 for either 1 or 2 cycles as a category 2A recommendation for patients with stages IA and IB pure seminoma.

If RT is delivered, the NCCN Guidelines recommend a total dose of 20.0 Gy (midplane) in 10 daily 2.0 Gy fractions,[40] given to an infradiaphragmatic area, including para-aortic lymph nodes; in special circumstances, it may include the ipsilateral ilioinguinal nodes.[41–44] Patients for whom RT is generally not given include those at higher risk for morbidity from therapy such as those with a history of pelvic surgery. Prophylaxis to the mediastinum is not provided, because relapse rarely occurs at this site.

For patients with stages IA and IB pure seminoma, adjuvant RT to include para-aortic nodes is also a category 2A recommendation in the NCCN Guidelines for Testicular Cancer, though active surveillance is preferred (see "Principles of Radiotherapy for Pure Testicular Seminoma" TEST-C, 1 of 5; available online, in these guidelines, at NCCN.org).

Follow-up After Primary Treatment for Pure Seminoma Stages IA and IB: In follow-up, distinguishing the different risk of recurrence associated with each treatment modality (surveillance vs adjuvant therapy) is important. An analysis of more than 5,000 stage I seminomas from various trials showed that, independent of the treatment modality, the risk of recurrence is highest in the first 2 years and decreases after that.[45] The NCCN Guidelines recommend performing testicular ultrasound if other recommended tests are equivocal.

Follow-up During Active Surveillance: The NCCN Guidelines include updated guidelines for follow-up of patients with stage 1 seminoma on active surveillance (see TEST-A, page 1 of 2; available online, in these guidelines, at NCCN.org). Follow-up for patients on surveillance includes a history and physical, with measurement of postorchiectomy 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 thereafter.[46–48]

How many imaging studies must be performed in patients on active surveillance is controversial. The NCCN Guidelines recommend abdominal/pelvic CT every 3, 6, and 12 months for 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.

No initial relapses in the lung have been reported in studies of patients with stage I seminoma managed using active surveillance; therefore, according to the NCCN Panel, routine chest imaging during surveillance is only indicated for patients with thoracic symptoms.

A clinical trial in the United Kingdom, entitled TRISST (MRC TE24/Trial of Imaging and Schedule in Seminoma Testis), is currently studying whether a reduced CT schedule or MRI could be used as a safe and effective alternative to standard CT-based surveillance in the management of stage I seminoma.[49]

Follow-up After Adjuvant Treatment (carboplatin or RT): The risk of recurrence 5 years after adjuvant treatment is less than 0.3% annually.[45] Follow-up of patients treated with adjuvant therapy (carboplatin or RT) includes a history and physical, with measurement of postorchiectomy serum tumor markers (AFP, beta-HCG, and LDH) performed every 6 to 12 months for the first 2 years and annually thereafter.

Patients treated with para-aortic radiation therapy have a slightly higher rate of pelvic relapse compared with those treated with "dog-leg" RT.[42,45,50,51]

In a meta-analysis of 2,466 patients, Mead et al[24] reported that recurrence rarely occurred after more than 3 years from treatment with either RT or carboplatin. Relapse occurred after 3 years only in 4 of 2,466 patients (0.2%).[24] Since the rate of recurrence for patients treated with chemotherapy and radia-

tion therapy beyond 3 years is very low, the NCCN Guidelines recommend performing abdominal and pelvic CT scans annually for 3 years in patients treated with radiotherapy or carboplatin. Chest radiographs should be obtained only when clinically indicated. Recurrences are treated according to the stage at relapse.[24]

Pure Seminoma Stage IS

Primary Treatment for Pure Seminoma Stage IS: By the AJCC definition, stage IS requires persistent elevation of serum tumor markers (LDH, AFP, and beta-HCG) after orchiectomy. Stage IS pure seminoma is very uncommon, and caution is warranted before intervention based on minimally elevated LDH or beta-HCG, as other causes may be responsible. Persistent elevation of serum markers is usually evidence of metastatic disease, which will show up radiographically if doubt exists in the diagnosis.

Follow-up After Primary Radiation Treatment for Pure Seminoma Stage IS: The NCCN Panel recommends repeating evaluation of serum markers and performing imaging studies to determine the extent of disease. If there is persistent elevation of markers, treatment with chemotherapy is similar to that of nonseminoma (see "Nonseminoma," page 790).

Pure Seminoma Stages IIA and IIB

Primary Treatment for Pure Seminoma Stages IIA: Stage IIA is defined as metastatic disease to lymph nodes, with a lymph node mass measuring less than or equal to 2 cm in diameter in greatest dimension on CT scan, and stage IIB as disease measuring greater than 2 but less than 5 cm in maximum diameter.

RT has been the mainstay of treatment in patients with stage IIA and IIB seminoma with low-volume disease.[52–54] The NCCN Panel prefers RT over chemotherapy for patients with stage IIA seminoma. The relapse rates are moderate (5%–6% for stage IIA), and overall survival is almost 100%.[52,54,55] The standard radiation field compared with stage I is extended from the para-aortic region to include an ipsilateral iliac field in 2 consecutive anteroposterior-posteroanterior phases without a break in between. The initial phase consists of radiation to modified dog-leg fields consisting of a dose of 20.0 Gy (midplane) in 10 daily 2.0 Gy fractions[41] or 25.5 Gy in 15 daily 1.7 Gy fractions.[56] The panel prefers modified dog-leg fields as described by Classen et al.[52] For details on field arrangement, see "Principles of Radiotherapy for Pure Testicular Seminoma" in the algorithm (available online at NCCN.org).

The second phase (cone down) of RT consists of daily 2.0 Gy fractions to a cumulative total dose of approximately 30 Gy for stage IIA and 36 Gy for selected patients with non-bulky stage IIB disease.[52] As with the management of stage I disease, prophylactic mediastinal radiation therapy is not indicated for stage II disease.[57]

For patients with stage IIB seminoma such as those with adenopathy measuring more than 3 cm,[58] chemotherapy with 4 courses of etoposide and cisplatin (EP) or 3 cycles of bleomycin, etoposide, and cisplatin (BEP) is the preferred alternative to radiotherapy.[55,59] For patients with stage IIA disease, chemotherapy with 4 cycles of EP or 3 cycles of BEP is an option for patients with multiple positive nodes.

Follow-up for Stages IIA and Non-bulky IIB Pure Seminoma After Primary Treatment: The recommended follow-up schedules after RT for patients with stage IIA and non-bulky IIB tumors include a history and physical with measurement of post-orchiectomy serum tumor markers (AFP, beta-HCG, and LDH), performed every 3 months for year 1 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 is recommended at 3 months, then at 6 and 12 months in year 1, and then annually for years 2 and 3 after RT and as clinically indicated thereafter.

The follow-up of patients with stage II bulky tumors treated with chemotherapy is similar to follow-up after chemotherapy for patients with stages II and III and is discussed in "Follow-up of Pure Seminoma Bulky Stage II and Stage III After Chemotherapy" (page 790).

Pure Seminoma Stages IIC and III

Primary Treatment for Pure Seminoma Stages IIC and III: Patients with stage IIC or III disease are those considered at either good or intermediate risk. All stage IIC and stage III seminoma is considered good-risk disease except for stage III disease with nonpulmonary visceral metastases (eg, bone, liver, brain), which is considered intermediate risk. Standard chemotherapy is used for both groups of patients. However, for patients with good risk, 3 cycles of BEP[60–62] or 4 cycles of EP [63–65] are recommended. In contrast, more-intensive chemotherapy (ie, 4 cycles

of BEP) is recommended for those with intermediate-risk disease.[66,67] All these chemotherapy options are category 1 recommendations.

Postchemotherapy Management of Pure Seminoma Stages IIA, IIB, IIC, and III: After chemotherapy, patients with stage IIA, IIB, IIC, and III are evaluated with serum tumor markers and a CT scan of the chest, abdomen, and pelvis. Patients are then classified according to the presence or absence of a residual mass and the status of serum tumor markers. Patients with normal markers and either no residual mass or residual mass of 3 cm or less need no further treatment. They should undergo surveillance as discussed in the next section, "Follow-up for Pure Seminoma Bulky Stage II and Stage III After Chemotherapy" (opposite column).

In cases of residual tumor greater than 3 cm and marker levels that are normal, a PET scan is recommended to assess whether there is residual viable tumor.[68] A PET scan has a high positive and negative predictive value with regard to the question of remaining disease in patients with residual masses after chemotherapy.[69] To reduce the incidence of false-positive results, the PET scan is typically performed at least 6 weeks after completion of chemotherapy. Notably, granulomatous disease, such as sarcoid, is a source of false-positive results. The NCCN Guidelines recommend a PET scan in patients with seminoma, a residual mass greater than 3 cm, and normal levels of markers, approximately 6 weeks after chemotherapy to decide whether to continue with surveillance or resume treatment.[68,70–74]

If the PET scan is negative, no further treatment is needed; however, the patient should undergo follow-up[75,76] as discussed in "Follow-up of Pure Seminoma Bulky Stage II and Stage III After Chemotherapy" (opposite column).

Since a positive PET scan is a strong indicator of residual active tumor, resection should be considered. Therefore, if technically feasible, retroperitoneal lymph node dissection (RPLND) may be considered (category 2A). The other option, if resection is not feasible, is second-line chemotherapy (category 2A). Cisplatin-based combination chemotherapy is used for second-line treatment.[77–79] The regimens are 4 cycles of TIP (paclitaxel, ifosfamide, cisplatin)[80] or 4 cycles of VeIP (vinblastine, ifosfamide, cisplatin).[78,79]

According to the NCCN Guidelines, second-line therapy for seminoma and nonseminoma is similar. It is discussed subsequently in "Second-line Therapy for Metastatic Germ Cell Tumors" (see page 794). Follow-up for these patients is also described.

Follow-up of Pure Seminoma Bulky Stage II and Stage III After Chemotherapy: The NCCN Panel-recommended follow-up schedules for patients with bulky stage II or stage III disease *after* treatment with chemotherapy *and* either no or 3 cm or smaller residual mass and normal tumor markers includes a history and physical and measurement of postorchiectomy serum tumor markers every 2 months for the first year, every 3 months for the second year, every 6 months for the third and fourth years, and annually for year 5. An abdominal/pelvic CT scan is recommended at 3 and 6 months and then as clinically indicated.[81] A PET scan may be performed as clinically indicated. Chest x-ray is recommended every 2 months during the first year, every 3 months during the second year, and annually during years 3 through 5. Chest CT is preferred over chest x-ray in patients with thoracic symptoms. Viable tumor cells have been found in tumors larger than 3 cm even with a negative PET scan after chemotherapy treatment.[82,83] The NCCN Panel notes that patients with PET-negative result and tumor residual mass measuring greater than 3 cm after chemotherapy should undergo an abdominopelvic CT scan every 6 months for the first year and then annually for 5 years.

Nonseminoma

Similar to the workup for seminoma, if nonseminoma is found, CT of the abdomen and pelvis should be performed, with chest imaging if needed. MRI of the brain and bone scan should be conducted in the case of clinical indicators (symptoms) of involvement. PET scanning does not contribute and routine use is not recommended for patients with nonseminoma.[84,85]

Elevated values of betaHCG, LDH, or AFP should be followed up with repeated tests. Nonseminoma includes mixed seminoma tumors and seminoma histology with elevated AFP. Postorchiectomy serum markers are important for TNM staging and to classify the patient with nonseminoma according to the IGCCCG risk classification into good-, intermediate-, and poor-risk groups.[21]

In patients of reproductive age, sperm banking must be discussed[14,15] with patients before they un-

dergo any therapeutic intervention that may compromise fertility, including surgery, RT, or chemotherapy.[16–18] If sperm banking is desired, it may be performed either before or after orchiectomy, but certainly prior to adjuvant therapy.

Stage-dependent treatment options after inguinal orchiectomy include surveillance, chemotherapy, and RPLND. Although the timing of the RPLND may vary, most patients with nonseminoma will undergo an RPLND for either diagnostic or therapeutic purposes at some point during treatment. The major morbidity associated with bilateral dissection is retrograde ejaculation, resulting in infertility. Nerve dissection techniques preserve antegrade ejaculation in 90% of cases.[86]

Nonseminoma Stage IA

Primary Treatment of Nonseminoma Stage IA: According to the NCCN Testicular Cancer Panel, two management options exist for patients with stage IA disease after orchiectomy: 1) surveillance;[87–91] and 2) nervesparing RPLND. The cure rate with either approach exceeds 95%. However, the high cure rate associated with surveillance depends on adherence to periodic follow-up examinations and subsequent chemotherapy for the 20% to 30% of patients who experience relapse. Surveillance is the preferred option for patients with stage 1A tumors. Patients who choose surveillance should agree to be adherent for follow-up. When RPLND is performed, it should be done using a nerve-sparing technique.[92,93] According to the NCCN Panel, the nerve-sparing RPLND is recommended within 4 weeks of a CT scan and within 7 to 10 days of repeat serum marker testing to ensure accurate presurgical staging.

Management of Nonseminoma Stage IA After RPLND: After RPLND, if the dissected lymph nodes are not involved with a tumor (pN0), no adjuvant chemotherapy is given. The patients should undergo surveillance. However, if the resected lymph nodes involve tumor, the decision whether to use adjuvant chemotherapy is based on the degree of nodal involvement. Surveillance is preferred over chemotherapy for patients with pN1 disease. Chemotherapy is preferred in patients with pN2 or pN3 disease. Surveillance is an option for patients with pN2 but is not an option for patients with pN3 disease. Recommended chemotherapy regimens include either EP or BEP. Two cycles of either regimen (EP or BEP) are recommended for patients with pN1 or pN2 disease.[94–100] For patients with pN3 disease, longer courses of chemotherapy with 4 cycles of EP or 3 cycles of BEP is recommended.

Follow-up for Nonseminoma Stage IA: In the updated NCCN Guidelines for Testicular Cancer, the long-term follow-up tests for patients with stage IA disease electing primary surveillance, post-RPLND, or post-chemotherapy include serum marker assessment, chest x-ray, and an abdominal CT scan. The frequency of these tests is outlined in the algorithm on TEST-B page 1 of 3, entitled "Follow-up for Nonseminoma" (available online, in these guidelines, at NCCN.org).

Nonseminoma Stage IB

Primary Treatment of Nonseminoma Stage IB: After orchiectomy, either nerve-sparing RPLND or adjuvant chemotherapy is an option to reduce the risk of relapse in patients with stage IB disease.

Several studies using 2 cycles of BEP as primary treatment for patients with stage I nonseminoma have been reported, with relapse-free survival seen in more than 95% of patients.[91,94,97,99–102] Based on these studies, the panel considers 1 to 2 cycles of BEP as primary chemotherapy to be an option. Late consequences of cisplatin-based chemotherapy have been reported based on long-term follow-up of patients.[38,103–107] A trial by Albers et al[108] after orchiectomy randomized patients with stage I disease to undergo unilateral RPLND (n = 191) or one adjuvant course of BEP (n = 191). After a median follow-up of 4.7 years, 2 relapses were reported in the group of patients treated with one course of adjuvant BEP and in 13 patients with relapse in the arm treated with RPLND (P=.0011). This study indicates that one course of BEP is active in patients and could be an option in patients unable to tolerate the toxicity of treatment. The comparator arm in this trial (unilateral RPLND) is not the standard treatment approach. Therefore, although the results of this study are promising, this merits further investigation comparing 1 cycle of BEP versus 2 cycles with longer follow-up.

Surveillance alone may be offered to selected patients with T2 disease (category 2B). Vascular invasion is a significant predictor of relapse when orchiectomy is followed by surveillance alone.[19] Surveillance is generally not recommended for T2

disease with vascular invasion because of the 50% chance of relapse. However, exceptions are made according to individual circumstances. When surveillance is decided in select patients with T2 disease, both the patient and the physician must be compliant with follow-up recommendations.

Management of Nonseminoma Stage 1B After Primary Treatment: The adjuvant treatment after primary nerve-sparing RPLND for patients with IB disease is similar to that described for stage IA in the previous section on "Management of Nonseminoma Stage 1A After RPLND" (page 791).

In the updated NCCN Guidelines, the long-term routine follow-up tests for select patients with T2 disease undergoing surveillance and for those who underwent chemotherapy include serum marker assessment, chest x-ray, and an abdominal/pelvic CT scan. The frequency of these tests varies depending on the adjuvant management strategy, and the frequency of the tests are outlined in the algorithm on TEST-B page 1 of 3 and 2 of 3, on "Follow-up for Nonseminoma" (available online, in these guidelines, at NCCN.org).

Nonseminoma Stage IS

Patients with stage IS disease exhibit a persistent elevation of serum tumor markers after orchiectomy but no radiographic evidence of disease. The elevated levels of AFP and beta-HCG after orchiectomy must be interpreted with caution, as the reason for marker elevation might be other than disseminated nonseminoma such as hepatobiliary disease, marijuana use, and hypogonadism.

Primary Treatment of Nonseminoma Stage IS: The consensus recommendation of the NCCN Panel is that these patients be treated with standard chemotherapy with either 4 cycles of EP or 3 cycles of BEP. Both are NCCN category 1 and either regimen is preferable to initial RPLND because these patients nearly always have disseminated disease.[109,110]

Management of Stage 1S Nonseminoma After Primary Treatment: The management of patients with stage IS nonseminoma after primary treatment with chemotherapy is described in "Advanced Metastatic Nonseminoma" (next page).

Nonseminoma Stage IIA

Primary Treatment of Nonseminoma Stage IIA: Treatment for patients with stage IIA nonseminoma depends on postorchiectomy serum tumor marker levels.

For patients with normal postorchiectomy levels of AFP and HCG, the NCCN Panel considers either primary RPLND (category 2A) or chemotherapy (category 2B) as treatment options for stage IIA.[111–115] The chemotherapy regimens include 4 cycles of EP or 3 cycles of BEP. Chemotherapy is considered particularly appropriate if the patient has multifocal disease.

For patients with persistently elevated AFP or HCG levels, the panel recommends induction chemotherapy. The data supporting this come from 2 retrospective studies of patients with low-stage nonseminoma treated by RPLND.[116,117] The presence of elevated postorchiectomy AFP or HCG levels was associated with a high risk of relapse.[116,117]

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

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

The Panel considers nerve-sparing bilateral RPLND a category 2A recommendation for patients with residual mass of 1 cm or greater and category 2B if the residual mass is less than 1 cm. A bilateral RPLND involves removal of lymphatic tissue between both ureters, spanning from the diaphragmatic crus to the bifurcation of the common iliac arteries. The rationale for this extended region of dissection is the greater likelihood of bilateral disease with greater tumor burden.[118] Referral to high-volume centers must be considered for RPLND after chemotherapy. Surveillance is an option for selected patients with negative markers or patients with residual mass less than 1 cm.

After primary nerve-sparing RPLND, the treatment options include either surveillance or chemotherapy. The treatment choice depends on the number of positive lymph nodes identified. For example, since RPLND is likely a curative procedure in patients with pathologic stage N0 (pN0), surveillance is the only option listed for this group. Surveillance and chemotherapy are options for patients with pN1 and pN2 disease. RPLND is a curative procedure in 60% to 90% of pN1 patients;[117,119,120] therefore, the NCCN

Panel prefers surveillance over chemotherapy for patients with pN1 disease. The risk of relapse in patients with pN2-pN3 disease is less than 50%.[117,119,121] With 2 cycles of adjuvant cisplatin-based chemotherapy, the risk of relapse after RPLND is generally less than 1%.[117,122,123] The Panel prefers 2 cycles of adjuvant chemotherapy for pN2 disease; and full course chemotherapy (not surveillance) is recommended for pN3 disease. Recommended adjuvant chemotherapy regimens for pN1 and pN2 consists of 2 cycles of BEP or 2 cycles of EP,[124] resulting in a nearly 100% relapse-free survival rate. For pN3 disease, the Panel recommends a longer chemotherapy course consisting of either 4 cycles of EP or 3 cycles of BEP.

If patients with stage IIA disease have persistent marker elevation (ie, stage IIA, S1), the primary treatment is chemotherapy as described for good-risk nonseminoma in subsequent sections.

Nonseminoma Stage IIB

Primary Treatment of Nonseminoma Stage IIB: Treatment for patients with stage IIB nonseminoma also depends on both postorchiectomy tumor marker levels and radiographic findings. When tumor markers are negative, the CT findings determine the proper course of treatment. If abnormal radiographic findings are limited to sites within the lymphatic drainage in the retroperitoneum (ie, the landing zone), 2 management options are available. One option is to perform nerve-sparing RPLND and to consider adjuvant treatment as described for patients with stage IIA disease. The second option is to treat with primary chemotherapy with either 4 cycles of EP or 3 cycles of BEP, followed by nerve-sparing RPLND or surveillance.

Both options of primary chemotherapy or primary RPLND are comparable options in terms of outcome, but side effects and toxicity are different.[112] The reported relapse-free survival with either approach is close to 98%.[119,124–129]

If metastatic disease (based on radiographic findings) is not confined to the lymphatic drainage (ie, multifocal lymph node metastases outside the lymphatic drainage sites), chemotherapy is recommended with either 4 cycles of EP or 3 cycles of BEP, followed by nerve-sparing RPLND or surveillance.

For patients with stage IIB disease with persistent marker elevation (stage IIB, S1), the primary treatment is chemotherapy as described for good-risk nonseminoma, including stages IS, IIC, and IIIA, in subsequent sections. Initial RPLND is not recommended in this situation.

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

Advanced Metastatic Nonseminoma

The primary chemotherapy regimens of choice for patients with advanced disease depends on the IGCCCG risk classification.[21] This classification categorizes patients as good, intermediate, or poor risk.[21] Also, patients with an extragonadal primary site, whether retroperitoneal or mediastinal, are treated with initial chemotherapy.

Primary Treatment of Good-Risk Nonseminoma: Based on the IGCCCG good-risk classification, this group includes patients with stages IS, IIA, and IIB (with persistent marker elevation), IIC, and IIIA. Treatment for good-risk GCTs were designed to decrease toxicity while maintaining maximal efficacy. Randomized clinical trials showed that this can be achieved by either substituting etoposide for vinblastine[130,131] or by eliminating or reducing the dose of bleomycin.[130,132] Presently 2 regimens are recommended by the NCCN Panel: 4 cycles of EP[64] or 3 cycles of BEP[60,62,133,134] (both category 2A). Both regimens are well tolerated and cure approximately 90% of patients with good risk.[135]

Primary Treatment of Intermediaterisk (stage IIIB) Nonseminoma: For patients with intermediate risk, the cure rate is approximately 70% with standard therapy using 4 cycles of BEP.[136,137] For patients with intermediate risk (stage IIIB), 4 cycles of BEP is a category 2A recommendation by the NCCN Testicular Cancer Panel.

Primary Treatment of Poor-risk (stage IIIC) Nonseminoma: In patients with poor-risk GCTs (stage IIIC), between 20% and 30% of all patients with metastatic GCTs are not cured with conventional cisplatin therapy and less than one half experience a durable complete response to 4 cycles of BEP; therefore, treatment in a clinical trial is preferred.[135] The NCCN Panel lists enrolling these patients in clinical trials as their preferred treatment option.

The standard chemotherapy regimen for patients with poor risk is 4 cycles of BEP. The regimen

containing VIP (etoposide, ifosfamide, cisplatin) was compared with BEP and found to be more toxic but equally effective. Therefore, 4 cycles of VIP may be used for those who may not tolerate bleomycin.[138]

Postchemotherapy Management for Good-, Intermediate-, and Poor-risk Nonseminoma: At the conclusion of induction chemotherapy, CT scans of the abdomen and pelvis are indicated, along with serum tumor marker assays. PET scans for residual disease have limited predictive value.

If a complete response to chemotherapy is found using radiographic imaging and the tumor markers are negative, the NCCN Panel lists management options depending on the original stage of the disease: surveillance (category 2B) if the original stage was IS; or either surveillance (category 2A) or bilateral RPLND using nerve-sparing technique if possible (category 2B)[76] if the original stage of disease was IIA, S1, IIB, S1, IIC, or IIIA.

If there is a partial response to chemotherapy or a residual mass is found and the serum tumor markers (AFP and beta-HCG) have normalized, then all sites of residual disease are resected.[139–141] If only necrotic debris or mature teratoma is encountered, no further therapy is necessary and patients must be put under surveillance. If embryonal, yolk sac, choriocarcinoma, or seminoma elements are found in the residual mass, 2 cycles of conventionally dosed chemotherapy (EP, VelP, VIP, or TIP) are administered.

The recommended follow-up tests and their frequencies during surveillance, after chemotherapy or after bilateral RPLND, are outlined in the algorithm on page TEST-B 2 of 3, entitled "Follow-up for Nonseminoma" (available online, in these guidelines at NCCN.org). After patients are rendered disease free, standard surveillance is initiated.

Patients who experience an incomplete response to first-line therapy are treated with second-line therapy (see subsequent section). The Panel prefers that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease in conjunction with best supportive care.

Second-Line Therapy for Metastatic Germ Cell Tumors

Patients who do not experience a durable complete response to first-line therapy or those who experience a recurrence can be divided into groups with a favorable or unfavorable prognosis based on prognostic factors. Prognostic factors can be used in deciding whether a patient is a candidate for conventional dose therapy or high-dose therapy with stem cell support as a second-line option. To determine the prognosis at initial diagnosis, the IGCCCG classification is used. However, for patients with progressive or relapsed disease after first-line treatment, several prognostic models have been reported.[142–144]

Favorable prognostic factors to conventional dose second-line chemotherapy include a testicular primary site, prior complete response to first-line therapy, low levels of postorchiectomy serum tumor markers, and low-volume disease.[142] Standard second-line therapy includes conventional-dose chemotherapy or high-dose chemotherapy. The conventional-dose regimen includes cisplatin and ifosfamide combined with either vinblastine or paclitaxel.[145]

If the patient experiences an incomplete response or relapse after second-line conventional-dose chemotherapy, the preferred third-line option, if the second- line therapy included conventional-dose chemotherapy, is high-dose chemotherapy[146,147] or chemotherapy in the context of a clinical trial. A surgical salvage could be considered if the relapse is in a solitary resectable site.

Unfavorable prognostic features include incomplete response to first-line treatment, high levels of serum markers, high-volume disease, and presence of extratesticular primary tumor. Patients with a testicular primary site and rising postorchiectomy serum tumor markers during first-line therapy are usually considered for high-dose programs. Chemotherapy options for patients with poor prognostic features include chemotherapy in the context of a clinical trial; conventional-dose second-line therapy (with VeIP or TIP); and high-dose chemotherapy (category 2B). Alternatively, the patients may be put on palliative chemotherapy or salvage surgery if feasible.[148,149] High-dose regimens include high-dose carboplatin plus etoposide followed by autologous stem cell transplant[143,150] or paclitaxel, and ifosfamide followed by high-dose carboplatin plus etoposide with stem cell support.[151]

A late relapse (>2 years after completion of primary therapy) occurs in 2% *to* 3% of survivors.[152–154] The Panel prefers surgical resection, if technically feasible.[148,155,156] Conventional-dose or high-dose chemotherapy are other options for patients with late relapses.

For patients with unfavorable prognosis and late relapses who do not experience complete response to second-line high-dose therapy, the disease is nearly always incurable; the only exception is the rare patient with elevated serum tumor markers and a solitary site of metastasis (usually retroperitoneal) who undergoes surgical resection.[157] Other options are participation in a clinical trial or palliative chemotherapy.

Palliative Therapy: All patients with either persistent or recurrent disease should be considered for palliative chemotherapy or RT. The palliative chemotherapy options for patients with intensively pretreated, cisplatin-resistant, or refractory GCT are combinations of gemcitabine with paclitaxel and/or oxaliplatin,[158–163] or oral etoposide.[164]

The recommendation for gemcitabine and oxaliplatin (GEMOX) is based on data from phase II studies.[158–160] These studies investigated the efficacy and the toxicity of GEMOX in patients with relapsed or cisplatin-refractory GCTs. The results showed that GEMOX is safe for patients with cisplatin-refractory testicular GCTs and may offer a chance of long-term survival.[158–160]

Gemcitabine and paclitaxel is another option that has shown promising results in a phase II study,[162] and long-term follow-up results with this combination show long-term disease-free survival in the rare patients who experienced progression after high-dose chemotherapy and had not received prior paclitaxel or gemcitabine.[163]

A phase II study of patients with treatment-refractory germ-cell tumors found the combination of gemcitabine, oxaliplatin, and paclitaxel to be effective with acceptable toxicity.[161] In a phase II study in patients who had previous treatment with cisplatin/etoposide combination regimens, high-dose etoposide and carboplatin with autologous bone marrow transplantation showed that single-agent oral etoposide was effective.[164]

For palliative therapy, the NCCN Testicular Cancer Panel recommends GEMOX[158–160]; gemcitabine with paclitaxel[162,163]; gemcitabine with oxaliplatin and paclitaxel[161]; or oral etoposide[164] (all are category 2A recommendations).

Treatment of Brain Metastases

The prognosis of patients with brain metastasis is poor.[165,166] Primary chemotherapy (using a cisplatin-based regimen) is indicated for patients in whom brain metastases are detected and for whom data support use of RT with chemotherapy.[166,167] If clinically indicated and feasible, surgical resection of the metastasis should also be performed.

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Individual Disclosures of the NCCN Testicular Cancer Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Neeraj Agarwal, MD	Bayer HealthCare; Dendreon Corporation; GlaxoSmithKline; and Takeda Pharmaceuticals North America, Inc.	None	Exelixis Inc.; Medivation, Inc.; and Takeda Pharmaceuticals North America, Inc.	3/4/15
Clair Beard, MD	None	None	None	4/10/15
Sam Bhayani, MD	None	None	Intuitive Surgical, Inc.; and SurgiQuest, Inc.	4/12/15
Graeme B. Bolger, MD	Eli Lilly and Company; Exelixis Inc.; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; Altor BioScience Corporation; Medivation, Inc.; Seattle Genetics, Inc.; Pfizer Inc.; Roche Laboratories, Inc.; and sanofi-aventis U.S.	Onyx Pharmaceuticals, Inc.	None	4/10/15
Sam S. Chang, MD	None	None	None	4/10/15
Toni K. Choueiri, MD	Exelixis Inc.	GlaxoSmithKline; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	4/10/15
Brian A. Costello, MD, MS	Novartis Pharmaceuticals Corporation; and Synergene	None	None	5/14/15
Ithaar H. Derweesh, MD	GlaxoSmithKline	None	None	4/15/15
Shilpa Gupta, MD	None	Genentech, Inc.; Seattle Genetics, Inc.; and Pfizer Inc.	None	4/12/15
Steven L. Hancock, MD	Elekta Ltd.; and Phillips Health Care	None	None	5/14/15
Eric Jonasch, MD	GlaxoSmithKline; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	GlaxoSmithKline; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	4/10/15
Jenny J. Kim, MD	None	AstraZeneca Pharmaceuticals LP; Genentech, Inc.; AVEO Pharmaceuticals, Inc.; and GlaxoSmithKline	None	6/23/14
Timothy M. Kuzel, MD	Bayer HealthCare; Bristol-Myers Squibb Company; CureTech Ltd.; Eisai Inc.; GlaxoSmithKline; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; Alton Pharmaceuticals Inc.; Argos Therapeutics, Inc.; AVEO Pharmaceuticals, Inc.; Biovex, Inc/Amgen; and Kyowa Hakko Kirin Co., Ltd.	Bayer HealthCare; Eisai Inc.; Novartis Pharmaceuticals Corporation; and Bionomics	Celgene Corporation; Genentech, Inc.; Jannsen Pharmaceutica Products, LP; Astellas US LLC; and Medivation, Inc.	2/22/15
Elaine T. Lam, MD	Bristol-Myers Squibb Company; Exelixis Inc.; Genentech, Inc.; Argos Therapeutics, Inc.; Peloton Therapeutics, Inc.; Rexahn Pharmaceuticals, Inc.; TRACON Pharmaceuticals, Inc.; and Roche Laboratories, Inc.	Seattle Genetics, Inc.	None	4/24/15
Clayton Lau, MD	None	None	None	5/15/15
Ellis G. Levine, MD[a]	TRACON Pharmaceuticals, Inc.	None	None	4/12/15
Daniel W. Lin, MD	Genomic Health, Inc.; Myriad Genetic Laboratories, Inc.; and GenomeDx	None	Genomic Health, Inc.	4/10/15
M. Dror Michaelson, MD, PhD	Eisai Inc.; Exelixis Inc.; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Argos Therapeutics, Inc.; TRACON Pharmaceuticals, Inc.; and Pfizer Inc.	Eisai Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Astellas US LLC; and Pfizer Inc.	None	5/20/15
Robert J. Motzer, MD	Bristol-Myers Squibb Company; Eisai Inc.; Genentech, Inc.; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	4/20/15
Thomas Olencki, DO	Bristol-Myers Squibb Company; Exelixis Inc.; Genentech, Inc.; TRACON Pharmaceuticals, Inc.; and Pfizer Inc.	Genentech, Inc.	None	4/15/15
Roberto Pili, MD	Pfizer Inc.	Active Biotech AB; Genentech, Inc.; Regeneron Pharmaceuticals, Inc.; and Pfizer Inc.	None	4/12/13
Elizabeth R. Plimack, MD, MS	Bristol-Myers Squibb Company; Dendreon Corporation; Eli Lilly and Company; GlaxoSmithKline; Merck & Co., Inc.; Acceleron Pharma, Inc.; and Pfizer Inc.	Bristol-Myers Squibb Company; Dendreon Corporation; Genentech, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	3/2/15
Edward N. Rampersaud, MD	None	None	None	4/13/15
Bruce G. Redman, DO	None	None	None	4/10/15
Charles J. Ryan, MD	None	None	None	6/17/14
Joel Sheinfeld, MD	None	None	None	6/17/14
Brian Shuch, MD	None	None	None	11/25/14
Kanishka Sircar, MD	None	None	None	4/11/15
Bradley G. Somer, MD	None	None	Bayer HealthCare	4/11/15
Richard B. Wilder, MD	None	None	None	5/14/15

[a]The following of disclosed that they have an Employment/Governing Board, Patent, Equity, or Royalty conflict: Ellis G. Levine, MD: UpToDate
The NCCN Guidelines Staff have no conflicts to disclose.