

Testicular Germ Cell Tumours

Effective Date: February 2023



Background

Testicular germ cell tumours (GCTs) account for about 1% of all new cancer cases in men (age-standardized incidence rate of 5.5 per 100,000 men in Canada); however, they are the most common type of cancer in adolescents and young adults aged 15 to 29 years. There are approximately 120 new cases of all types of testicular cancer in Alberta each year, most of which are GCTs. Testicular GCTs are a highly curable type of cancer with five-year survival rates of over 95%. [\[link\]](#)

There are two main histological types of testicular GCTs: seminomas and nonseminomas. Among seminomas, the most common subtypes are classic, anaplastic, or spermatocytic. Nonseminomas can be classified as choriocarcinoma, embryonal carcinoma, teratoma, and yolk sac tumours.¹ Staging of testicular germ cell tumours is currently based on the 8th edition (2017) of the American Joint Committee on Cancer's AJCC Cancer Staging Manual. The objective of this guideline is to outline management decisions for seminomas and nonseminoma germ cell tumours of the testicle.

Questions

1. What are the appropriate management and follow-up strategies for seminomas?
2. What are the appropriate management and follow-up strategies for nonseminomas?

Search Strategy

For the 2021 update the PubMed database was searched for clinical trials relating to testicular cancer from 2016-2021. Additionally, the optimal chemotherapy duration, time to relapse, and optimal blood work for follow-up was investigated. For a full list of search strategies, see Appendix A.

Target Population

Adult patients with a diagnosis or suspicion of testicular cancer.

Recommendations

Initial diagnosis and management

Staging

- A. CT chest/abdomen/pelvis
- B. Ultrasound of scrotum to image testicles
- C. CBC and differential
- D. Creatinine.
- E. Tumour markers (β -hCG, LDH, α FP)
 - i. Should be obtained pre- and post- orchiectomy
 - ii. Staging is based on post-orchiectomy markers
- F. Brain imaging (preferably MRI) if:
 - i. Neurologic symptoms

- ii. Extensive lung metastases
- iii. Pure choriocarcinoma
- iv. B-HCG >5000 IU/L
- v. IGCCCG Poor risk disease
- G.** Bone scan if relevant symptoms
- H.** PET scans should only be used to evaluate residual masses post chemotherapy for seminoma; PET scan should not otherwise be routinely used

Treatment

- A.** Radical inguinal orchiectomy is the standard initial treatment.
- B.** In rare instances, orchiectomy can be deferred in patients with life-threatening metastatic disease when a diagnosis of NSGCT (ex. unequivocally elevated AFP and/or B-HCG >5000) or seminoma (biopsy of metastatic site) is made, so as to not delay chemotherapy. Orchiectomy can be later performed after chemotherapy.

Seminomas

T1-4, N0, M0 (Stage I Seminomas):

Primary Therapy

- A.** Management options include primary surveillance, adjuvant radiotherapy or adjuvant chemotherapy.²
- B.** Surveillance is the preferred option and is indicated for the individual who will adhere with the surveillance protocol (below).
- C.** Patients with a higher risk for recurrence (e.g. presence of a tumour >4 cm and/or rete testes involvement) should discuss risk factors with oncologists and could be offered radiotherapy; however, even patients in the high risk group have a 70-80%³ chance of being relapse free without adjuvant treatment, as such surveillance remains the preferred option.
- D.** Radiotherapy: 20-25 Gy in 10-20 fractions, to para-aortic ± ipsilateral pelvic lymph nodes (“dog leg” or “hockey stick”).
- E.** Chemotherapy (carboplatin AUC 7 x 1-2 cycles) can be considered in select cases and should be reviewed in multidisciplinary rounds.
- F.** The possibility of semen cryopreservation should be discussed.

[Follow-up \(click\)](#)

T1-4, N1-2, M0 (Stages IIA and IIB Seminomas):

Indications include retroperitoneal lymph node disease <5 cm in diameter.

- A. Stage T1-4, N1, M0, enlarged node <2 cm (Stage IIA).
- B. Stage T1-4, N2, M0, enlarged node(s) 2-5 cm (Stage IIB).

Preparation for Therapy

- A. Baseline CBC, Creatinine.
- B. Discuss semen cryopreservation with the patient.

Primary Therapy Options

- A. External-beam radiotherapy^{4, 5}
 - i. Include para-aortic and ipsilateral pelvic nodes to 20-25Gy (“dog leg” or “hockey stick”).
 - ii. Boost grossly involved nodes by 10 Gy.

- B. Chemotherapy⁶⁻⁸
 - i. Consider BEP × 3 cycles when optimal radiotherapy not possible; EP × 4 cycles may be considered in patients with contraindication to bleomycin.
 - ii. Consider BEP × 3 cycles, in extensive stage IIB disease (same as stage IIC); EP × 4 cycles may be considered in patients with contraindication to bleomycin.

Post-Therapy Evaluation

- A. P/E.
- B. Tumour markers.
- C. CXR (or CT thorax).
- D. CT abdomen/ pelvis (new baseline).

Residual Disease (see section on residual disease below)

[Follow-up \(click\)](#)

T1-4, N3, M0, T1-4, Nx, M1 (Stages IIC, and III Seminomas):

Indications include retro-peritoneal lymph node disease >5 cm in diameter, or distant metastases.

Preparation for Therapy

- A. Baseline CBC, biochemistry, liver function tests, alkaline phosphatase.
- B. Discuss semen cryopreservation with the patient.

Primary Therapy

- A. Cisplatin-based combination chemotherapy.^{7, 8, 13}
- B. Good risk as per IGCCC: BEP × 3; EP × 4 may be considered if bleomycin is contraindicated.
- C. Intermediate risk as per IGCCC: BEP × 4; VIP x 4 may be considered if contraindication to

bleomycin.

D. Consider prophylactic anticoagulation to reduce risk of venous thromboembolic disease during chemotherapy.

E. Primary prophylaxis with G-CSF is required for patients receiving ifosfamide.

Management of Residual Disease

A. If residual mass <3cm, PET scan is not recommended; patients should be surveilled.

B. If residual mass > 3 cm, consider PET scan 6-12 weeks after day 21 of the last cycle.

C. If PET is positive, cases should be reviewed in multidisciplinary rounds for discussion of best therapeutic approach. Generally, these can be observed over time, especially if mildly positive. In cases where FDG-PET remains strongly positive over time and/or the mass is growing, complete surgical resection or biopsy is the management of choice; Radiation is an option in select cases, although this has been inadequately studied.

Follow-Up:

Table 1. Seminomas Follow-up^{14, 15}

Year since treatment completion	1	2	3	4-5	7 and 9
Stage I (T _{any} ,N0,M0)	Every 6 months: P/E, CT abdo/pelvis (blood markers optional) Every 12 months: hormone levels.	Every 6 months: P/E, CT abdo/pelvis (blood markers optional)	Every 6 months: P/E, CT abdo/pelvis (blood markers optional)	Every 12 months: P/E, CT abdo* (blood markers optional)	P/E, CT abdo, hormone levels (blood markers optional)
Stage II/III (T _{any} ,N+,M0 or T _{any} ,N _{any} M1)	Every 4 months: P/E, blood markers, CXR, CT abdo/pelvis (+ chest in stage III) Every 12 months: hormone levels	Every 6 months: P/E, blood markers, CXR, CT abdo/pelvis(+ chest in stage III) Every 12 months: hormone levels	Every 12 months: P/E, blood markers, hormone levels, CXR		P/E, Blood markers, hormone levels, CXR

P/E = physical exam, CXR = chest x-ray, markers = alpha-fetoprotein (αFP), beta-human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH) hormone levels: LH (Luteinizing hormone), FSH (Follicular stimulating hormone), total testosterone

A. To reduce radiation risk/exposure, consideration of low dose CT scans is recommended where possible/feasible.

B. If abnormality with hormone testing, endocrinology and/or urology referral should be considered.

C. Unless high risk features are present (i.e. tumour size >4 cm, lymphovascular invasion, or rete testis invasion), consider discharge to primary care provider after year 5 (i.e. for year 7 and 9 surveillance).¹⁶

Nonseminoma

T1-4, N0, M0, S0 (Stage I Nonseminomas):

Indications include disease localized to testicle only and normalization of tumour markers post radical orchidectomy (t ½ = 24-48 hours for β-hCG, 5-7 days for αFP).

Primary Therapy^{18, 19}

A. Options include surveillance (see below), bilateral nerve sparing RPLND, or adjuvant chemotherapy.

C. For patients in any risk group, surveillance is the preferred option. RPLND and adjuvant BEP chemotherapy x 1 cycle are options in select cases.

- i. High risk features for relapse include pure embryonal histology, lymphovascular invasion, and rete testis invasion.¹⁶
- ii. If choosing surveillance – measuring tumour markers monthly in year one is recommended.¹⁶
- iii. If RPLND is performed and lymph node metastases are present, adjuvant chemotherapy may be considered – see section below on Stage II NSGCT.

Follow-up (click)

T1-4, N0, M0, S+ (Stage I-S) and T1-4, N+, M0 (Stage II Nonseminomas):

Indications include

A. Clinical T1-4, N0, M0, (S+): failed marker normalization post radical orchidectomy for clinical stage I disease.

B. Clinical T1-4, N+, M0:

- i. Relapsed disease in the retroperitoneal lymph nodes (RPLN) on surveillance post radical orchidectomy.
- ii. Clinical N+: RPLN+ on staging CT at presentation.
- iii. Pathologic T1-4, N+, M0: pathologic N + post RPLND (see below).

Preparation for Therapy

A. Baseline CBC and differential, biochemistry, liver function tests, alkaline phosphatase, tumor markers.

B. Discuss semen cryopreservation with the patient.

Primary Therapy Options

For Clinical Stage II-A marker-negative disease, an initial period of surveillance is recommended with an interval scan in 6-8 weeks. If the lesion is shrinking, then can proceed with observation. If stable or growing, then consider treatment.

A. Cisplatin-based combination chemotherapy²⁰⁻²² is the preferred option for Clinical Stage II-A with

markers positive and for Clinical Stage II-B, with or without marker elevation

- i. Good risk (IGCCC): BEP x 3.
 - ii. Intermediate/poor risk (IGCCC): BEP x 4; VIP x 4 may be considered if there is contraindication to bleomycin or in patients at increased risk to bleomycin induced pulmonary toxicity.
 - a. Consider complete bilateral RPLND if post chemotherapy RP masses > 1.0 cm.
 - 1. Role of consolidation chemotherapy is unclear.
 - b. Post-resection treatment depends on histology:
 - 1. Necrosis/fibrosis (40-50% of cases): surveillance.
 - 2. Teratoma (30-40% of cases): surveillance.
 - 3. Residual embryonal, yolk sac, choriocarcinoma, or seminomatous elements at RPLND (15-20% of cases): Surveillance or adjuvant chemotherapy (see below) are options, although the role of chemotherapy remains unclear.
- B.** RPLND as primary treatment can be considered for selected patients. RPLND is the preferred option for Clinical Stage II-A with negative markers
- i. Treatment options following RPLND based on pathological staging (PS); also include pathologic stage II following RPLND for clinical stage I:
 - a. Pathologic stage N0 or mature teratoma: surveillance.
 - b. Pathologic stage N1: surveillance (preferred), or adjuvant EP x 2 cycles.
 - c. Pathologic stage N2: adjuvant EP x 2 (preferred), or surveillance.
 - d. Pathologic stage N3: BEP x 3 or EP x 4 cycles.

[Follow-up \(click\)](#)

T1-4, N1-3, M+ (Stage III Nonseminomas):

Preparation for Therapy

- A.** Baseline CBC and differential, biochemistry, liver function tests, alkaline phosphatase, tumor markers.
- B.** Discuss semen cryopreservation with the patient.

Primary Therapy

- A.** Cisplatin-based combination chemotherapy is preferred:
 - i. Good risk (IGCCCG): BEP x 3 is the preferred option; EP x 4 may be considered if contraindication to bleomycin.
 - ii. Intermediate/poor risk (IGCCCG): BEP x 4; VIP x 4 may be considered if there is contraindication to bleomycin or in patients at increased risk to bleomycin induced pulmonary toxicity.
- B.** Consider prophylactic anticoagulation to reduce risk of venous thromboembolic disease during chemotherapy.
- C.** Primary prophylaxis with G-CSF is required for patients receiving ifosfamide.

- D.** Consider surgical resection of post chemotherapy RP masses >1.0 cm with normalization of tumour markers if previously elevated.
- E.** Consider resection of any residual mass in mediastinum/ lung; these sites are associated with higher risk of teratoma and viable NSGCT.
- i.** Post resection treatment depends on histology.²³
 - a.** Necrosis/fibrosis – observe.
 - b.** Teratoma – observe.
 - c.** Residual embryonal, yolk sac, choriocarcinoma, or seminomatous elements – treatment with adjuvant chemotherapy is controversial. Cases should be discussed in a multidisciplinary rounds.
- F.** Patients with brain metastases should have neurosurgical input +/- an RO consult.

Follow-Up:

Table 2. Non-Seminomas Follow-up¹⁶

Year of follow-up	1	2	3	4-5
Stage I (T1-4, N0, M0)	Every 2 months*: P/E, blood markers, CXR Every 4 months: CT abdo/pelvis Every 12 months: hormone levels	Every 3 months: P/E, blood markers, CXR Every 6 months: CT abdo/pelvis Every 12 months: hormone levels	Every 4 months: P/E, blood markers, CXR. CT as clinically indicated. Every 12 months: hormone levels	Every 6 months: P/E, blood markers, CXR. CT as clinically indicated. CT abdo/pelvis at end of year 5. Every 12 months: hormone levels
Stage II (T1-4, N+, M0)	Every 2 months: P/E, blood markers, CXR Every 4 months: CT area of disease Every 12 months: hormone levels	Every 3 months: P/E, blood markers, CXR Every 6 months: CT area of disease Every 12 months: hormone levels	Every 4 months: P/E, blood markers, CXR CT as clinically indicated. Every 12 months: hormone levels	Every 6 months: P/E, blood markers, CXR. CT as clinically indicated. CT abdo/pelvis at end of year 5. Every 12 months: hormone levels
Stage III (T1-4, N+, M+)	Every 2 months: P/E, blood markers, CXR Every 4 months: CT area of disease Every 12 months: hormone levels	Every 3 months: P/E, blood markers, CXR Every 6 months: CT area of disease Every 12 months: hormone levels	Every 4 months: P/E, blood markers, CXR CT as clinically indicated. Every 12 months: hormone levels	Every 6 months: P/E, blood markers, CXR. CT as clinically indicated. CT chest/abdo/pelvis at end of year 5. Every 12 months: hormone levels

P/E = physical exam, CXR = chest x-ray, blood markers = alpha-fetoprotein (αFP), beta-human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH), hormone levels: LH (Luteinizing hormone), FSH (Follicular stimulating hormone), total testosterone

- A.** *For patients with higher risk of relapse (i.e. lymphovascular invasion, rete testis invasion, or embryonal subtype¹⁶), measure tumour markers every month in year 1.
- B.** To reduce radiation risk/exposure, consideration of low dose CT scans is recommended where possible/feasible.
- C.** If abnormality with hormone testing, endocrinology and/or urology referral should be considered.
- D.** Years 1-3 follow-up should be conducted in a cancer centre.
- E.** Years 4-5 follow-up can be conducted in the community by their primary care provider.

Salvage Chemotherapy For Patients Relapsing Post-BEP Chemotherapy:^{7, 24-29}

Indications include

- A. Primary cisplatin refractory disease.
- B. Relapse following cisplatin-based chemotherapy.
- C. Note: consider the possibility of growing teratoma syndrome; these patients do not have relapsed viable germ cell tumour.

Primary Therapy

- A. The following discussion is limited to patients who relapse within two years of completion of their primary therapy.
- B. Patients can be divided into good and poor risk based on the following clinical and laboratory parameters at the time of relapse:

Table 3. Risk categories for patients who relapse within two years of completion.

Good Risk	Poor Risk
Gonadal Primary	Non-gonadal primary
Seminoma	Non-seminoma
CR or PR as best response to first-line chemotherapy	PR/SD/PD as best response to first line chemotherapy
Relapse > 6 months after completion of first-line chemotherapy	Relapse < 6 months after completion of first-line chemotherapy
α FP < 100	α FP > 100
β -hCG < 1000	β -hCG > 1000

- C. There are two approaches to the management of patients relapsing after primary chemotherapy
 - i. High dose chemotherapy (HDCT) and peripheral blood stem cell transplantation (PBSCT).
 - ii. Standard dose salvage chemotherapy.

Treatment is based on risk category

A. Good Risk:

- i. Standard dose chemotherapy: TIP (preferred) or VIP x 4 cycles.
- ii. For VIP/TIP failures or relapses, HDCT and PBSCT can be performed.
- iii. For patients relapsing after standard dose salvage chemotherapy, and HDCT and PBSCT can be considered for palliative chemotherapy; agents include gemcitabine, oxaliplatin, etoposide, and paclitaxel.

B. Poor Risk:

- i. Patients who are poor risk at relapse should be considered early for HDCT and PBSCT, as they may not be well enough to consider this treatment in the third line setting.
- ii. Standard dose chemotherapy: TIP or VIP x 4 cycles.

HDCT and PBSCT³⁰⁻³²

A. Refer patients to local stem cell transplant program for management of stem cell collection and transplant.

Adjunctive Care For All Patients

A. Patients with brain metastases should be referred to multidisciplinary rounds for review.

- i. Management options may include radiotherapy and/or neurosurgery.

B. After completion of all chemotherapy, resection of any residual masses should be performed.

Unique Clinical Situations

Late Relapses:

A. A late relapse is defined as relapse occurring >2 years after completion of primary chemotherapy.

B. This does not occur frequently, and as such, all cases should be reviewed in a multidisciplinary setting.

C. These patients have disease that is more chemotherapy resistant and immediate surgical resection of recurrent disease should be undertaken if feasible, irrespective of the level of tumour markers.

D. Whether or not to offer chemotherapy post-surgical resection in this setting is controversial but could be considered.

E. TIP has been used with modest success in patients who relapse late that are not surgical candidates.

Non-Testicular Germ Cell Tumours (GCT):

A. Please refer to the guidelines on extragonadal germ cell tumours and CNS germ cell tumours located here [\[link\]](#).

Appendix A. Detailed Search Strategy

Search 1: "testicular neoplasms"[MeSH Terms] OR ("testicular"[All Fields] AND "neoplasms"[All Fields]) OR "testicular neoplasms"[All Fields] OR ("testicular"[All Fields] AND "cancer"[All Fields]) OR "testicular cancer"[All Fields]

Search 2: Non-Systematic investigation into stage I seminoma patients using 1 or 2 courses of carboplatin.

Search 3: (("testicular neoplasms"[MeSH Terms] OR ("testicular"[All Fields] AND "neoplasms"[All Fields]) OR "testicular neoplasms"[All Fields] OR ("testicular"[All Fields] AND "cancer"[All Fields]) OR "testicular cancer"[All Fields]) AND ("recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "relapse"[All Fields] OR "relapses"[All Fields] OR "relapsing"[All Fields] OR "relapsed"[All Fields] OR "relapser"[All Fields] OR "relapsers"[All Fields])) AND (meta-analysis[Filter]) (Results=17)

Search 4: (("testicular neoplasms"[MeSH Terms] OR ("testicular"[All Fields] AND "neoplasms"[All Fields]) OR "testicular neoplasms"[All Fields] OR ("testicular"[All Fields] AND "cancer"[All Fields]) OR "testicular cancer"[All Fields]) AND ("recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "relapse"[All Fields] OR "relapses"[All Fields] OR "relapsing"[All Fields] OR "relapsed"[All Fields] OR "relapser"[All Fields] OR "relapsers"[All Fields])) AND (clinicaltrialphaseiii[Filter] OR meta-analysis[Filter]) (Results=27)

Search 5: (("testicular neoplasms"[MeSH Terms] OR ("testicular"[All Fields] AND "neoplasms"[All Fields]) OR "testicular neoplasms"[All Fields] OR ("testicular"[All Fields] AND "cancer"[All Fields]) OR "testicular cancer"[All Fields]) AND ("recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "relapse"[All Fields] OR "relapses"[All Fields] OR "relapsing"[All Fields] OR "relapsed"[All Fields] OR "relapser"[All Fields] OR "relapsers"[All Fields])) AND (clinicaltrialphaseiii[Filter]) (Results=10)

Search 6: Non-Systematic investigation into guideline recommendations for follow-up blood work.

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Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial GU Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial GU Tumour Team who were not involved in the guideline's development, including radiation oncologists, medical oncologists, urologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2005.

Maintenance

A formal review of the guideline will be conducted in 2023. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

αFP, Alpha fetoprotein; β-hCG, Beta-human chorionic gonadotropin; CBC, Complete blood count; CT, Computed tomography; CXR, Chest X-ray; FSH, Follicular stimulating hormone; GCT, Germ cell tumour; LDH, Lactate dehydrogenase; LH, Luteinizing hormone; P/E, Physical exam;

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GU Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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