

TESTICULAR GERM CELL TUMOURS

Effective Date: March 2016

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team 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.

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);¹ however they are the most common type of cancer in adolescents and young adults aged 15 to 29 years.² There are approximately 120 new cases of all types of testicular cancer in Alberta each year, most of which are GCTs.³ Testicular GCTs are a highly curable type of cancer with five-year survival rates of well over 90%.²

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.⁴ Staging of testicular germ cell tumours is currently based on the seventh edition (2010) of the American Joint Committee on Cancer's AJCC Cancer Staging Manual.⁵ A detailed description of the staging can be found in the Appendix. The objective of this guideline is to outline management decisions for seminomas and nonseminoma germ cell tumours of the testicle.

GUIDELINE QUESTIONS

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

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit [handbook](#). The guideline was originally developed in 2005 and then updated in the years 2007, 2009, 2011, 2012, 2013 and 2014. The follow-up recommendations were updated in March 2016.

SEARCH STRATEGY

Ovid MEDLINE and EMBASE (1965 to August 2011) and clinical practice guideline databases, including the Cochrane Library and the National Guidelines Clearinghouse, were searched for evidence relevant to this topic. For the most recent update of this guideline, the search terms 'testicular cancer' or 'seminoma' or 'nonseminoma' were used to search for clinical trials in humans, published in English between 2011 and 2012 February. A total of 20 citations were identified from the MEDLINE and EMBASE databases. Studies were excluded if they were phase I, did not include seminoma or non-seminoma patients, did not focus on treatment (i.e. pathology, genetics, etc.), were retrospective in nature without a comparison group, and did not look at survival or recurrence outcomes, and studies that were not published in English (10 citations were excluded). The literature was again updated in 2013 July using the search strategy described above. A total of 19 citations were identified; of these, four were considered relevant; however three were retrospective observational (i.e., non-comparative) studies and did not meet the inclusion criteria. Therefore, one study was included as new evidence to inform the guideline recommendations. Only minor modifications were made for the 2014 update. For the update of the follow-up recommendations, MEDLINE, EMBASE, Pubmed, and the Cochrane Library were searched using terms

related to follow-up, such as “survivorship”, “recurrence”, “continuity of patient care”, and “testicular cancer”. A total of 985 articles were retrieved, of which one was used to inform the recommendations. Recent guidelines from other developers were also reviewed.

RECOMMENDATIONS

SEMINOMAS

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

Indications include disease localized to testicle only, post-radical orchidectomy.

Management

Staging⁵

- CXR
- CT abdomen/pelvis; CT chest if positive abdominal CT or abnormal CXR.
- CBC
- Creatinine
- Tumour markers (β -hCG, LDH, α FP)

Primary Therapy

- Therapeutic options include surveillance or adjuvant chemotherapy.⁶
- Surveillance is indicated for the individual who will comply with the surveillance protocol (below)
- 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 greater than 65% chance of being relapse free without adjuvant treatment, as such surveillance remains an preferred option.
- Radiotherapy: 20-25 Gy in 10-20 fractions, to para-aortic \pm ipsilateral pelvic lymph nodes (“dog leg” or “hockey stick”).
- Chemotherapy (carboplatin AUC 7 x 2 courses) can be considered in select cases.
- The possibility of sperm banking should be discussed.

*Surveillance protocol*⁷

- Years 1-3: P/E, tumour markers, CT abdomen and pelvis every 6 months; CXR every 12 months.
- Years 4-10: P/E, tumour markers, CT abdomen every 12 months. Pelvic imaging may be added at the discretion of the physician.

Follow-up^{8,9}

Evaluation post-radiotherapy or chemotherapy (re-staging), then:

- Years 1-3: P/E, tumour markers, CT abdomen and pelvis every 6 months; CXR every 12 months.
- Years 4-10: P/E, tumour markers, CT abdomen every 12 months. Pelvic imaging may be added at the discretion of the physician.
- Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner.
- Years 4-10 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner.

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

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

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

Management

Staging

- Tumour markers (β -hCG, α FP, LDH)
- CT chest, abdomen and pelvis
- Bone scan, if clinically indicated

Preparation for Therapy

- Baseline CBC, Creatinine
- Discuss sperm banking with the patient

Primary Therapy

External-beam radiotherapy^{10,11}

- Include para-aortic and ipsilateral pelvic nodes to 20-30Gy (“dog leg” or “hockey stick”).
- Boost grossly involved nodes by 10 Gy.

*Chemotherapy*¹²⁻¹⁴

- Consider BEP \times 3 cycles when optimal radiotherapy not possible; EP \times 4 cycles may be considered in patients with contraindication to bleomycin.
- Consider BEP \times 3 cycles, in extensive stage IIB disease (same as stage IIC); EP \times 4 cycles may be considered in patients with contraindication to bleomycin.

Residual Disease

- If the residual mass >3 cm, consider a PET scan 4-12 weeks after day 21 of the last cycle.
- If PET scan is positive, decisions should be made using a multi-disciplinary approach.
- Due to the difficulty of surgical resection and radio-sensitivity of seminoma, consider biopsy and/or radiotherapy. If required, surgery can be performed in the future.

Follow-up

Post-Therapy Evaluation

- P/E
- tumour markers
- CXR (or CT thorax)
- CT abdomen/ pelvis (baseline post-RT)

Evaluation of Residual Disease

- PET scan for evaluation of residual disease.¹⁵⁻¹⁸
- If there is no residual disease, evaluate post-completion of therapy with CT abdomen/pelvis.

Post-Therapy Surveillance

- Year 1: P/E, tumour markers, CXR, CT abdomen and pelvis every 4 months.
- Year 2: P/E, tumour markers, CXR, CT abdomen and pelvis every 6 months.

- Year 3-10: P/E, tumour markers every 12 months. CXR, CT as clinically indicated.
- Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner.
- Years 4-10 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner.

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.

Management

Staging

- Tumour markers (β -hCG, α FP, LDH)
- CT chest, abdomen, pelvis
- CT head (if symptomatic)
- Bone scan, CT brain, if clinically indicated
- PET if indicated¹⁹

Preparation for Therapy

- Baseline CBC, biochemistry, liver function tests, alkaline phosphatase
- Discuss sperm banking with the patient

Primary Therapy

- Cisplatin-based combination chemotherapy.^{13,14,20}
- Good risk as per IGCCC: BEP \times 3; EP \times 4 may be considered if bleomycin is contraindicated.
- Intermediate risk as per IGCCC: BEP \times 4.

Management of Residual Disease

- If residual mass > 3 cm, consider PET scan 4-12 weeks after day 21 of the last cycle.
- If PET is positive, decisions should be made using a multi-disciplinary approach due to the difficulty of surgical resection and radio-sensitivity of seminoma. Consider biopsy and/or radiotherapy. If required, surgery can still be performed in the future.²¹

Follow-up

Evaluation post completion of therapy should include baseline restaging and then:

- Year 1: P/E, tumour markers, CXR, CT abdomen and pelvis every 4 months.
- Year 2: P/E, tumour markers, CXR, CT abdomen and pelvis every 6 months.
- Year 3-10: P/E, tumour markers every 12 months. CXR and CT as clinically indicated.
- Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner.
- Years 4-10 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner.

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).

Management

Staging²²

- Clinical history and physical
- CT abdomen/pelvis
- CXR or CT chest
- CBC
- Tumour markers (αFP, β-hCG, LDH)

Primary Therapy

- Surveillance (see below) or template RPLND; the decision for surveillance should consider the higher risk of metastatic disease in patients with pure embryonal histology and lymphovascular invasion.
- If lymph node metastases are present and completely excised, consider adjuvant chemotherapy.

Follow-up²³

Surveillance protocol

- Year 1: P/E, tumour markers, CXR every 2 months; CT abdomen and pelvis every 4 months.**
**For patients at higher risk of relapse (i.e. lymphovascular invasion, rete testis invasion, or embryonal subtype on pathology), measure tumour markers monthly in year 1.
- Year 2: P/E, tumour markers, CXR every 3 months. CT abdomen and pelvis every 6 months.
- Year 3: P/E, tumour markers, CXR every 4 months. CT as clinically indicated.
- Years 4-5: P/E, tumour markers, CXR every 6 months. CT as clinically indicated. At the end of year 5, CT abdomen and pelvis.
- If pathologically node negative post-LN dissection, the risk of relapse in the abdomen is very low. CT of the abdomen may be done at decreased frequency at physician's discretion.
- Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner.
- Years 4-5 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner.

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

Indications include:

- *Clinical T1-4, N0, M0, (S+)*: failed marker normalization post radical orchidectomy for clinical stage I disease
- *Clinical T1-4, N+, M0*:
 - a. Relapsed disease in the retroperitoneal lymph nodes (RPLN) on surveillance post radical orchidectomy
 - b. Clinical N+: RPLN+ on staging CT at presentation
 - c. Pathologic T1-4, N+, M0: pathologic N + post RPLND (see below)

Management

Staging²²

- Tumour markers (αFP, β-hCG, LDH)
- CT chest, abdomen, and pelvis
- Bone scan, CT brain, if clinically indicated

Preparation for Therapy

- Baseline CBC, biochemistry, liver function tests, alkaline phosphatase
- Discuss sperm banking with the patient

Primary Therapy

- Cisplatin-based combination chemotherapy.²⁴⁻²⁶
 - Good risk (IGCCC): BEP x 3
 - Intermediate/poor risk (IGCCC): BEP x 4; VIP may be considered if there is contraindication to bleomycin or in patients at increased risk to bleomycin induced pulmonary toxicity.
- Consider complete bilateral RPLND if post chemotherapy RP masses > 1.0 cm.
- Role of consolidation chemotherapy is unclear. Post-resection treatment depends on histology:
 - Necrosis/fibrosis (40-50% of cases): observe
 - Teratoma (30-40% of cases): observe
 - Residual embryonal, yolk sac, choriocarcinoma, or seminomatous elements (15-20% of cases): adjuvant chemotherapy with EP x 2, TIP x 2, or VIP x 2
- RPLND as primary treatment can be considered for selected clinical stage IIA patients with normal markers, ipsilateral LN within landing zone, patient's preference or refusal of chemotherapy.
 - Treatment options following RPLND based on pathological staging (PS); also include pathologic stage II following RPLND for clinical stage I:
 - Pathologic stage N0 or mature teratoma: observe
 - Pathologic stage IIA: observation preferred, may use adjuvant EP x 2 or BEP x 2
 - Pathologic stage IIB: adjuvant EP x 2 or BEP x 2
 - Pathologic stage IIC: primary chemotherapy as for good risk disease

Follow-up

Evaluation post chemotherapy or RPLND should include baseline restaging and then:

- Year 1: P/E, tumour markers, CXR every 2 months. CT every 4 months of area of known disease based on IGCCC risk group.
- Year 2: P/E, tumour markers, CXR every 3 months. CT every 6 months of area of known disease based on IGCCC risk group.
- Year 3: P/E, tumour markers, CXR every 4 months. CT as clinically indicated based on IGCCC risk group.
- Years 4-5: P/E, tumour markers, CXR every 6 months. CT as clinically indicated. At the end of year 5, CT abdomen and pelvis.
- Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner.
- Years 4-5 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner.

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

Indications include presenting with distant metastatic disease.

ManagementStaging⁵

- Tumour markers (αFP, β-hCG, LDH)
- CT abdomen/pelvis
- CT chest
- Bone scan, CT brain, if clinically indicated

Preparation for Therapy

- Baseline CBC, biochemistry, liver function tests, alkaline phosphatase
- Discuss sperm banking with the patient

Primary Therapy

- Cisplatin-based combination chemotherapy is preferred:
 - a. Good risk (IGCCC): BEP × 3 or EP × 4 may be considered if contraindication to bleomycin.
 - b. Intermediate/poor risk (IGCCC): BEP × 4; VIP may be considered if there is contraindication to bleomycin or in patients at increased risk to bleomycin induced pulmonary toxicity.
- Consider surgical resection of post chemotherapy RP masses >1.0 cm or <90% volume shrinkage from pre-chemotherapy size with normalization of tumour markers if previously elevated.
- Consider resection of any residual mass in mediastinum/ lung; these sites are associated with higher risk of teratoma and viable NSGCT.
- PET remains investigational due to high false negative rate and difficulty in detecting mature teratoma in studies.
- Post resection treatment depends on histology.²⁷
 - a. Necrosis/fibrosis – observe
 - b. Teratoma – observe
 - c. Residual embryonal, yolk sac, choriocarcinoma, or seminomatous elements - chemotherapy with EP × 2, TIP × 2, or VIP × 2
- Patients with brain metastases should be given whole brain radiotherapy (to be given up-front while chemo-therapy is ongoing) ± neurosurgical opinion for isolated disease.

Follow-up

Post chemotherapy or surgical intervention should include baseline restaging and then:

- Year 1: P/E, tumour markers, CXR every 2 months. CT area of known disease every 4 months based on IGCCC risk group.
- Year 2: P/E, tumour markers, CXR every 3 months. CT area of known disease every 6 months based on IGCCC risk group.
- Year 3: P/E, tumour markers, CXR every 4 months. CT as indicated based on IGCCC risk group.
- Years 4-5: P/E, tumour markers, CXR every 6 months. CT as clinically indicated. At the end of year 5, CT abdomen and pelvis.
- Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner.
- Years 4-5 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner.

SALVAGE CHEMOTHERAPY FOR PATIENTS RELAPSING POST-BEP CHEMOTHERAPY ^{13,28-33}

Indications include:

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

Management
Staging ²²

- CT chest
- CT abdomen/pelvis
- CBC
- Chemistry profile including: electrolytes, creatinine, albumin, alkaline phosphatase, ALT, total protein, LDH, α FP, β -hCG
- CT head and bone scan if clinically indicated

Primary Therapy

The following discussion is limited to patients who relapse within two years of completion of their primary therapy.

Patients can be divided into good and poor risk based on the following clinical and laboratory parameters at the time of relapse:

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

There are two approaches to the management of patients relapsing after primary chemotherapy:

- Standard dose salvage chemotherapy
- High dose chemotherapy (HDCT) and peripheral blood stem cell transplantation (PBSCT)

Treatment is based on risk category:

- *Good Risk:*
 - Standard dose chemotherapy: TIP or VIP x 4 cycles.
 - For VIP/TIP failures or relapses, HDCT and PBSCT can be performed.
 - 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.

- **Poor Risk:**
 - Standard dose chemotherapy: TIP or VIP x 4 cycles
 - 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.

HDCT and PBSCT ³⁴⁻³⁶

- Prior to HDCT and PBSCT, standard dose chemotherapy should be administered to debulk the tumour and facilitate stem cell collection.
 - 1-2 cycles of chemotherapy may be administered depending on how quickly the stem cell transplantation procedure can be undertaken.
 - Regimens used to debulk may include VIP or TIP; ifosfamide, carboplatin, and etoposide (ICE) have also been used.
- The conditioning regimen for the transplant should consist of high dose carboplatin and etoposide.
- Enough stem cells should be collected in order to conduct a tandem transplant.

ADJUNCTIVE CARE FOR ALL PATIENTS

- Patients with brain metastases should be given whole brain radiotherapy concurrently while chemotherapy is ongoing. Neurosurgical opinion for isolated metastases may also be considered.
- After completion of all chemotherapy, resection of any residual masses should be performed.

UNIQUE CLINICAL SITUATIONS

Late Relapses

- A late relapse is defined as relapse occurring >2 years after completion of primary chemotherapy.
- 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.
- Whether or not to offer chemotherapy post surgical resection in this setting is controversial but could be considered.
- TIP has been used with modest success in patients who relapse late that are not surgical candidates.

Non-Testicular Germ Cell Tumours (GCT)

Please refer to the guidelines on extragonadal germ cell tumours ³⁷ and CNS germ cell tumours. ³⁸

DISCUSSION

Seminoma

A recent review of the literature by Cancer Care Ontario concluded that post-orchidectomy treatment does not impact survival in stage I seminoma and that survival rates are over 95%, regardless of whether patients receive adjuvant radiotherapy, adjuvant chemotherapy, or surveillance only.⁶ In the interest of limiting toxicity or preventing the induction of secondary cancers, surveillance may be the preferred option;^{6,8,39,40} however, the patient must be compliant with the recommended surveillance protocol. The SWENOTECA study reported recurrence rates of 14.3% in stage I patients receiving surveillance alone (versus 3.9% with carboplatin and 0.8% with radiotherapy).³⁹ Similar results have been reported elsewhere.^{41,42} Even among high risk patients (e.g. tumour >4 cm and/or rete testes involvement), the risk of recurrence with surveillance alone is less than 35%.⁴³ If radiotherapy is given, it should be delivered as

20-25 Gy in 10-20 fractions to the para-aortic lymph nodes, plus or minus the ipsilateral pelvis lymph nodes (e.g. “dog leg” or “hockey stick”). If carboplatin is given, which should only be in select cases, it should be administered as carboplatin (AUC 7 x 2 courses).

With nodal involvement, primary therapy of seminoma should consist of external-beam radiotherapy (20-30 Gy) to the para-aortic nodes and ipsilateral pelvic nodes (e.g. “dog leg” or “hockey stick”).^{10,11} Disease free survival at three years, in stage IIA and IIB patients treated with radiotherapy, has reached 89%.¹¹ Relapse free survival at 5 years is also excellent: 91.7% for stage IIA and 89.7% for stage IIB patients.⁴⁴ Radiotherapy is often followed by a boost of 10 Gy to grossly involved nodes.^{8,11} Three cycles of bleomycin, etoposide, and cisplatin (BEP) remains the standard chemotherapy regimen when radiotherapy is not an option.¹²⁻¹⁴ Four cycles of etoposide and cisplatin (EP) can be given in patients with a contraindication to bleomycin; however, overall survival at eight years was better in patients receiving three cycles of BEP (92% vs. 83%; hazard ratio of death = 0.38, 95% CI=0.15-0.97; P=.037).⁴⁵

Primary therapy in advanced stage seminoma consists of cisplatin-based combination chemotherapy: three cycles of BEP for good risk patients with substitution of four cycles of EP permitted if bleomycin is contraindicated; and four cycles of BEP for intermediate risk patients.^{13,14,20} Etoposide (165 mg/m² days 1 to 3 or 100 mg/m² on days 1 to 5) and cisplatin (35mg/m² days 1 to 3 or 20 mg/m² on days 1 to 5) every 21 days resulted in a complete response for 92.7% (76 of 82 patients). Of these patients, 72 responded to chemotherapy alone, while four responded to chemotherapy plus complete excision of residual viable GCT; with a median follow-up of 63 months, 87% (71 of 82 patients) were disease free.¹³

For residual disease larger than 3 cm and PET scan-confirmed disease, the recommended treatment strategy is to incorporate a multi-disciplinary approach involving the use of biopsy and/or radiotherapy, with possibility of salvage surgery at a later date.²¹ In post-chemotherapy patients with advanced seminoma who underwent either complete resection of tumour and of surrounding lymph nodes (n=32) or multiple biopsies (n=23), following detection of a mass by CT, success of resection was dependent on how well the tumour was defined. Of 27 patients with a post-chemotherapy mass larger than 3 cm on CT, eight patients (30%) had residual tumour. Resection was performed in 78% of patients with well-defined masses on CT and 44% of patients with poorly-defined masses on CT.²¹

Nonseminomas

Cisplatin-based combination chemotherapy is the standard of care in the management of nonseminoma. In good-prognosis metastatic nonseminoma patients (n=395), who received four cycles of cisplatin (20 mg/m² on days 1 to 5) plus etoposide (120 mg/m² on days 1, 3, and 5), with or without bleomycin (30 mg weekly), complete responses were achieved in 95% (189 of 200 patients) and 87% (169 of 195 patients), respectively (P=.0075), with chemotherapy alone or after post-chemotherapy surgery. Two patients treated with BEP died of bleomycin pulmonary toxicity.²⁶ Similar results were observed in patients with disseminated germ cell tumors (n=171): as compared to three cycles of cisplatin (20 mg/m² on days 1 to 5 or 35mg/m² days 1 to 3) plus etoposide (100 mg/m² on days 1 to 5 or 165mg/m² days 1 to 3) followed by surgical resection, the addition of bleomycin (30 IU/wk for 9 consecutive weeks) resulted in significantly better rates of failure-free status (86% vs. 69%; P=.01) and overall survival (95% vs. 86%; P=.01).²⁵ Efforts have been made to reduce the number of cycles of chemotherapy and have shown favorable results. The SWENOTECA trial⁴⁶ showed that in patients with no vascular invasion, recurrence rates with one cycle of bleomycin, etoposide, and cisplatin (BEP) were only 1.3% (vs. 0% for 2 cycles and 11.5% for no treatment); in patients with vascular invasion, one cycle of BEP resulted in a recurrence rate of 3.2% (vs. 0% for 2 cycles and 41.7% for no treatment).

In clinical stage I patients with pathologic stage II disease, retroperitoneal lymph node dissection (RPLND) alone is curative in 50% to 90% of cases.^{24,47-49} RPLND is recommended for all patients with initial bulky metastases (3 cm or larger in diameter) in the retroperitoneum, regardless of the findings on post-therapy follow-up.^{27,50} Furthermore, the presence of vascular invasion is also being considered as an indication for RPLND, as the risk of micrometastases increased from 15% in clinical stage I nonseminoma without vascular invasion to 50% in clinical stage I nonseminoma with vascular invasion. For the latter, one of the treatment options is RPLND (with chemotherapy, if positive LN).⁵¹ In patients with late relapse, RPLND can be used as salvage treatment in patients who are resistant to chemotherapy.⁵⁰

Stage I patients treated with orchidectomy alone have high cure rates overall. A large cohort study of 1,226 patients found an overall relapse rate of 30.6% at five years after orchidectomy and identified specific risk factors associated with relapse: rete testis invasion, vascular invasion, and presence of embryonal carcinoma.²³ Patients with all three identified factors had a 50% five-year risk of relapse, those with only vascular invasion had an 18% risk, and those with no factors had a 12% risk. The authors proposed a risk-adapted surveillance protocol, which has been adapted for the above recommendations.²³

Salvage Treatment

Salvage treatment consists of four cycles of standard dose chemotherapy with paclitaxel, ifosfamide, cisplatin (TIP) or vinblastine, ifosfamide, cisplatin (VeIP). Following failure of VeIP or TIP, HDCT and PBSCT can be performed. Among patients (n=135) with progressive, disseminated GCTs after treatment with cisplatin and etoposide, VeIP salvage chemotherapy every 21 days resulted in the achievement of disease-free status in 67 patients (49.6%).²⁸ In patients with relapsed GCTs, four cycles of TIP salvage chemotherapy every 21 days with granulocyte colony-stimulating factor, followed by resection of the residual tumour, resulted in a complete response rate of 77% (23 of 30 patients), with only two recurrences at a median follow-up of 33 months.⁵²

Following salvage therapy with one to two cycles of standard dose VeIP or TIP chemotherapy, high dose chemotherapy and peripheral blood stem cell transplantation may be used to treat recurrent disease. High dose carboplatin and etoposide have been used.^{29-35,53,54} In patients with recurrent seminoma (n=48), high-dose carboplatin and etoposide followed by PBSCT resulted in a complete response rate of 79% (38 of 48 patients) and an overall survival rate of 75% at a median follow-up of 45.6 months.⁵⁴ The addition of cyclophosphamide has been shown to cause severe myelosuppression and treatment-related deaths in 12% of patients³⁶ as well as cases of cardiomyopathy⁵⁵ and neutropenic colitis.^{56,57} A prospective trial comparing one cycle of VIP (cisplatin, 100 mg/m²; etoposide, 375 mg/m²; ifosfamide, 6 g/m²) plus three cycles of high-dose CE (carboplatin, 1500 mg/m²; etoposide, 1500 mg/m²) versus three cycles of VIP plus one cycle of high-dose CEC (carboplatin, 2200 mg/m²; etoposide, 1800 mg/m²; cyclophosphamide, 6400 mg/m²), both of which were followed by autologous stem-cell reinfusion, demonstrated similar outcomes. Patients with relapsed or refractory GCT (n=211) were randomly assigned; however, the study was stopped early because of excess treatment-related mortality in the CEC group (14% vs. 4%; p=.01). Progression-free survival (5-year) did not differ between groups (47% in the CE group vs. 45% in the CEC group; p=.454). Overall survival (5-year) differed between groups, but not significantly (49% in the CE group vs. 39% in the CEC group; p=.057).⁵⁸ Therefore, high dose chemotherapy should be limited to a platinum-etoposide combination only.

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services, Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
αFP or AFP	alpha fetal protein
ALT	alanine transaminase
AUC	area under the curve
BEP	bleomycin, etoposide, cisplatin
CBC	complete blood count
CBCD	CBC, differential
CNS	central nervous system
CR	Complete response
CS	clinical stage
CT	computed tomography
CXR	chest x-ray
EP	etoposide, cisplatin
GCT	germ cell tumours
Gy	unit of radiation dosage
β-hCG	beta human chorionic gonadotropin
HDCT	high dose chemotherapy
ICE	ifosamide, carboplatin, etoposide
IGCCC	International Germ Cell Consensus Classification
LDH	lactate dehydrogenase
LN	lymph node
NCCN	National Comprehensive Cancer Network
PBSCT	peripheral blood stem cell transplantation
P/E	physical evaluation
PET	positron emission tomography
PR/SD/PD	partial response, stable disease, progressive disease
PS	pathological stage
RP	retroperitoneal
RPLN	retroperitoneal lymph node
RT	radiation therapy
TIP	paclitaxel, ifosamide, cisplatin
VeIP	vinblastine, ifosamide, cisplatin
VIP	etoposide, ifosamide, platinum

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APPENDIX A: Cancer Staging Manual (American Joint Committee on Cancer, 2010)

Primary Tumour (T)

Tx: primary tumour cannot be assessed

T0: No evidence of primary tumour (e.g. histologic scar in testis)

Tis: Intratubular germ cell neoplasia (carcinoma in situ)

T1: Tumour limited to the testis and epididymis without vascular/lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis

T2: Tumour limited to the testis and epididymis with vascular/lymphatic invasion, or tumour extending through the tunica albuginea with involvement of the tunica vaginalis

T3: Tumour invades the spermatic cord with or without vascular/lymphatic invasion

T4: Tumour invades the scrotum with or without vascular/lymphatic invasion

Regional Lymph Nodes (N)

Nx: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis with a lymph node mass ≤ 2 cm in greatest dimension and ≤ 5 nodes positive, none > 2 cm in greatest dimension

N2: Metastasis with a lymph node mass > 2 cm but not > 5 cm in greatest dimension; or > 5 nodes positive, none > 5 cm; or evidence of extranodal extension of tumour

N3: Metastasis with a lymph node mass > 5 cm in greatest dimension

Distant Metastasis (M)

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis

M1a: Non-regional nodal or pulmonary metastasis

M1b: Distant metastasis other than to non-regional lymph nodes and lung

Serum Tumour Markers (S) (*N indicates the upper limit for normal for the LDH assay*)

SX: Marker studies not available or not performed

S0: Marker study levels within normal limits

S1: LDH $< 1.5 \times N$ **AND** β -hCG (mIU/ml) < 5000 **AND** AFP (ng/ml) < 1000

S2: LDH $1.5-10 \times N$ **OR** β -hCG (mIU/ml) $5000-50,000$ **OR** AFP (ng/ml) $1000-10,000$

S3: LDH $> 10 \times N$ **OR** β -hCG (mIU/ml) $> 50,000$ **OR** AFP (ng/ml) $> 10,000$

APPENDIX B: International Germ Cell Consensus for Nonseminoma (IGCCC)

Good Prognosis: Max = 0

Testis/retroperitoneal primary site=0 **AND** No non-pulmonary visceral metastases=0 **AND** AFP good=0 **AND** β -hCG good=0 **AND** LDH good=0

Intermediate Prognosis: Max = 1

Testis/retroperitoneal primary site=0 **AND** No non-pulmonary visceral metastases=0 **AND** AFP intermediate=1 **OR** β -hCG intermediate=1 **OR** LDH intermediate=1

Poor Prognosis: Max = 2

Mediastinal primary site=2 **OR** Non-pulmonary visceral metastases=2 **OR** AFP poor=2 **OR** β -hCG poor=2 **OR** LDH poor=2

APPENDIX C: Follow-up Schedule Post-Treatment
Stage I Seminoma (T1-4, N0, M0)

Year since treatment completion	Month 6	Month 12
1	<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo/ pelvis	<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo/ pelvis <input type="checkbox"/> Chest x-ray
2	<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo/ pelvis	<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo/ pelvis <input type="checkbox"/> Chest x-ray
3	<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo/ pelvis	<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo/ pelvis <input type="checkbox"/> Chest x-ray
4		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo*
5		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo*
6		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo*
7		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo*
8		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo*
9		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo*
10		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> CT abdo*

*May add pelvic imaging at physicians discretion

Tumour markers: AFP, b-HCG, and LDH

Stage II/III Seminoma

Year since treatment completion	Month 4	Month 6	Month 8	Month 12
1	<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> Chest x-ray <input type="checkbox"/> CT abdo/ pelvis		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> Chest x-ray <input type="checkbox"/> CT abdo/ pelvis	<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> Chest x-ray <input type="checkbox"/> CT abdo/ pelvis
2		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> Chest x-ray <input type="checkbox"/> CT abdo/ pelvis		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> Chest x-ray <input type="checkbox"/> CT abdo/ pelvis
3		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> Chest x-ray <input type="checkbox"/> CT abdo/ pelvis		<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers <input type="checkbox"/> Chest x-ray <input type="checkbox"/> CT abdo/ pelvis
4				<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers [†]
5				<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers [†]
6				<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers [†]
7				<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers [†]
8				<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers [†]
9				<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers [†]
10				<input type="checkbox"/> Physical exam <input type="checkbox"/> Tumour markers [†]

[†]Chest x-ray and CT as clinically indicated

Tumour markers: AFP, b-HCG, and LDH

Stage I Non-Seminoma (T1-4, N0, M0, S0)

Year since treatment completion	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
1*		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-AP		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-AP		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-AP
2			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-AP			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-AP
3**				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR
4**						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR
5**						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-AP

P/E = Physical exam; TM = tumour markers (AFP, b-HCG, LDH); CXR = chest x-ray; CT-AP = CT abdominal & pelvis

*For patients with higher risk of relapse (i.e. lymphovascular invasion, rete testis invasion, or embryonal subtype), measure tumour markers every month in year 1.

** CT as clinically indicated

Stage I/II Non-Seminoma (T1-4, N0, M0, S+ and T1-4, N+, M0)

Year since treatment completion	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
1		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz
2			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz
3*				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR
4*						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR
5*						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-AP

P/E = Physical exam; TM = tumour markers (AFP, b-HCG, LDH); CXR = chest x-ray; CT-AP = CT abdominal & pelvis; CT-dz = CT area of known disease

* CT as clinically indicated

Stage III Non-Seminoma (T1-4, N1-3, M+)

Year since treatment completion	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
1		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR		<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz
2			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR			<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-dz
3*				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR				<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR
4*						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR
5*						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR						<input type="checkbox"/> P/E <input type="checkbox"/> TM <input type="checkbox"/> CXR <input type="checkbox"/> CT-AP

P/E = Physical exam; TM = tumour markers (AFP, b-HCG, LDH); CXR = chest x-ray; CT-AP = CT abdominal & pelvis; CT-dz = CT area of known disease

* CT as clinically indicated