

About the Authors



Deepro Chowdhury, MD, FRCPC

Dr. Deepro Chowdhury is a clinical research fellow in genitourinary and thoracic malignancies at Princess Margaret Cancer Centre. He graduated from Carleton University with a combined honours in Humanities and Biology before pursuing his medical degree at the Michael G. DeGroot School of Medicine in Hamilton, Ontario. He completed his internal medicine and medical oncology residencies at the University of Ottawa. His research interests include real-world evidence analyses as well as the use of biomarkers to guide clinical decision-making. He was awarded a Hold'Em For Life Grant to explore the use of circulating tumour DNA to guide clinical decision-making in advanced urothelial cancer.

Affiliations: Princess Margaret Cancer Centre, Division of Medical Oncology and Hematology



Rachel Glicksman, MD, MSC, FRCPC

Dr. Rachel Glicksman is a Radiation Oncologist at Princess Margaret Cancer Centre, University Health Network and Assistant Professor in the Department of Radiation Oncology at the University of Toronto. Dr. Glicksman received her MD degree from Queen's University, MSc degree from University of Toronto and completed residency at the University of Toronto.

Affiliations: Princess Margaret Cancer Centre, Department of Radiation Oncology



Robert J. Hamilton, MD, MPH, FRCSC

Dr. Hamilton is a urologic oncologist at Princess Margaret Cancer Centre and Associate Professor in the Department of Surgery (Urology) at the University of Toronto, Canada. His clinical and research interests are in prostate cancer and testicular cancer. In prostate cancer, he is exploring the role of pharmacogenomics to personalize chemoprevention, with a particular interest in statin medications. He also has interests in oligometastatic disease and molecular imaging modalities. In testicular cancer his interests include novel biomarkers and studying means to minimize treatment morbidity. Dr. Hamilton trained at the University of Toronto; completed a Masters of Public Health at The University of North Carolina at Chapel Hill and a research fellowship at Duke University. He completed a fellowship at Memorial Sloan-Kettering Cancer Centre.

Affiliations: Princess Margaret Cancer Centre, Department of Urology



Di Maria Jiang, MD, MSc, FRCPC

Dr. Maria Jiang is a GU medical oncologist at Princess Margaret Cancer Center (PM) and an Assistant Professor at University of Toronto. She received her Medical Oncology Residency in Toronto, fellowship at PM, and Master of Science degree in Clinical Epidemiology at the Harvard School of Public Health. Her research interest includes the use of targeted therapies in GU malignancies. Dr. Jiang has received multiple research grant awards and is developing several investigator initiated trials. She has also received the Medical Oncology Training Program outstanding teaching award, nominated by residents.

Affiliations: Princess Margaret Cancer Centre, Division of Medical Oncology and Hematology

Management of Stage I–II Testicular Germ Cell Tumours: Current Treatment Paradigm and Future Perspectives

Deepro Chowdhury, MD, FRCPC
Rachel Glicksman, MD, MSc, FRCPC
Robert J. Hamilton, MD, MPH, FRCSC
Di Maria Jiang, MD, MSc, FRCPC

Introduction

Testicular cancer is the most common solid tumour in males aged 15–44 years, with an estimated 1,300 new cases in Canada in 2024.¹ Over 90% are germ cell tumours (GCTs) originating from spermatocyte precursors, with most arising in the testes.² Risk factors include cryptorchidism, gonadal dysgenesis, genetic syndromes such as Klinefelter syndrome, family history, and possibly cannabis use.²

This review summarizes the evidence-based diagnosis and management strategies of clinical stage I (CSI) and II (CSII) testicular GCTs used at the Princess Margaret Cancer Centre (PM), highlighting potential clinical pitfalls and future directions.³

Workup, Diagnosis, and Staging

Most testicular GCTs present as a palpable testicular mass. Radical orchiectomy serves both diagnostic and therapeutic purposes. Pre- and post-orchiectomy tumour markers (TMs) and computed tomography (CT) chest abdomen pelvis should be obtained.⁴

Staging Classification

Testicular GCTs are staged using the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging (**Table 1**), which considers primary tumour extent, lymph node involvement, metastatic sites, and post-orchiectomy serum TM levels (S).⁵ A potential pitfall is using pre-orchiectomy TMs for staging, which can lead to over- or under-treatment.

Histologic Classification and Tumour Markers

GCTs are classified as pure seminomas (45%) or non-seminomas (NSGCTs, 55%) based on histology to guide prognosis and management.⁴ NSGCTs include embryonal carcinoma (EC), yolk sac tumour, choriocarcinoma, and teratoma.⁶

Pure seminomas do not secrete alpha-fetoprotein (AFP) but can produce some human chorionic gonadotrophin in the blood (B-HCG) with syncytiotrophoblast differentiation. Rising AFP should be treated as NSGCT, even if pathology reports pure seminoma. Choriocarcinomas secrete B-HCG, yolk sac tumours secrete AFP, while EC may result in modest elevations of both. Teratomas are generally marker-negative but may secrete some AFP. Due to its low specificity,⁷ LDH alone should not guide treatment decisions for early-stage GCT.⁴

A potential clinical pitfall is basing treatment decisions on persistent low-level TM elevations, without considering false positives. AFP may be elevated in the 10–15 ng/mL range due to heterophile antibodies, liver dysfunction, or hereditary factors.^{8,9} B-HCG may show false positives due to hypogonadism, heterophile antibodies, marijuana use, or certain medications.¹⁰ A consistent rise in TMs helps differentiate active GCT from false positives.

Management of Stage I-II Seminoma

With appropriate management, patients with CSI-CSII seminoma have long-term survival rates approaching 100% (Table 2), highlighting the need to minimize overtreatment and unnecessary toxicity. At PM, patients are managed in the Multidisciplinary Testes Clinic, which involves experienced uro-oncologists, radiation, and medical oncologists.

CSI Seminoma

Approximately 85% of patients with CSI seminoma are cured with orchiectomy alone.¹¹ Historically, rete testes invasion (RTI) and a primary tumour size of ≥ 4 cm were considered risk factors for relapse,¹² although not consistently validated.¹¹ A recent multicentre study refined risk stratification using lymphovascular invasion (LVI) and three categories of tumour size (<2 cm, >2–5 cm, or >5 cm). Five-year relapse rates were

8% in very low-risk, 20% in low-risk, and 44% in high-risk disease.¹³ Only 2.3% of patients had high-risk disease.

Another Danish nationwide study identified elevated preorchietomy b-HCG, LDH, testicular hilum invasion and LVI as independent risk factors, with five-year relapse rates ranging from 6% (no-risk factors) to 62% (all four risk factors), although only 10% of patients had 3 or 4 risk factors. These contemporary models require further external validation.¹⁴

Active Surveillance for CSI Seminoma

Active surveillance is preferred for patients with CSI seminoma.⁴ Most relapses (95%) occur in retroperitoneal lymph nodes (RPLNs), mainly within the first two years (73%).¹⁵ Virtually all patients who relapse can be cured with subsequent radiation or chemotherapy (Table 2).

Our published surveillance protocol includes physical examination, including the contralateral testicle, bloodwork, and low-dose CT scans without intravenous (IV) contrast. CTs of the abdomen and pelvis are obtained every 6 months until year 3, CT abdomen only at years 4, 5, 7, and 9, and chest X-ray at year 9 (see Table 3).¹⁶

Use of magnetic resonance imaging (MRI) versus contrast-enhanced CT and fewer (three total) versus more (seven) scans were explored in the Phase III TRISST trial.¹⁷ MRI was non-inferior, but fewer scans resulted in numerically higher, though not statistically significant, rates of Stage $\geq$ IIC relapse (2.8% versus 0.3%) requiring chemotherapy. At PM, we use non-contrast low-dose CT to minimize radiation exposure, eliminate IV access, and shorten imaging time, with excellent outcomes.¹⁸ Due to the numerically higher advanced relapse rate with three scans, and limited accessibility of MRI, our surveillance protocol remains unchanged.

Adjuvant Radiotherapy for CSI Seminoma

Adjuvant radiotherapy (20 Gy in 10 fractions or 25 Gy in 20 fractions to the para-aortic lymph nodes with or without ipsilateral pelvic lymph nodes) reduces the relapse risk for CSI seminoma from 15–20% to 5%.^{19–21} However, most patients are cured with orchiectomy alone. Given the high likelihood of cure upon relapse (with radiotherapy or chemotherapy), adjuvant radiotherapy carries risk of overtreatment for most patients and is therefore not the favoured approach. Toxicities include fatigue, nausea, vomiting, peptic ulcer disease, infertility, cardiovascular disease,^{22–24}

and secondary malignancies (standardized incidence ratio [SIR]: 1.62, 95% confidence interval [CI]: 1.43–1.83).²⁵ Additionally, continued surveillance of the abdomen and pelvis (if not treating ipsilateral pelvis) remains necessary.

Adjuvant Chemotherapy for CSI Seminoma

One cycle of adjuvant carboplatin (AUC 7) reduces relapse risk in CSI seminoma comparably to adjuvant radiotherapy (see **Table 2**). The MRC TE19/EORTC 30982 study showed long-term relapse-free survival (RFS) for both modalities, with a lower risk of contralateral testicular relapse in the carboplatin group (relapse rate in contralateral testicle 0.2% versus 1.2% in favour of adjuvant carboplatin).²⁶ The SWENOTECA study reported relapse rates of 15.5% with surveillance versus 9.3% with adjuvant carboplatin in patients with one or more risk factors.²⁷ Despite a risk-adapted strategy, adjuvant carboplatin likely leads to overtreatment and unnecessary toxicity, including fatigue, myelosuppression, infection, nausea, and vomiting. Secondary malignancies (SIR: 0.96, 95% CI: 0.26–2.45) and rarely cardiovascular disease (SIR: 1.44, 95% CI: 0.39–3.69).²⁸ Therefore it is not the preferred approach at PM. Relapses after adjuvant carboplatin may also have more aggressive tumour biology.²⁹

CSII Seminoma

Up to 30% of CSIIA seminomas have benign (pN0) RPLNs, which may regress spontaneously.³⁰ Short-interval imaging (6–8 weeks) and TM reassessment can help avoid this pitfall.^{4,31} Treatment should proceed only if metastatic RPLNs are unequivocal (enlarging, rising TMs or confirmed on biopsy).⁶

Definitive Radiotherapy for CSIIA or CSIIB Seminoma

Radiotherapy delivered to the para-aortic lymph nodes and ipsilateral pelvic lymph nodes known as the “dog-leg” or “modified dog-leg” approach using 3-dimensional conformal radiotherapy (20–25 Gy to the entire volume with a boost to gross disease to a total dose of 30–36 Gy) is preferred for CSIIA/B seminoma due to lower toxicity compared to chemotherapy, and excellent long-term outcomes (**Table 2**).³² National Comprehensive Cancer Network (NCCN) guidelines suggest a 3 cm cut-off in the trans-axial axis,³³ but recent data suggest low relapse rates with radiation even with RPLNs >5 cm in

select patients.³² Treatment decisions require multidisciplinary input, and consideration of patient preferences.

Most relapses following radiotherapy (>95%) are out-of-field,³⁴ and can be successfully treated with 3 cycles of chemotherapy, achieving 10-year overall survival (OS) rates of 91%.³⁴ However, when both radiotherapy and chemotherapy are used, the risk of long-term toxicities, particularly secondary malignancies, is likely higher.³⁵

Chemotherapy for CSIIA or CSIIB Seminoma

Relapse rates after chemotherapy are numerically lower (8–14%) than radiotherapy (11–21%), particularly in CSIIB disease (5% vs. 12%).³⁶ Given its more unfavourable toxicity profile, chemotherapy is typically reserved for patients with rising TMs or bulky CSIIB disease, the definition of which is not standardized.

The standard chemotherapy regimen is three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide-cisplatin (EP), if the patient is unable to tolerate bleomycin.⁶ Sperm banking should be offered prior to chemotherapy.³⁷ Acute toxicities include fatigue, alopecia, nausea, vomiting, myelosuppression, neutropenic infections, renal dysfunction, skin toxicity, and venous thromboembolism. Bleomycin-induced lung injury occurs in up to 10% of patients and can rarely be fatal.³⁸ Risk factors include smoking history, pre-existing lung disease, age >50 years, and renal impairment.³⁹ Hearing loss and peripheral neuropathy can occur in 20–40% of patients.³⁹ Other long-term risks include tinnitus, chronic kidney disease, infertility, secondary malignancy, cardiovascular disease, Raynaud’s phenomenon, and avascular necrosis of the hip.

The SAKK 01/10 Phase II trial recently evaluated the combination of one cycle of carboplatin (AUC 7) followed by radiotherapy, and reported 3-year progression-free survival (PFS) of 93.7%, which did not meet the pre-specified 95% target.⁴⁰ Given these data, along with concerns for increased long-term toxicity with combination therapy, this approach is not adopted at PM.

Primary RPLND for CSIIA and CSIIB Seminoma

Three Phase II studies, SEMS (n=55), PRIMETEST (n=33), and COTRIMS (n=30), have evaluated retroperitoneal lymph node dissection (RPLND), mainly open surgery, in marker-negative CSIIA and CSIIB seminoma.^{41–43} With a median

TNM Staging	Unit	Value
Primary Tumour (pT)	pTX	Primary tumour cannot be assessed
	pT0	No evidence of primary tumour
	pTis	Germ cell neoplasia <i>in situ</i>
	pT1	Tumour limited to testis (including rete testis invasion) without lymphovascular invasion
	pT1a*	Tumour <3 cm in size
	pT1b*	Tumour ≥3 cm in size
Regional Lymph Nodes (pN and cN)	pT2	Tumour limited to the testis (including rete testis invasion) with lymphovascular invasion OR Tumour invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
	pT3	Tumour directly invades spermatic cord soft tissue with or without lymphovascular invasion
	pT4	Tumour invades scrotum with or without lymphovascular invasion
	NX	Regional lymph node cannot be assessed
	pN0	No regional lymph node metastasis
	pN1	Metastasis with a lymph node mass ≤2 cm in greatest dimension and ≤5 positive nodes, none >2 cm in greatest dimension
Distant Metastasis (M)	pN2	Metastasis with a lymph node mass >2 cm but not >5 cm in greatest dimension; or >5 positive nodes, none >5 cm in size; or evidence of extranodal extension of tumour
	pN3	Metastasis with a lymph node mass >5 cm in greatest dimension
	M1	Distant metastases present
	M1a	Non-retroperitoneal nodal or pulmonary metastases
Serum tumour markers (S)	M1b	Non-pulmonary visceral metastases
	SX	Serum marker studies not available or performed
	S0	Marker study levels within normal limits
	S1	LDH <1.5 × normal and HCG (IU/L) <5,000 and AFP (ug/L) <1,000
	S2	LDH 1.5–10 × normal or HCG (IU/L) 5,000–50,000 or AFP (ug/L) 1,000–10,000
	S3	LDH >10 × normal or HCG (IU/L) >50,000 or AFP (ug/L) >10,000

Stage Grouping			
Stage	Tumour	Node	Metastasis
0	pTis	N0	M0
I	pT1-4	N0	M0
IA	pT1	N0	M0
IB	pT2	N0	M0
	pT3	N0	M0
	pT4	N0	M0
IS	Any T	N0	M0
II	Any T	N1-3	M0
IIA	Any T	N1	M0
	Any T	N1	M0
	Any T	N2	M0
IIB	Any T	N2	M0
	Any T	N3	M0
	Any T	N3	M0
III	Any T	Any N	M1
IIIA	Any T	Any N	M1a
	Any T	Any N	M1a
IIIB	Any T	N1-3	M0
	Any T	Any N	M1a
	Any T	N1-3	M0
IIIC	Any T	Any N	M1a
	Any T	Any N	M1b
	Any T	Any N	Any S
			Serum Factor
			S0
			SX
			S0
			S0
			S0
			S0
			S1-3
			SX
			S0
			S1
			S0
			S1
			S0
			S1
			SX
			S0
			S1
			S2
			S2
			S3
			S3
			Any S

Table 1. TNM Staging of Testicular GCTs; adapted from Hamilton et al., CUAJ 2022.⁴

* T1a and T1b subclassification applies only to pure seminoma.

Abbreviations: AFP: alpha-fetoprotein, HCG: human chorionic gonadotrophin, LDH: lactate dehydrogenase.

Histology	Stage	Treatment Modality	RFS	OS
Seminoma	CSI	Active Surveillance	85%	100%
		Adjuvant Radiotherapy	95%	100%
		Adjuvant Chemotherapy (carboplatin)	90.7–97.8%	100%
	CSIIA	Radiotherapy	95%	100%
		Primary RPLND	70–89%	100% ¹
		Chemotherapy	93%	100%
	CSIIB	Radiotherapy	88%	100%
		Primary RPLND	70–89%	100% ¹
		Chemotherapy	95%	100%
NSGCT	CSI	Active Surveillance	75%	100%
		Adjuvant Radiotherapy	NR	NR
		Adjuvant RPLND	91.60%	100%
		Adjuvant Chemotherapy (BEP)	>95%	100%
	CSIIA	Primary RPLND	80%²	100%
		Chemotherapy	>95%	100%
	CSIIB	Primary RPLND	80% ²	100%
		Chemotherapy	98%	100%
Seminoma and NSGCT	CSIIC	Chemotherapy	95%	96%

Table 2. Efficacy Outcomes for CSI–CSIIC Testicular GCTs by Treatment Modality; *courtesy of Deepto Chowdhury, MD, FRCPC, Rachel Glicksman, MD, MSC, FRCPC, Robert J. Hamilton, MD, MPH, FRCSC, and Maria Jiang, MD, MSc, FRCPC.*

Preferred treatment approaches at PM are bolded.

¹ Median follow-up 22–32 months only

² >90% of patients with S0 disease

Abbreviations: BEP: bleomycin, etoposide, and cisplatin, CS: clinical stage, GCT: germ cell tumour, NR: Not recommended, NSGCT: nonseminomatous germ cell tumour, OS: overall survival, RFS: relapse-free survival, RPLND: retroperitoneal lymph node dissection

Time Post Orchiectomy	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Year 1					CT A&P*							CT A&P CXR** serum LH, FSH, free & total testosterone
Year 2						CT A&P						CT A&P CXR serum LH, FSH, free & total testosterone
Year 3						CT A&P						CT A&P CXR serum LH, FSH, free & total testosterone
Year 4												CT Abdo*** ONLY serum LH, FSH, free & total testosterone
Year 5												CT Abdo ONLY serum LH, FSH, free & total testosterone
Year 7												CT Abdo ONLY serum LH, FSH, free & total testosterone
Year 9												CT Abdo ONLY serum LH, FSH, free & total testosterone

Table 3. Princess Margaret Cancer Centre Surveillance Protocol for CSI Seminoma; courtesy of Deepro Chowdhury, MD, FRCPC, Rachel Glicksman, MD, MSC, FRCPC, Robert J. Hamilton, MD, MPH, FRCSC, and Maria Jiang, MD, MSc, FRCPC.

CT A&P* (Abdomen & Pelvis) first 3 years

CXR** (Chest X-Ray)

CT Abdo*** (Abdomen) only after 3 years

follow-up of 22–32 months, two-year relapse-free survival (RFS) ranged from 70% to 89%, with most recurrences occurring out-of-field (>90%). The PRIMETEST trial was terminated early due to high relapse rates (30%)⁴²; however, all relapses were successfully salvaged with additional surgery or chemotherapy.

Across all three studies, grade >3 short-term complications were observed in 3.6–13% of patients, and included paralytic ileus, chylous ascites, lymphoceles requiring drainage, and pulmonary emboli. Rates of anejaculation were ≤10%, and other long-term surgical complications were rare.⁴¹ The American Urology Association (AUA) now recognizes RPLND as an option for select patients with RPLNs ≤3 cm who wish to avoid chemotherapy or radiotherapy.⁴³ However, higher relapse rates than standard of care, variations in patient selection, and surgical technique across centres remain concerns. PM has not adopted this approach outside of a clinical trial setting, pending data from larger studies with longer follow-up, consistent with the European Urological Association (EAU) recommendations.³¹ The THERATEST trial (NCT06309745) is ongoing and compares RPLND to radiotherapy in seminoma with RPLN <3 cm.

Clinical Stage IIC (CSIIc) Seminoma

CSIIc seminoma is treated with chemotherapy according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification.⁴⁵ Post-chemotherapy residual masses ≥3 cm may contain viable tumour in up to 30% of cases based on historical data.⁴⁶ Fludeoxyglucose positron emission tomography (FDG-PET) has been studied in this setting⁴⁷ but is used infrequently due to its low positive predictive value.⁴

Management of Stage I-II NSGCT

CSI NSGCT

Approximately 75% CSI NSGCT are cured with orchiectomy alone.⁴⁸ Risk factors include lymphovascular invasion (LVI) (30%) and EC-predominant disease (50%).⁴⁹ About 75% of relapses occur in RPLNs.⁵⁰ Data from the Danish Testicular Cancer Registry recently showed hilar soft tissue invasion, tumor size (log 2), LVI and EC (absent vs <50% vs ≥50%) were independent risk factors for relapse, with 5-year

relapse risk ranging from <5% (no risk factors) to >85% (all 4 risk factors).⁵¹ External validation is warranted.

Active Surveillance for CSI NSGCT

Active surveillance is the preferred approach for CSI NSGCT4 (the PM surveillance protocol is included in **Table 4**).⁴⁸ Even in high-risk cases, 50% are cured with orchiectomy alone.⁵⁰ Most relapses (90%) occur within the first two years,¹⁵ and are effectively treated with primary RPLND or chemotherapy.^{50,52}

Adjuvant Chemotherapy for High-Risk CSI NSGCT

Some centres offer a risk-adapted approach using one cycle of adjuvant BEP for CSI NSGCT with LVI and/or predominant EC histology, reducing relapse risk to <5%.⁵³ Two cycles of adjuvant chemotherapy yield similar RFS but with increased toxicity and are generally not recommended.³¹ Up to 37% of relapses after adjuvant BEP occur beyond 2 years, underscoring the need for long-term surveillance.⁵⁴

The decision to use adjuvant chemotherapy should balance its efficacy in reducing relapse (and risk of requiring 3 cycles of chemotherapy subsequently) against the chance of avoiding chemotherapy and its potential toxicities altogether.⁵⁵ There is also some concern that relapses following adjuvant chemotherapy may be more treatment-resistant,⁵⁴ although data is limited.

RPLND for High-Risk CSI NSGCT

A German Phase III study compared RPLND with one cycle of adjuvant BEP. Following RPLND, 18% of patients received additional adjuvant BEP. The 12-year relapse rate was higher with RPLND (8.4%) than with adjuvant BEP (1.6%).⁵⁶ Only about one-third of patients had pathologic nodal involvement at the time of surgery, highlighting the significant risk of over-treatment.⁵⁷ RPLND is rarely used at PM in this context.

CSII NSGCT

Patients with CSIIa disease should undergo short-interval CT scans (6–8 weeks) and serial TMs to differentiate benign lymphadenopathy (20–30%), teratoma, and viable GCT.³⁰ If TMs remain negative, shrinking lesions are likely benign and can be observed. Persistent, slow-growing cystic lesions may indicate teratoma, warranting RPLND.

Time Post Orchiectomy	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Year 1	Markers* Markers	Markers	Markers CT A&P*** CT Thorax	Markers	Markers	Markers CT A&P CT Thorax	Markers CT A&P CT Thorax	Markers	Markers	Markers	Markers CT A&P CT Thorax Serum LH, FSH, free & total testosterone	Markers CT A&P CT Thorax Serum LH, FSH, free & total testosterone
Year 2	Markers	Markers	Markers	Markers	Markers	Markers	Markers	Markers	Markers	Markers	Markers CT A&P CT Thorax Serum LH, FSH, free & total testosterone	Markers CT A&P CT Thorax Serum LH, FSH, free & total testosterone
Year 3			Markers	Markers	Markers	Markers	Markers	Markers	Markers	Markers	Markers Serum LH, FSH, free & total testosterone	Markers Serum LH, FSH, free & total testosterone
Year 4					Markers	Markers	Markers	Markers	Markers	Markers	Markers Serum LH, FSH, free & total testosterone	Markers Serum LH, FSH, free & total testosterone
Year 5											Markers CT A&P CT Thorax Serum LH, FSH, free & total testosterone	Markers CT A&P CT Thorax Serum LH, FSH, free & total testosterone
Transition to primary care after 5 years. No ongoing imaging/labs required. Physical surveillance of remaining testis.												

Table 4. Princess Margaret Cancer Centre Surveillance Protocol for CSI NSGCT; courtesy of Deepto Chowdhury, MD, FRCPC, Rachel Glicksman, MD, MSC, FRCPC, Robert J. Hamilton, MD, MPH, FRCSC, and Maria Jiang, MD, MSc, FRCPC.

Markers* (HCG, AFP, LDH)
CT A&P*** (CT Scan of Abdomen and Pelvis)

Primary RPLND for CSIIA and CSIIB NSGCT

For marker-negative CSIIA NSGCT, primary RPLND is associated with a higher relapse rate (20%) than chemotherapy (<5%); however, it avoids chemotherapy toxicities⁵⁸ and is the preferred approach. Relapses post-RPLND are mostly out-of-field when performed at experienced centres,⁴ and are highly curable with chemotherapy.

For CSIIB NSGCT, relapse rates after primary RPLND reach 50%,⁵⁹ and chemotherapy is often preferred. No standardized criteria exist for selecting primary RPLND versus chemotherapy⁶⁰ but TM levels, lymph node (LN) size and distribution may help guide decision making. Patients with an unequivocal rise in TM or rapidly progressing disease should receive chemotherapy.

After RPLND, two cycles of adjuvant chemotherapy can reduce relapse rates (e.g., N2 disease from ≥50% to <5%).⁶¹ However, this undermines the goal of primary RPLND, which is achieving cure without chemotherapy.

Chemotherapy for CSIIA, CSIIB, and CSIIC NSGCT

For CSIIA and CSIIB NSGCT, chemotherapy has lower relapse rates (<5%) than RPLND at the cost of increased short- and long-term toxicity.⁵⁸ CSIIC disease, regardless of TM status, should be treated with chemotherapy (see **Table 2**).⁶²

Post-chemotherapy, residual masses over 1 cm warrant RPLND to remove any teratoma (to avoid growing teratoma syndrome or somatic transformation) or viable chemo-resistant GCT.⁴

Future Directions

Molecular biomarkers such as micro RNAs (miRNAs), particularly miR371,⁶³ have shown excellent sensitivity (80–100%) and specificity (90–100%),⁶⁴ and may be particularly valuable for detecting marker-negative GCTs.⁶⁵

For metastatic NSGCT treated with chemotherapy, miR371 has shown prognostic value^{66–68} and promising ability to assess residual masses (negative predictive value of 100% in NSGCT <3 cm).⁶⁶ However, miR371 has limited ability to detect teratoma⁶⁹; with miR375 co-testing this may be improved.⁷⁰ Further prospective studies, such as the ongoing SWOG S1823 trial (NCT04435756), are needed. Circulating tumour DNA (ctDNA)⁷¹ also shows potential utility in detecting molecular residual disease post-treatment.⁷²

Conclusions

CSI and CSII testicular GCTs are highly curable. Management strategies are tailored to histology, tumour burden, stage, and patient preferences, with an emphasis on minimizing treatment toxicities. Multidisciplinary evaluation is essential, and treatment at experienced centres optimizes outcomes. Ongoing research, including RPLND in CSIIA-CSIIB seminoma and biomarkers, such as miRNA and ctDNA, may enable personalized treatment strategies pending confirmatory data.

For other surveillance protocols including post primary RPLND, radiation or chemotherapy, please refer to page 20–26 **here**.

Correspondence

Di Maria Jiang, MD, MSc, FRCPC
Email: di.jiang@uhn.ca

Financial Disclosures

D.C.: None declared.
R.G.: None declared.
R.H.: None declared.
D.M.J.: None declared.

References

1. Testicular Cancer Statistics [Internet]. Canadian Cancer Society. 2024 [cited 2025 Feb 5]. Available from: <https://cancer.ca/en/cancer-information/cancer-types/testicular/statistics>
2. Oosterhuis JW, Looijenga LHJ. Human germ cell tumours from a developmental perspective. *Nat Rev Cancer*. 2019;19(9):522–37.
3. Busch J, Seidel C, Zengerling F. Male extragonadal germ cell tumors of the adult. *Oncol Res Treat*. 2016;39(3):140–4.
4. Hamilton RJ, Canil C, Shrem NS, Kuhathaas K, Jiang M Di, Chung P, et al. Canadian Urological Association consensus guideline: Management of testicular germ cell cancer. *Can Urol Assoc J*. 2022;16(6):155–73.
5. Amin MB, Edge SB, Greene F, eds. *AJCC Cancer Staging Manual*, 8th ed. Chicago, IL: American Joint Committee on Cancer; 2017. 25
6. Cancerous Tumours of the Testicle [Internet]. Canadian Cancer Society. [cited 2025 Feb 5]. Available from: <https://cancer.ca/en/cancer-information/cancer-types/testicular/what-is-testicular-cancer/cancerous-tumours>
7. Dieckmann KP, Simonsen-Richter H, Kulejewski M, Anheuser P, Zecha H, Isbarn H, et al. Serum tumour markers in testicular germ cell tumours: frequencies of elevated levels and extents of marker elevation are significantly associated with clinical parameters and with response to treatment. *Biomed Res Int*. 2019;2019:5030349.
8. Ball D, Rose E, Alpert E. Alpha-fetoprotein levels in normal adults. *Am J Med Sci*. 1992 Mar;303(3):157–9.
9. Germà JR, Llanos M, Tabernero JM, Mora J. False elevations of alpha-fetoprotein associated with liver dysfunction in germ cell tumors. *Cancer*. 1993 Oct;72(8):2491–4.
10. Ballieux BEPB, Weijl NI, Gelderblom H, van Pelt J, Osanto S. False-Positive serum human chorionic gonadotropin (hCG) in a male patient with a malignant germ cell tumor of the testis: a case report and review of the literature. *Oncologist*. 2008;13(11):1149–54.
11. Chung P, Daugaard G, Tyldesley S, Atenafu EG, Panzarella T, Kollmannsberger C, et al. Evaluation of a prognostic model for risk of relapse in stage I seminoma surveillance. *Cancer Med (Malden, MA)*. 2015;4(1):155–60.
12. Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. *J Clin Oncol Off J Am Soc Clin Oncol*. 2002;20(22):4448–52.
13. Boormans JL, Sylvester R, Anson-Cartwright L, Glicksman RM, Hamilton RJ, Hahn E, et al. Prognostic factor risk groups for clinical stage I seminoma: an individual patient data analysis by the European Association of Urology Testicular Cancer Guidelines Panel and Guidelines Office. *Eur Urol Oncol*. 2024;7(3):537–43.
14. Wagner T, Toft BG, Lauritsen J, Bandak M, Christensen IJ, Engvad B, et al. Prognostic Factors for Relapse in Patients With Clinical Stage I Testicular Seminoma: A Nationwide, Population-Based Cohort Study. *J Clin Oncol*. 2024;42(1):81–9.
15. Kollmannsberger C, Tandstad T, Bedard PL, Cohn-Cedermark G, Chung PW, Jewett MA, et al. Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. *J Clin Oncol*. 2015;33(1):51–7.
16. Lieng H, Warde P, Bedard P, Hamilton RJ, Hansen AR, Jewett MAS, et al. Recommendations for followup of stage I and II seminoma: The Princess Margaret Cancer Centre approach. *Can Urol Assoc J*. 2018;12(2):59–66.
17. Joffe JK, Cafferty FH, Murphy L, Rustin GJS, Sohaib SA, Gabe R, et al. Imaging modality and frequency in surveillance of stage I seminoma testicular cancer: results from a randomized, Phase III, noninferiority trial (TRISST). *J Clin Oncol*. 2022;40(22):2468–78.
18. Chung P, O'Malley ME, Jewett MAS, Bedard PL, Panzarella T, Sturgeon J, et al. Detection of relapse by low-dose computed tomography during surveillance in stage I testicular germ cell tumours. *Eur Urol Oncol*. 2019;2(4):437–42.
19. Warde P, Gospodarowicz MK, Panzarella T, Catton CN, Sturgeon JF, Moore M, et al. Stage I testicular seminoma: results of adjuvant irradiation and surveillance. *J Clin Oncol*. 1995;13(9):2255–62.
20. Fosså SD, Horwich A, Russell JM, Roberts JT, Cullen MH, Hodson NJ, et al. Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. *J Clin Oncol*. 1999;17(4):1146.
21. Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Horwich A, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). *J Clin Oncol*. 2005;23(6):1200–8.
22. Aass N, Fosså SD, Høst H. Acute and subacute side effects due to infra-diaphragmatic radiotherapy for testicular cancer: a prospective study. *Int J Radiat Oncol Biol Phys*. 1992;22(5):1057–64.
23. Fosså SD, Aass N, Kaalhus O. Radiotherapy for testicular seminoma stage I: treatment results and long-term post-irradiation morbidity in 365 patients. *Int J Radiat Oncol Biol Phys*. 1989;16(2):383–8.
24. van den Belt-Dusebout AW, de Wit R, Gietema JA, Horenblas S, Louwman MWJ, Ribot JG, et al. Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol*. 2007;25(28):4370–8.
25. Horwich A, Fossa SD, Huddart R, Dearnaley DP, Stenning S, Aresu M, et al. Second cancer risk and mortality in men treated with radiotherapy for stage I seminoma. *Br J Cancer*. 2014;110(1):256–63.
26. OLIVER RTD, MEAD GM, RUSTIN GJS, JOFFE JK, AASS N, COLEMAN R, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). *J Clin Oncol*. 2011;29(8):957–62.

27. Tandstad T, Ståhl O, Dahl O, Haugnes HS, Håkansson U, Karlsdóttir Á, et al. Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). *Ann Oncol.* 2016;27(7):1299–304.
28. Powles T, Robinson D, Shamash J, Moller H, Tranter N, Oliver T. The long-term risks of adjuvant carboplatin treatment for stage I seminoma of the testis. *Ann Oncol.* 2008;19(3):443–7.
29. Fischer S, Tandstad T, Wheeler M, Porfiri E, Fléchon A, Aparicio J, et al. Outcome of men with relapse after adjuvant carboplatin for clinical stage I seminoma. *J Clin Oncol.* 2017;35(2):194–200.
30. McAlpine K, Clark R, Spiess PE, Necchi A, Gage K, Hamilton RJ. The importance of repeat imaging prior to treatment decision-making in testicular cancer: commentary from the Inaugural Global Society of Rare Genitourinary Tumors Summit. *Clin Genitourin Cancer.* 2023;21(3):418.e1–418.e6.
31. Patrikidou A, Cazzaniga W, Berney D, Boormans J, de Angst I, Di Nardo D, et al. European Association of Urology Guidelines on testicular cancer: 2023 update. *Eur Urol.* 2023;84(3):289–301.
32. Glicksman RM, Jiang DM, Bedard PL, Ye XY, Anson-Cartwright L, Billfalk-Kelly A, et al. Clinical outcomes of stage IIA/IIB seminoma treated with radiation therapy and chemotherapy: should regional therapy be considered the preferred treatment approach? *Int J Radiat Oncol Biol Phys.* 2025;122(1):109–116.
33. Gilligan, Timothy; Lin, Daniel; Adra, Nabil; Aggarwal, Rahul et al. Testicular Cancer [Internet]. National Comprehensive Cancer Network. 2025 [cited 2025 Feb 5]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf
34. Terbuch A, Posch F, Bauernhofer T, Jost PJ, Partl R, Stranzl-Lawatsch H, et al. Patterns of disease progression and outcome of patients with testicular seminoma who relapse after adjuvant or curative radiation therapy. *Int J Radiat Oncol.* 2022;113(4):825–32.
35. Huddart RA, Norman A, Shahidi M, Horwich A, Coward D, Nicholls J, et al. Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J Clin Oncol.* 2003;21(8):1513–23.
36. Giannatempo P, Greco T, Mariani L, Nicolai N, Tana S, Farè E, et al. Radiotherapy or chemotherapy for clinical stage IIA and IIB seminoma: a systematic review and meta-analysis of patient outcomes. *Ann Oncol.* 2015;26(4):657–68.
37. Garcia-del-Muro X, Maroto P, Gumà J, Sastre J, López Brea M, Arranz JA, et al. Chemotherapy as an alternative to radiotherapy in the treatment of stage IIA and IIB testicular seminoma: a Spanish Germ Cell Cancer Group Study. *J Clin Oncol.* 2008;26(33):5416–21.
38. O'Sullivan JM, Huddart RA, Norman AR, Nicholls J, Dearnaley DP, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Ann Oncol.* 2003;14(1):91–6.
39. Fung C, Dinh PJ, Ardeshir-Rouhani-Fard S, Schaffer K, Fossa SD, Travis LB. Toxicities associated with cisplatin-based chemotherapy and radiotherapy in long-term testicular cancer survivors. *Adv Urol.* 2018;2018:8671832.
40. Papachristofilou A, Bedke J, Hayoz S, Schratzenstaller U, Pless M, Hentrich M, et al. Single-dose carboplatin followed by involved-node radiotherapy for stage IIA and stage IIB seminoma (SAKK 01/10): a single-arm, multicentre, phase 2 trial. *Lancet Oncol.* 2022;23(11):1441–50.
41. Daneshmand S, Cary C, Masterson T, Einhorn L, Adra N, Boorjian SA, et al. Surgery in Early metastatic seminoma: a phase II trial of retroperitoneal lymph node dissection for testicular seminoma with limited retroperitoneal lymphadenopathy. *J Clin Oncol.* 2023;41(16):3009–18.
42. Hiester A, Che Y, Lusch A, Kuß O, Niegisch G, Lorch A, et al. Phase 2 single-arm trial of primary retroperitoneal lymph node dissection in patients with seminomatous testicular germ cell tumors with clinical stage IIA/B (PRIMETEST). *Eur Urol.* 2023;84(1):25–31.
43. Heidenreich A, Paffenholz P, Hartmann F, Seelemeyer F, Pfister D. Retroperitoneal lymph node dissection in clinical stage IIA/B metastatic seminoma: Results of the COlogne Trial of Retroperitoneal Lymphadenectomy In Metastatic Seminoma (COTRIMS). *Eur Urol Oncol.* 2024;7(1):122–7.
44. Stephenson A, Bass EB, Bixler BR, Daneshmand S, Kirkby E, Marianes A, et al. Diagnosis and treatment of early-stage testicular cancer: AUA Guideline Amendment 2023. *J Urol.* 2024;211(1):20–5.
45. Beyer J, Collette L, Sauvé N, Daugaard G, Feldman DR, Tandstad T, et al. Survival and new prognosticators in metastatic seminoma: results from the IGCCCG-Update Consortium. *J Clin Oncol.* 2021;39(14):1553–62.
46. Ravi R, Ong J, Oliver RT, Badenoch DF, Fowler CG, Hendry WF. The management of residual masses after chemotherapy in metastatic seminoma. *BJU Int.* 1999;83(6):649–53.
47. De Santis M, Becherer A, Bokemeyer C, Stoiber F, Oechsle K, Sellner F, et al. 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. *J Clin Oncol.* 2004;22(6):1034–9.
48. Sturgeon JF, Moore MJ, Kakiashvili DM, Duran I, Anson-Cartwright LC, Berthold DR, et al. Non-risk-adapted surveillance in clinical stage I nonseminomatous germ cell tumors: the Princess Margaret Hospital's experience. *Eur Urol.* 2011;59(4):556–62.
49. Zengerling F, Beyersdorff D, Busch J, Heinzelbecker J, Pfister D, Ruf C, et al. Prognostic factors in patients with clinical stage I nonseminoma—beyond lymphovascular invasion: a systematic review. *World J Urol.* 2022;40(12):2879–87.
50. Kollmannsberger C, Moore C, Chi KN, Murray N, Daneshmand S, Gleave M, et al. Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy. *Ann Oncol.* 2010;21(6):1296–301.

51. Wagner T, Toft BG, Lauritsen J, Bandak M, Christensen IJ, Engvad B, et al. Prognostic factors for relapse in patients with clinical stage I testicular non-seminoma: A nationwide, population-based cohort study. *Eur J Cancer*. 2024;202:114025.
52. Hamilton RJ, Nayan M, Anson-Cartwright L, Atenafu EG, Bedard PL, Hansen A, et al. Treatment of Relapse of Clinical Stage I Nonseminomatous Germ Cell Tumors on Surveillance. *J Clin Oncol*. 2019;37(22):1919-26.
53. Tandstad T, Ståhl O, Håkansson U, Dahl O, Haugnes HS, Klepp OH, et al. One course of adjuvant BEP in clinical stage I nonseminoma mature and expanded results from the SWENOTECA group. *Ann Oncol*. 2014;25(11):2167-72.
54. Fischer S, Tandstad T, Cohn-Cedermark G, Thibault C, Vincenzi B, Klingbiel D, et al. Outcome of men with relapses after adjuvant bleomycin, etoposide, and cisplatin for clinical stage I nonseminoma. *J Clin Oncol*. 2020;38(12):1322-31.
55. Hiester A, Fingerhut A, Niegisch G, Siener R, Krege S, Schmelz HU, et al. Late toxicities and recurrences in patients with clinical stage I non-seminomatous germ cell tumours after 1 cycle of adjuvant bleomycin, etoposide and cisplatin versus primary retroperitoneal lymph node dissection – A 13-year follow-up analysis of a phase III trial cohort. *Eur J Cancer*. 2021;155:64-72.
56. Hiester A, Fingerhut A, Niegisch G, Siener R, Krege S, Schmelz HU, et al. Late toxicities and recurrences in patients with clinical stage I nonseminomatous germ cell tumor after one cycle of adjuvant BEP versus primary retroperitoneal lymph node dissection: A 13-years follow-up analysis of a phase III trial cohort. *J Clin Oncol*. 2020;38(15_suppl):5512.
57. Nicolai N, Tarabelloni N, Gasperoni F, Catanzaro M, Stagni S, Torelli T, et al. Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: safety and efficacy analyses at a high volume center. *J Urol*. 2018;199(3):741-7.
58. Stephenson AJ, Bosl GJ, Motzer RJ, Bajorin DF, Stasi JP, Sheinfeld J. Nonrandomized comparison of primary chemotherapy and retroperitoneal lymph node dissection for clinical stage IIA and IIB nonseminomatous germ cell testicular cancer. *J Clin Oncol*. 2007;25(35):5597-602.
59. Ghandour R, Ashbrook C, Freifeld Y, Singla N, El-Asmar JM, Lotan Y, et al. Nationwide Patterns of Care for Stage II Nonseminomatous Germ Cell Tumor of the Testicle. *Eur Urol Oncol*. 2020;3(2):198-206.
60. Neuenschwander A, Lonati C, Antonelli L, Papachristofilou A, Cathomas R, Rothermundt C, et al. Treatment outcomes for men with clinical stage II nonseminomatous germ cell tumours treated with primary retroperitoneal lymph node dissection: a systematic review. *Eur Urol Focus*. 2023;9(3):541-6.
61. Williams SD, Stablein DM, Einhorn LH, Muggia FM, Weiss RB, Donohue JP, et al. Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. *N Engl J Med*. 1987;317(23):1433-8.
62. Gillessen S, Sauvé N, Collette L, Daugaard G, de Wit R, Albany C, et al. Predicting outcomes in men with metastatic nonseminomatous germ cell tumors (NSGCT): results from the IGCCCG Update Consortium. *J Clin Oncol*. 2021;39(14):1563-74.
63. Ditonno F, Franco A, Manfredi C, Fasanella D, Abate M, La Rocca R, et al. The role of miRNA in testicular cancer: current insights and future perspectives. *Medicina (B Aires)*. 2023;59(11).
64. Ahmadi H, Jang TL, Daneshmand S, Ghodoussipour S. MicroRNA-371a-3p as a blood-based biomarker in testis cancer. *Asian J Urol*. 2021;8(4):400-6.
65. Lobo J, Leão R, Gillis AJM, van den Berg A, Anson-Cartwright L, Atenafu EG, et al. Utility of serum miR-371a-3p in predicting relapse on surveillance in patients with clinical stage I testicular germ cell cancer. *Eur Urol Oncol*. 2021;4(3):483-91.
66. Leão R, van Agthoven T, Figueiredo A, Jewett MAS, Fadaak K, Sweet J, et al. Serum miRNA predicts viable disease after chemotherapy in patients with testicular nonseminoma germ cell tumor. *J Urol*. 2018;200(1):126-35.
67. Rosas Plaza X, van Agthoven T, Meijer C, van Vugt MATM, de Jong S, Gietema JA, et al. miR-371a-3p, miR-373-3p and miR-367-3p as serum biomarkers in metastatic testicular germ cell cancers before, during and after chemotherapy. *Cells*. 2019;8(10).
68. Mego M, van Agthoven T, Gronesova P, Chovanec M, Miskovska V, Mardiak J, et al. Clinical utility of plasma miR-371a-3p in germ cell tumors. *J Cell Mol Med*. 2019;23(2):1128-36.
69. Lafin JT, Kenigsberg AP, Meng X, Abe D, Savelyeva A, Singla N, et al. Serum small RNA sequencing and miR-375 assay do not identify the presence of pure teratoma at postchemotherapy retroperitoneal lymph node dissection. *Eur Urol Open Sci*. 2021;26:83-7.
70. Nappi L, Thi M, Adra N, Hamilton RJ, Leao R, Lavoie JM, et al. Integrated expression of circulating miR375 and miR371 to identify teratoma and active germ cell malignancy components in malignant germ cell tumors. *Eur Urol*. 2021;79(1):16-9.
71. Sykes J, Kaldany A, Jang TL. Current and evolving biomarkers in the diagnosis and management of testicular germ cell tumors. *J Clin Med*. 2024;13(23).
72. Hassoun R, Cary C, Masterson TA, Laliotis G, Sharma S, Dutta P, et al. Utility of circulating tumor DNA (ctDNA) as a predictive biomarker for disease monitoring in patients with non-seminomatous germ-cell tumor (NSGCT). *J Clin Oncol*. 2024;42(4_suppl):500-500.