Chapter
14

Metastatic Germ Cell Tumors

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LEARNING OBJECTIVES

- To know the staging evaluation for a patient with germ cell tumors (GCTs): Every patient with a diagnosis of a testicular tumor should have a contrast enhanced CT scan of the chest, abdomen and pelvis.
- To understand the risk stratification of patients with advanced GCTs: The international Germ Cell Cancer Collaboration Group (IGCCCG) risk stratification system is used to classify patients into good/intermediate/poor risk GCT. This guides further management and is also prognostic.
- To know about the chemotherapy regimens for advanced GCTs: The BEP (Bleomycin, Etoposide and Cisplatin) regimen is the most commonly used for GCTs. The number of cycles depends on the IGCCCG risk category of the patient.
- To understand the peri-chemotherapy precautions: Hydration, thromboembolic prophylaxis, and monitoring for pulmonary and renal toxicity are the considerations when the patient is on chemotherapy.
- To understand the management of post-chemotherapy residual lesions in seminoma: It is still not very clear what is the best management for patients with post-chemotherapy residual masses in seminoma. Most decisions are guided by the findings of a FDG PET-CT.
- To understand the management of post-chemotherapy residual lesions in NSGCT: A post-chemotherapy retroperitoneal lymph node dissection (RPLND) is the standard of care for all residual lesions larger than 1 cm.
- To know of the settings in which RPLND is performed: The different settings in which a RPLND is performed include: Primary RPLND for stage 1 and stage 2A GCTs with normal tumor markers, post-chemotherapy RPLND, salvage RPLND, desperation RPLND and RPLND for growing teratoma syndrome.
- To know the templates for RPLND: A standard bilateral template RPLND entails removal of all nodal tissue within a template bounded by the left renal vein superiorly, the crossing of the ureters over the common iliac arteries inferiorly and both ureters laterally.
- To understand the concept of modified template RPLND: A modified template RPLND may be performed in patients with low burden of disease in an attempt to limit surgical morbidity.
- To know about the follow-up protocol: All patients following completion of treatment for advanced GCTs should be asked to follow-up as per a fixed protocol which includes regular evaluation with tumor markers, physical examination and imaging.

Case Scenario

A 23-year-old unmarried male presented with a right testicular swelling. On scrotal ultrasound, a well-defined enhancing mass of 4 x 3 cm size was seen in the right testis; the left testis was normal. The tumor markers for this patient were as follows: AFP 393, bHCG 16,355 and LDH 741. A CT scan of the chest, abdomen and pelvis showed multiple retroperitoneal nodal masses, largest being a 5.8 × 4 cm para-aortic node. There were also 3 lung nodules, largest being a 1.7 × 1.4 cm lesion in the left upper lobe (Fig. 14.1A and B).

1. **What is the next step?**
   Ans:
   - Patients with metastatic GCT require chemotherapy and RPLND which may affect their fertility potential.[1]

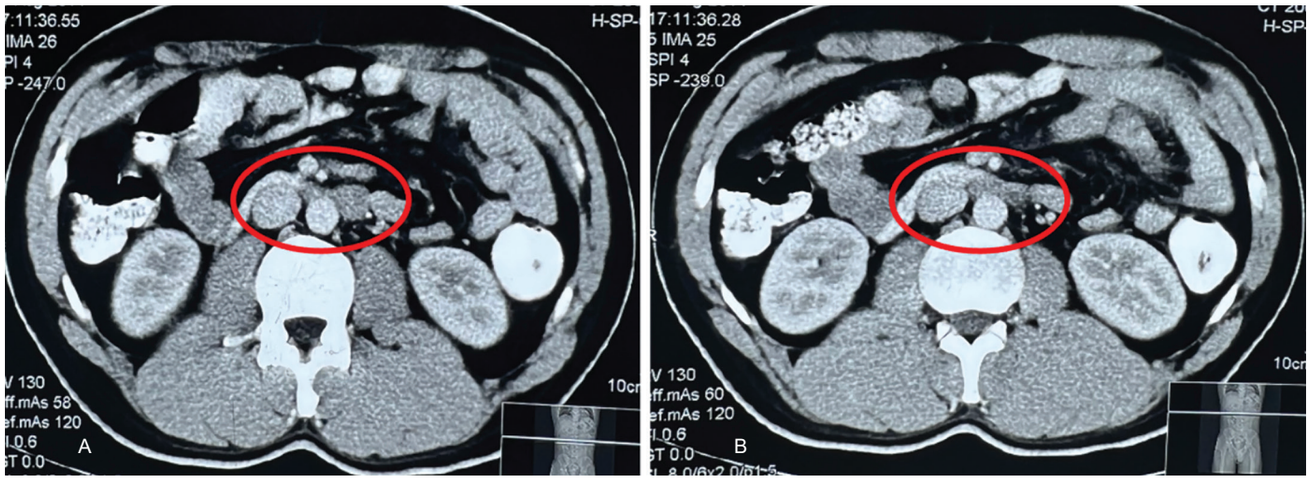

Fig. 14.1A and B: CT Image showing retroperitoneal nodes

- A baseline sperm count should be done and sperm banking should be discussed where family is not completed apart from radical orchiectomy.

2. Is orchiectomy always the first step?

Ans:

- For males who present with clinically advanced disease, we perform a radical orchiectomy prior to chemotherapy whenever possible.
- Despite this, there are some males who present with life-threatening advanced disease who undergo systemic chemotherapy prior to orchiectomy ("delayed orchiectomy"). This chemotherapy is started on the basis of raised tumor markers which suggest the diagnosis of NSGCT. For patients with only raised LDH, where the clinical suspicion is of a seminoma, a biopsy of the retroperitoneal mass is performed and the presence of seminoma is confirmed prior to starting the chemotherapy.
- Brain and testis are considered immune-privileged sites owing to a blood–brain barrier and a blood–testis barrier (BTB) respectively making them less penetrable to systemic chemotherapy. However, whether this BTB remains working in a disease-infiltrated testis is questioned and the need for post-chemotherapy delayed orchidectomy is being revisited.[2–4]
- Histopathological examination of tissue from retroperitoneum as well as from the testis in patient undergoing delayed orchiectomy and RPLND have shown disparity for response to chemotherapy.
- Complete resolution of tumor in the testis and residual tumor in the retroperitoneum cannot be answered by BTB only and possibly could be due to tumor heterogeneity.
- A delayed orchiectomy should be performed later in such select patients where the chemotherapy was given upfront.[3,4]

3. What is the imaging done for systemic staging?

Ans:

- A high-resolution computed tomography (CT) scan of the chest, abdomen and pelvis is recommended for staging.
- MRI of the brain is performed if brain metastases are suspected. (Neurologic symptoms, β-hCG >5000 IU/L, AFP >10,000 ng/ml, chorio-carcinoma or extensive disease like multiple lung metastasis, non-pulmonary visceral metastasis.)
- Positron emission tomography (PET) scan is of limited utility in the initial staging of patients with testicular germ cell tumors (GCTs).

4. What is the pattern of lymph node involvement and how to identify malignant node on a CT?

Ans:

- CT is essential for accurately determining the extent of nodal and metastatic spread in GCTs.
- GCTs primarily spread to retroperitoneal lymph nodes through lymphatic and venous pathways originating from the gonads. The spread follows on right-side along the gonadal vein, involving aortocaval or paracaval nodes, and since left gonadal vein drains into left renal vein, left-sided GCTs typically metastasize to left paraaortic nodes below the left renal hilum. Contralateral spread is rare without ipsilateral nodal involvement.
- Nodal disease above the level of renal hila is considered metastatic and falls under M staging.[6,7]

- The accuracy of CT in identifying malignant nodes depends on the size cut-off. Using a threshold of 4 mm or larger, sensitivity is excellent (>90%), but specificity decreases to 58%. Raising the cut-off to 10 mm increases specificity to almost 100%, but sensitivity drops to 37–47%. A recommended short axis diameter of 8 mm, especially in high-risk patients with lymph-vascular invasion or an embryonal predominance, is commonly used to define suspicious lymph nodes on CT.
- Additionally, morphologic features like shape (round or spiculated) and enhancement (heterogeneous, central necrosis) provide suspicion of positive lymph nodes.
- Also, surrounding organ involvement and ureteral obstruction with hydronephrosis can be identified.

5. What is the risk stratification of advanced germ cell tumor?

Ans:

- For males with advanced GCTs, management does not differ for seminoma and NSGCTs. Instead, treatment is selected based on the International Germ Cell Cancer Collaborative Group (IGCCCG) risk stratification system.
- Males with seminoma are categorized as having good- or intermediate-risk disease. Males with NSGCTs are categorized as having good-, intermediate-, or poor-risk disease based on the sites of disease involvement and tumor marker levels.
- With the advancement in chemotherapy, the 5-year survival rates have increased for both metastatic seminoma and non-seminomatous tumors from the initial IGCCCG series [9–11] (Table 14.1).

TABLE 14.1: The International Germ Cell Cancer Collaboration Group (IGCCCG) classification of advanced germ cell tumors (GCTs)

Seminomas		***Non-seminomas***	
Good risk		**Good risk**	
All of the following:		**All of the following:**	
Any primary site	5-year PFS: 89% (CI, 87–90)	Testicular or retroperitoneal primary tumors	5-year PFS: 90% (95% CI, 89–91)
No metastases to organs other than the lungs and/or lymph nodes	OS: 95% (CI, 94–96)	No metastases to organs other than the lungs and/or lymph nodes	OS: 96% (95–96%)
Normal serum AFP		Serum AFP <1000 ng/ml, β-hCG <5000 mIU/ml, and LDH <3 times the upper limit of normal	
Intermediate risk		**Intermediate risk**	
All of the following:		**All of the following:**	
Any primary site	5-year PFS: 79% (95% CI, 70–85)	Testicular or retroperitoneal primary tumors	5-year PFS: 78% (76–80%)
Metastases to organs other than the lungs and/or lymph nodes	OS: 88% (95% CI, 80–93)	No metastases to organs other than the lungs and/or lymph nodes Serum AFP 1000 to 10,000 ng/ml or Serum β-hCG 5000 to 50,000 mIU/ml or	OS: 89% (88–91%)
		LDH 3 to 10 times the upper limit of normal	
Normal serum AFP			
		Poor risk	
No patients classified as poor risk		**Any of the following:**	
		Mediastinal primary with or without metastases	5-year PFS: 54% (95% CI, 52–56)
		Metastases to organs other than the lungs and/or lymph nodes	
		Serum AFP >10,000 ng/ml or β-hCG >50,000 mIU/ml or LDH >10 times the upper limit of normal	OS: 67% (95% CI, 65–69)

- These recent studies also identified lactate dehydrogenase (LDH) proved to be an additional adverse prognostic factor for patients with advanced seminomas. Good prognosis patients with LDH above 2.5 x upper limit of normal had a 3-year PFS of 80% (95% CI, 75 to 84) and a 3-year OS of 92% (95% CI, 88 to 95) versus 92% (95% CI, 90 to 94) and 97% (95% CI, 96 to 98) in the group with lower LDH[10] (Table 14.1).
- For NSGCTs, a prognostic model was developed and independently validated. This model identified a new cutoff of lactate dehydrogenase at a 2.5 upper limit of normal and increasing age and presence of lung metastases as additional adverse prognostic factors. An online calculator is provided (https://www.eortc.org/IGCCCG-Update).[11]

6. What is the chemotherapy regimen for advanced GCTs?

Ans:

- **Good-risk disease**: For males with good-risk GCTs, three cycles of bleomycin, etoposide, and cisplatin (BEP) are recommended. For those with compromised pulmonary function, four cycles of EP is recommended to avoid bleomycin-related toxicity.
- **Intermediate-or poor-risk disease:** For males with intermediate-risk or poor-risk disease, four cycles of BEP are recommended. An alternative regimen of etoposide, ifosfamide, and cisplatin (VIP) is preferred for patients at risk of bleomycin-induced lung injury.
- Table 14.2 depicts the BEP regimen.[12]
- Table 14.3 depicts the VIP regimen:[13] Similar efficacy as BEP but causes more myelotoxicity

7. What are criteria monitored by the medical oncologists while administration of chemotherapy for GCTs?

Ans:

- **Pre-treatment considerations:**
  - *Hydration:* Induce diuresis with at least 2000 ml of NS to minimize cisplatin nephrotoxicity. Maintain urine flow of at least 100 ml/hour for 2 hours before and after cisplatin administration.
  - Emesis risk is high (>90% frequency of emesis). Prior use of antiemetics is a must.
  - *Vesicant/irritant properties:* Bleomycin, etoposide, and cisplatin are irritants. Avoid extravasation.
  - *Myelo-stimulation prophylaxis:* Primary prophylaxis with G-CSF is not indicated.
  - *Dose adjustment for liver/renal dysfunction:* Bleomycin contraindicated if baseline creatinine >2.0 mg/dl. Consider lower initial doses of cisplatin or etoposide for hepatic or renal dysfunction.
- **Monitoring parameters:**
  - CBC with differential and platelet count weekly during treatment.
  - Basic metabolic panel prior to each treatment cycle.
  - Baseline pulmonary function tests (PFTs), including DLCO, before and during bleomycin therapy.
- **Toxicity:**
  - *Myelotoxicity:* Begin each cycle on schedule. Reduce etoposide dose by 25% if febrile neutropenia or thrombocytopenic bleeding occurs. Administer G-CSF if neutrophil count 2500 cells/µl or platelets 100,000/µl.

TABLE 14.2: The BEP regimen

Drug	*Dose and route*	*Administration*	*Days*
Bleomycin	30 units IV per dose	Dilute in 50 ml NS and administer over 10 minutes	1, 8, 15
Etoposide	100 mg/m^2 IV per day	Dilute in 500 ml NS (concentration < 0.4 mg/ml) and administer over one hour	1–5
Cisplatin	20 mg/m^2 IV per day	Dilute in 250 ml NS and administer over two hours	1–5

Repeat the cycle every 21 days

TABLE 14.3: The VIP regimen

Drug	*Dose and route*	*Administration*	*Days*
Etoposide	75 mg/m^2 IV per day	Dilute in 500 ml NS and administer over one hour	1–5
Ifosfamide	1200 mg/m^2 IV per day	With Mesna protection	1–5
Cisplatin	20 mg/m^2 IV per day	Dilute in 250 ml NS and administer over two hours	1–5

Repeat the cycle every 21 days

- *Pulmonary toxicity:* Maximum lifetime bleomycin dose should not exceed 400 mg. Discontinue if clinical/radiographic evidence of pulmonary injury or DLCO decline 25%.
- *Neurologic toxicity:* Discontinue cisplatin if neuropathy interferes with function. Peripheral neuropathies may occur after prolonged courses. Consider benefit–risk balance.
- *Renal toxicity:* Discuss treatment goals and risks of cisplatin nephrotoxicity in the setting of renal impairment (creatinine >2.0 mg/dl or GFR <50 ml/min).

Case Scenario *(Contd.)*

The patient received 4 cycles of BEP. Tumor markers 4 weeks after the completion of chemotherapy had normalized. A response evaluation CECT revealed that 2 of the three lung lesions had completely resolved while one lesion in the left upper lobe showed no interval decrease in size. The size of the para-aortic LN had decreased to 3 × 2 cm. There were no new lesions. Figure 14.2 showing residual retroperitoneal node.

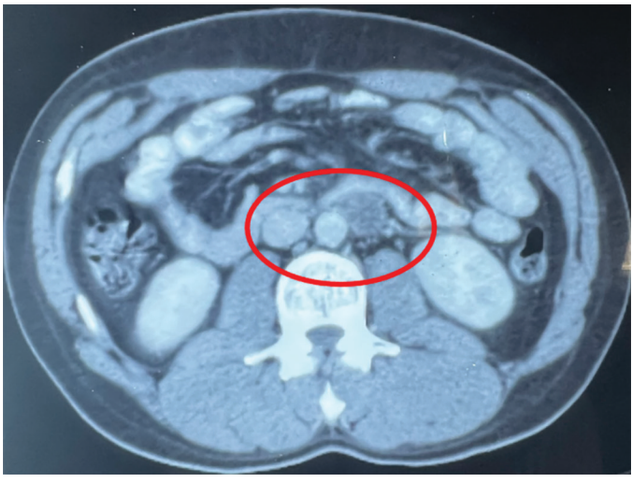

Fig. 14.2: Residual retroperitoneal node

8. What is the management of post-chemotherapy residual lesions?

Ans: The management of post-orchiectomy/post-chemotherapy depends on the histologic type of germ cell tumor (GCT):

A. Seminoma[14,15]

For seminomas, the response evaluation scan is a FDG PET/CT which is performed 8–10 weeks after the completion of the chemotherapy.

- No evidence of residual disease: Surveillance
- Residual mass < 3 cm: Masses <3 cm invariably have necrosis or fibrosis only, therefore, surveillance is a reasonable option.
- Residual mass >3 cm: FDG PET has a high NPV for these lesions, meaning that residual masses with no FDG uptake, even if larger than 3 cm, can be safely observed.[16] However, the PPV of FDG PET is only around 25–30% and thus irradiating all lesions which are >3 cm with FDG uptake would lead to considerable overtreatment. The results of the SEMPET trial have not been replicated in other multicentric cohort studies. Studies are evaluating if any cut-off value of SUV_{max} can predict if the residual mass has actual residual disease.
- If there is progressive disease accompanied with high β-hCG, then salvage chemotherapy should be initiated.
- If there is progressive disease without elevation of β-hCG, then a biopsy from the mass should be performed before starting salvage chemotherapy.
- RPLND for post-chemotherapy seminoma is rarely performed in the present day because of the high morbidity associated with the surgery as a result of severe desmoplastic reaction.

B. Nonseminomatous germ cell tumor

- In contrast to seminoma, there is no role for FDG-PET scans in the work-up of residual disease seen on CT of males with NSGCT.[17] FDG-PET is neither sufficiently sensitive in detecting nodes that contain viable tumor nor can it reliably differentiate teratoma from fibrosis.
- The role of surgery for residual retroperitoneal lesions of <1 cm is uncertain, the alternative option is close surveillance, with risk of recurrence up to 6–9%.[18]
- For males who have normalized their serum tumor markers but have imaging evidence of retroperitoneal lymph node(s) larger than 1 cm, a retroperitoneal lymph node dissection (RPLND) is recommended.[5,14] RPLND should be performed within 6–8 weeks of the last chemotherapy, within 4 weeks of a CT scan and 7–10 days of markers assessment.
- Second line chemotherapy is offered when the tumour markers show elevation after completion of the first line chemotherapy.

9. What histopathology one can except following the resection of residual masses for NSGCT?

Ans:

- The differential diagnosis of residual masses present at the completion of chemotherapy includes:[19]
  - Necrosis or fibrosis (40 to 50%)

- Mature or immature teratoma (30 to 40%)
- Residual non-teratomatous germ cell tumor (GCT) (10 to 15%)

- Unfortunately, it is generally not possible to distinguish these possibilities on imaging. For example, multiple factors may predict the histology of residual retroperitoneal masses in males with NSGCT, including the presence of teratomatous elements in the primary tumor, levels of serum tumor markers prior to chemotherapy, and the degree of reduction in mass size during chemotherapy.[20]

10. Why is resection of residual masses in NSGCT done when the possibility of residual tumor is only 10–20%?

Ans:

- The goal of resecting residual masses is to remove any residual teratoma or viable germ cell tumor (GCT). In addition, the resection of residual cancer is necessary in order to guide decisions about whether to administer additional chemotherapy.
- There are multiple reasons to resect residual teratoma even though most teratomas behave in an indolent manner:
  - Teratomas are relatively resistant to the chemotherapy and radiation therapy (RT) regimens for testicular GCTs because they are relatively slow growing tumors. Therefore, surgery is the only reliable way to eliminate them.
  - Viable GCT may coexist with teratoma, which can lead to clinical recurrence if not resected.
  - Malignant transformation of mature teratoma can occur. Sarcomas or carcinomas arising from a teratoma are resistant to chemotherapy and are associated with a poor prognosis.
  - Indolent growth of a teratoma may compromise vital organ function and/or cause pain and other symptoms (growing teratoma syndrome).

11. What is growing teratoma syndrome?

Ans:

- Benign teratomatous elements may enlarge during or after chemotherapy, mimicking progressive or relapsed disease first described by Logothetis.[21]
- Two primary theories have been put forth: The first suggests that chemotherapy selectively targets immature malignant cells while leaving teratoma cells unaffected, and the second proposes that chemotherapy accelerates the process of de-differentiation, leading malignant cells to transform into benign mature teratoma cells.
- In patients who meet Logothetis' criteria, suspicion should arise for the presence of growing teratoma syndrome, which includes three key elements: Progressive enlargement of masses during or following systemic chemotherapy, a return to normal levels of previously elevated serum tumor markers, and the identification of mature teratoma in prior histological analyses.
- Complete surgical resection is indicated rather than additional chemotherapy.

12. What are the different settings in which RPLND is performed in GCTs?

Ans:

1. **Primary RPLND:** This is done for stage 1 and stage 2A GCTs with normal tumor markers. It is an established option for stage 1 NSGCT when the patient has high risk featured in the pathology of the orchidectomy. Although traditionally, primary RPLND has not been utilized for stage 1 seminoma, recent studies like SEMS, COTRIMS have evaluated the role primary RPLND in stage 1 seminoma and have demonstrated its feasibility and acceptable oncological outcomes.
2. **Post-chemotherapy RPLND:** This is done for all advanced NSGCTs which have a residual lesion more than 1 cm in size after completion of first-line chemotherapy with normalized tumor markers.
3. **Salvage RPLND:** When the tumor markers fail to normalize after completion of first-line chemotherapy, second-line chemotherapy is the standard of care. If the tumor markers have normalized or reduced to very low levels after the second-line chemotherapy, then salvage RPLND is performed. This is done even if the residual lesion is less than 1 cm in size.
4. **Desperation RPLND:** Occasionally, tumor markers continue to rise during chemotherapy and the RPLND needs to be performed as a desperate measure.
5. **RPLND for growing teratoma syndrome:** Occasionally, the retroperitoneal nodal mass continues to grow even though the tumor markers have normalized. This suggests the presence of teratoma in that nodal mass.

13. What is the template for a RPLND?

Ans:

- The standard of care for a post-chemotherapy RPLND is a complete bilateral template RPLND
- The boundaries are as follows:
  - Cranial: The left renal vein

  - Caudal: The point of crossing of the ureters over the common iliac arteries
  - Laterally: Both ureters
- A standard bilateral template RPLND entails removal of the following nodal packets: Paracaval, precaval, inter-aortocaval, pre-aortic, para-aortic.
- Retrocaval and retro-aortic tissue is removed if there was disease prior to initiation of chemotherapy.

14. What are the indications for a modified template RPLND?

Ans:

- The concept of modified template has come into being in an attempt to reduce the morbidity associated with extensive dissection and also to allow for at least one side nerves to be preserved during a RPLND.
- The right-side template includes removal of the paracaval, precaval and inter-aortocaval lymph nodes.
- The left template includes removal of the para-aortic and inter-aortocaval lymph nodes.
- Studies have shown that in well-selected patients, a modified template RPLND is not oncologically inferior to standard template dissection.[22,23]
- These patients are those with IGCCCG good risk disease who have residual nodal burden less than 5 cm.

15. What is the role of nerve-sparing RPLND?

Ans:

- A bilateral nerve-sparing RPLND should be performed whenever feasible.
- These nerves are the post-ganglionic sympathetic nerve fibres which are responsible for bladder neck closure at the time of ejaculation. Damage to these nerves will lead to retrograde ejaculation.
- A modified template RPLND aims to preserve one-side nerves which has also been shown to result in antegrade ejaculation in 70% patients.
- However, preservation of the nerve fibres should never be given priority over removing all nodal tissue in the described template.

16. What are the surgical approaches for RPLND?

Ans:

- The most commonly used approach is the open midline transperitoneal one.
- However, this requires bowel mobilization which leads to post-operative ileus in some patients.
- The midline extraperitoneal approach avoid bowel mobilization and is associated with earlier bowel recovery.
- The laparoscopic and robotic approaches have also been described. These are usually utilized for primary RPLNDs and in post-chemotherapy RPLNDs with small residual disease.[24]

Scan QR Code for Video on **RPLND**

VIDEO 3

17. What is the role of resection of extra-retroperitoneal disease in GCTs?

Ans:

- **Lung lesions:** Patients with persistent intra-thoracic masses following cisplatin-based chemotherapy should undergo resection of disease if technically feasible. Prognosis following resection is favourable; over 80 percent can be expected to achieve long-term survival. Lung lesions should be resected, if feasible, irrespective of the pathology of the RPLND specimen as the degree of concordance between the 2 sites is only 60–70%.
- **Mediastinal disease:** In contrast to GCTs that are metastatic to the mediastinum, GCTs that arise in the mediastinum carry a very poor prognosis despite chemotherapy or a multimodality approach.

18. How are these patients followed up?

Ans: Patients are followed up as given in Table 14.4.

TABLE 14.4: Germ cell tumours

Modality	*Year 1*	*Year 2*	*Year 3*	*Years 4 and 5*
Tumor markers + doctor visit	4 times	4 times	2 times	2 times
Chest X-ray	1–2 times	Once	Once	Once
Abdominopelvic magnetic resonance imaging (MRI)/ computed tomography (CT)	1–2 times	At 24 months	Once at 36 months	Once at 60 months
Thorax CT	1–2 times	At 24 months	Once at 60 months	Once at 60 months

Fertility and Sexual Aspects

Testicular tumors and its treatment with chemotherapy/ RPLND affect the fertility potential of the patients.

Patients should be counselled regarding future infertility and need for semen cryopreservation. Patients may recover from the chemotherapy and have an improvement in their semen parameters and regain fertility. However, semen cryopreservation should be offered to all patients of testicular cancer as it is more cost-effective than other treatments for fertility in the future. Usually, 2–3 semen samples are used for cryopreservation depending on the semen quality. With advancements in *in-vitro* fertilization techniques, any cryopreserved semen sample, even when it contains only a few sperms, could be used for subsequent infertility treatment. However, the utilization rates of preserved semen are low, possibly due to regaining normal fertility, use of cryopreserved semen after the follow-up period of the study or death due to disease or treatment.[1,25]

SUMMARY

- A contrast enhanced CT scan of the chest, abdomen and pelvis is the standard imaging evaluation for patients with GCTs.
- Patients with advanced GCTs are classified as per the IGCCCG risk stratification.
- Bleomycin + Etoposide + Cisplatin (BEP) is the most commonly used chemotherapy regimen for advanced GCTs. The number of cycles depend on the IGCCCG risk category.
- Patients with IGCCCG good risk disease receive 3 cycles of BEP while intermediate and poor risk patients receive 4 cycles.
- For seminomas, a FDG PET/CT is done 8–10 weeks after completion of the chemotherapy. FDG PET CT has a high NPV but low PPV for the presence of residual seminoma.
- For non-seminomas, a CECT of the chest, abdomen and pelvis is done 4 weeks after completion of chemotherapy. Any residual disease more than 1 cm in size warrants a RPLND.
- Persistently raised tumor markers after first line chemotherapy warrants the use of second line chemotherapy like VIP or TIP. If markers normalize after the second line chemotherapy, then a salvage RPLND is performed.
- If the retroperitoneal mass continues to grow in size even after normalization of tumors markers, then this suggests a growing teratoma syndrome, for which a RPLND is performed.
- The standard template of RPLND is bounded by the left renal vein superiorly, the crossing of the ureters over the common iliac arteries inferiorly and the two ureters laterally.
- A modified template RPLND may be performed in patients with good risk IGCCCG disease and limited nodal burden.
- A unilateral or bilateral nerve sparing RPLND helps preserve antegrade ejaculation.
- Lung lesions should always be resected when feasible.
- A strict follow-up schedule with physical examination, tumor markers and imaging should be followed.

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