Review Article

Testicular Tumour

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Abstract

Testicular cancer is rare, but it is the commonest cause of malignancy in young men. Painless scrotal masses must be investigated with ultrasound imaging and tumour marker assay before being treated with radical inguinal orchidectomy. For unknown reasons, the incidence of this cancer increased in Caucasian population. The incidence of testicular germ cell tumour has doubled in past 40 years. An annual increase of 3-6% is reported in Caucasian population. But the mortality rate has been stable or decreasing due to improvement in treatment.

In the past, metastatic testicular cancer was usually fatal, but recent advances in treatment, including high-dose chemotherapy and stem cell rescue, have considerably improved the prognosis. Indeed, testicular cancer is a bright spot in the oncological landscape and are now considered the model for the treatment of solid tumors. We looked into the epidemiology, presentation, classification, work up, staging, various treatment modalities and prognosis of testicular tumour in this article.

Key words: Testicular tumour.

Introduction

Primary testicular tumors are the most common solid malignant tumor in men between the ages of 20 and 35 years . For unknown reasons, the incidence of this cancer has increased during the last century.[1] Most testicular tumours are derived from the germ cells of the testis, although about 5% of testicular tumours may be derived from other cells, including Leydig cells and lymphocytes (lymphoma).[2] The cause of testicular tumours is unknown, but several predisposing factors are recognized.

The classification of testicular germ cell tumours is confusing because different systems and non-seminomatous components. The USA and WHO classifications focus particularly on the range and degree of differentiation of tissue types within the tumours, whereas the British classification regards all mixed tumours as teratomas (because of their capacity to produce tissues from all three germ layers) and then bases secondary classification on the degree of differentiation.

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Any solid, firm mass within the testis should be considered testicular cancer until proven otherwise. Prompt diagnosis and early treatment are required for cure. Testicular cancer may be painless, in which case they are sometimes ignored by the patient. In patients with scrotal pain, testicular cancer must be differentiated form epididymitis. The clinician should consider the full differential diagnosis of a testicular mass, which includes not only epididymitis but epididymo-orchitis, testicular torsion hydrocele, hernia, hematoma, spermatocele, varicocele, and syphiliticgumma.[3]

Testicular cancers are highly curable, even in patients with metastatic disease at diagnosis. The prognosis depends upon the histologic type of cancer (seminoma versus nonseminoma), stage, and other features such as tumor marker and type of metastatic disease. Cure rates for good-risk disease are nearly 90-95%.

Various risk factors have been associated with testicular tumors, but the specific etiology is not known. Cryptorchidism, genetic predisposition, family history and prior testicular cancer are important etiological factor. Undescended testis has forty times more chance of developing testicular cancer. (Fig-10 &11)

Painless swelling or nodule of one testicle is the most common presenting symptom. On the physical exam this mass or nodule cannot be separated from the testis. Dull ache or heavy sensation in the lower abdomen could be presenting symptom. Patients who experience a hematoma with trauma should undergo evaluation to rule out testicular cancer.

Disseminated disease have symptoms of lymphatic or hematogenous spread. Presenting symptom could be neck mass in supraclavicular lymph node, anorexia, nausea and other gastrointestinal symptom. Bulky retroperitoneal disease could present as back pain. Cough, chest pain, hemoptysis and shortness of breath could be presenting symptom of mediastinal adenopathy or lung metastatic disease.

Classification

Approximately 95% of testicular tumors are germ cell tumors. These are divided into two types: pure seminoma (no non-seminomatous element) & non-seminomatous germ cell tumors.[4]

A. Germ cell tumour
   1. Seminoma
   2. Non seminma (Teratoma)

B. Mixed germ cell tumour

C. Yok sac tumour

D. Sex cord stromal tumor (Sertoli cell, Lyedig cell tumor)

E. Lymphoma

Seminoma

In addition to pure seminomas, which constitute roughly 50% of pure germ cell tumors, a seminomatous component is present in 20% of mixed germ cell tumors. Serum tumor markers are usually at normal levels, but if syncytiotropho-blastic giant cells are present, beta-hCG may be elevated. Seminoma looks like clear or vacuolated cells with well-defined cell margin. Most tumours have variable degree of lymphocytic infiltrate. (Fig-7). Classical seminoma has three variant-cribriform, pseudo-glandular and tubular.

Non-seminoma

- Embryonal carcinomas constitute about 2% of all testicular germ cell tumors but are histological type in 85% of mixed germ cell tumors. They have large pleomorphic cells with different architectural patterns (fig-6).
- Teratomas are part of the mixed germ cell tumor and are generally benign but have the potential for metastasis. They have elements from all three germ layers: ectoderm, endoderm, and mesoderm. In patients with residual disease after chemotherapy, teratoma is found in approximately 45% of resected specimens.
- Choriocarcinomas are the least common type of non-seminoma but are very aggressive. Widespread hematological metastasis can occur very early in the disease course; the retroperitoneum may be spared. Choriocarcinomas are associated with increased levels of beta-hCG.
- Yolk cell tumors, also called endodermal sinus tumor, are the most common testicular tumor in infants and young children. In adults, pure yolk cell tumors are rare, but yolk cell elements are found in approximately 40% of mixed germ cell tumors. Yolk cell tumors are associated with elevated alpha fetoprotein levels but they do not produce beta-hCG.

Mixed germ cell tumors (those containing two or more germ cell types) constitute approximately one third of testicular cancer (fig-2). Mixed germ cell tumor behaves like non-seminomas. The average age at diagnosis is older than 30 years. (fig-1)

Diagnostic workup

Ultrasonogram of the scrotum- USG has 100% accuracy for diagnosis of testicular malignancy. Seminoma has hypoechoic homogenous appearance. Non-seminoma appears as complex cystic and solid masses (fig-5)

USG of the abdomen and Chest x-ray are minimum requirement for staging of the tumour.

USG or CT Scan of the abdomen is necessary to see the enlargement of the para-aortic lymph nodes in the abdomen. (fig-4)

Chest x-ray shows pulmonary metastasis in the form of multiple cannon ball especially in non-seminoma. (fig-3)

Tumour markers

Blood must be taken for marker evaluation before surgical removal of the testis. This is important for staging and also for postoperative follow up and to know the response of the treatment and surveillance.

α-fetoprotein (AFP) is produced by the yolk sac elements and is elevated in 50-70% of NSGCT. It is not usually elevated in pure seminoma. Its half-life is about 5 days.

β-human chorionic gonadotrophin (β-HCG) is produced by trophoblastic elements in the tumour. It is raised in 40-60% of NSGCTs & in up to 30% of pure seminomas. It has a half-life of 1 day.

Lactate dehydrogenase (LDH) is less specific, but is more common in seminoma.

Overall, 90% of NSGCTs elaborate at least one tumour marker, while markers are elevated in <40% of seminomas.[5]

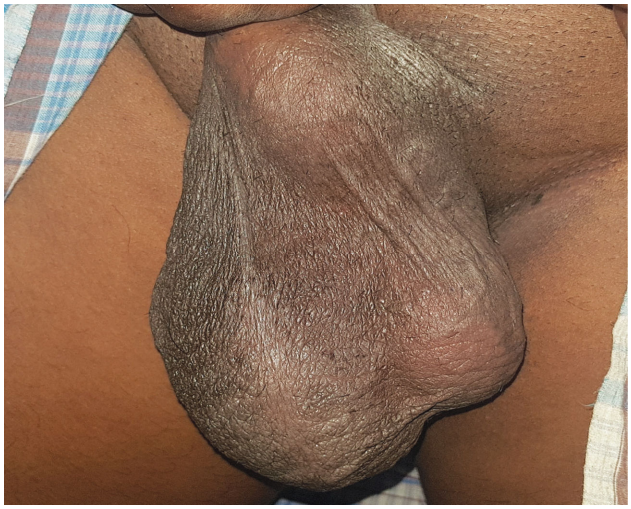
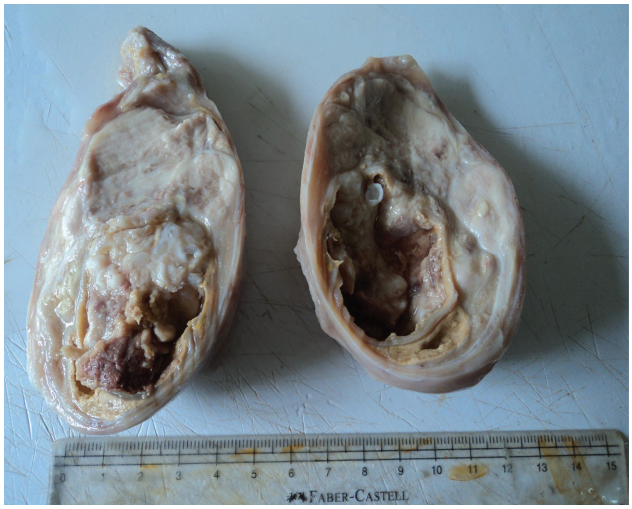


Fig-1



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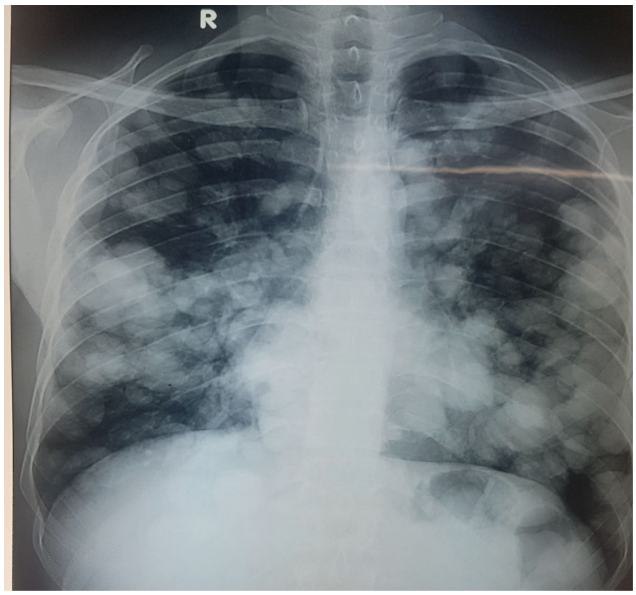

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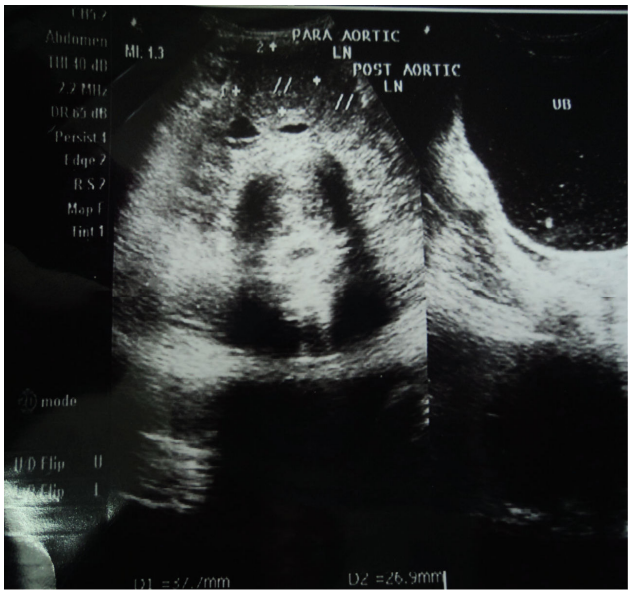

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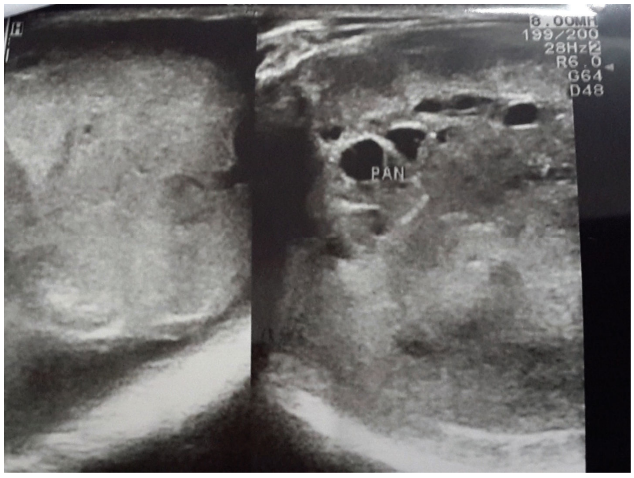

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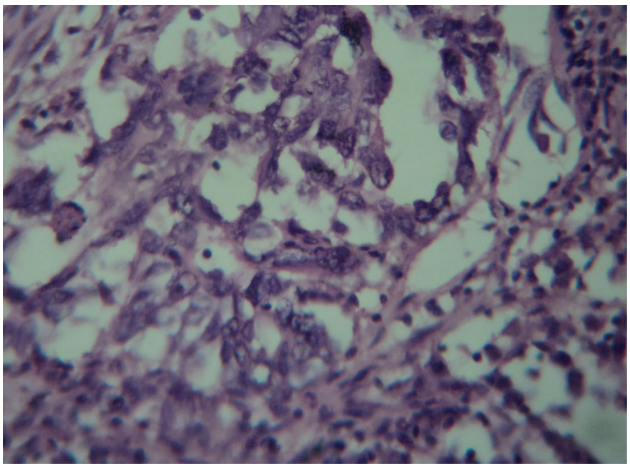

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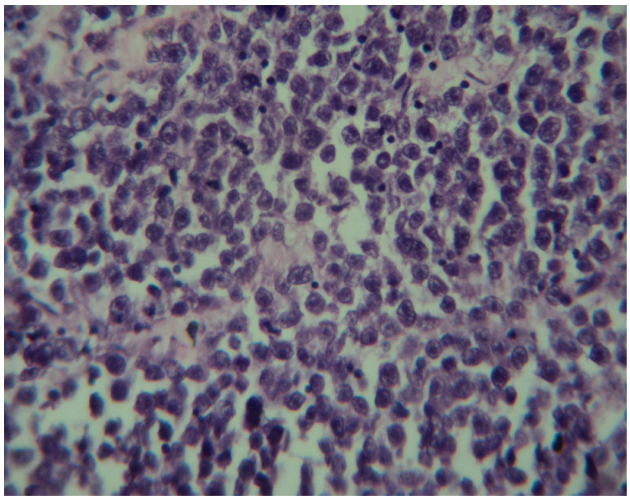

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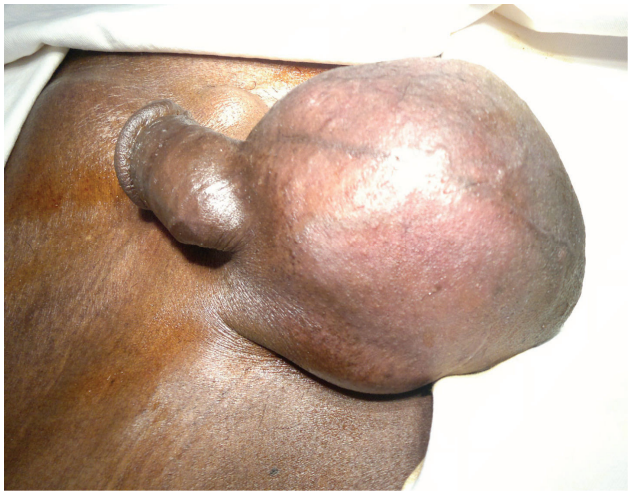

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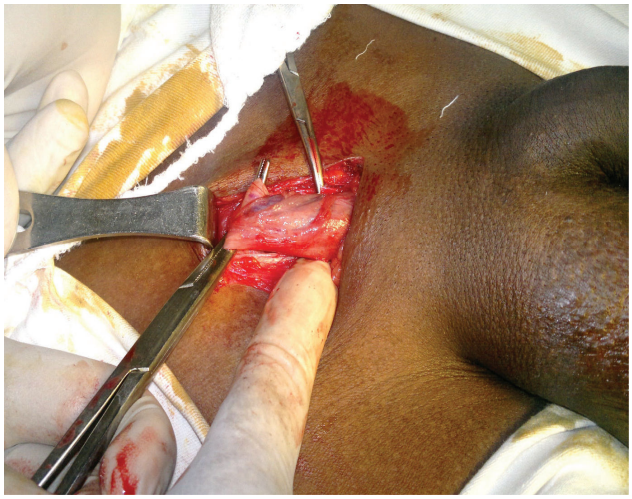

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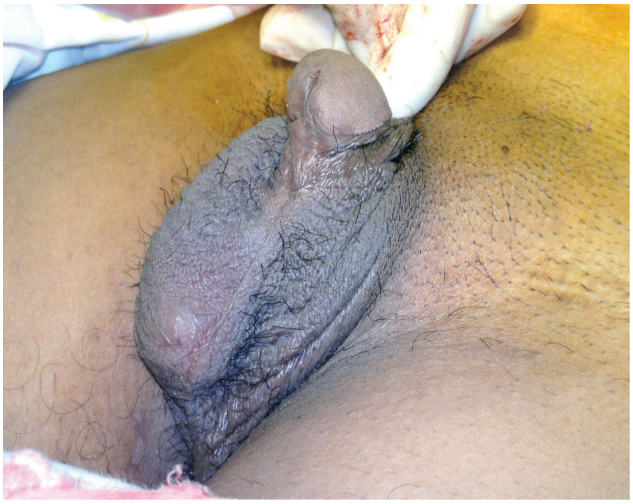

Fig-10

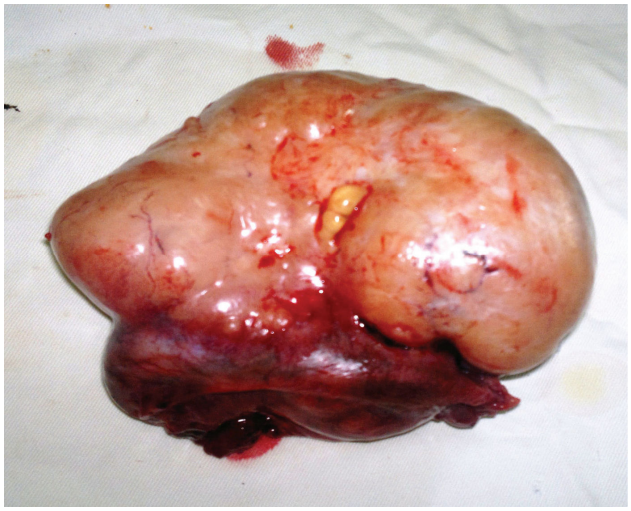

Fig-11

Table-I: Pattern of pathology of testicular tumour in JIMCH in last 4 years

Age in years	Pathology
35	Mixed emryonalcarcinoma+ Choriocarcinoma
32	Seminoma ((Intra-abdominal)
35	Seminoma (Intra-abdominal
45	Seminoma
33	Seminoma
18	Teratocarcinoma
24	Teratoma
20	Mixed embryonal carcinoma+ Seminoma
25	Yolk sac tumour

Table-II: Distribution of Pathological subtypes of GCT, based on 649 patient of Royal Marsden Hospital, UK.[6]

Type of pathology	Percentage
Pure seminoma	360(55%)
Embryonal carcinoma	87(13.5%)
Teratocarcinoma	75(11.5%)
Choriocarcinoma	12(1.8%)
Yolk sac tumour	8(1.2%)
Teratoma	24(3.7%)
Mixed Embryonal carcinoma Seminoma	58(8.9%)
Mixed Teratocarcinoma Seminoma	17(2.6%)
Mixed Choriocarcinoma Seminoma	1(0.2%)
Mixed Teratoma seminoma	8(1.2%)

According to Table II, more than half of the GCT was pure Seminoma (55%), followed by Embryonal Carcinoma (13.5%) and Teratocarcinoma (11.5%). The next were Mixed Embryonal Carcinoma Seminoma (8.9%) and Mixed teratocarcinoma Seminoma (2.6%).

Staging

American Joint Committee on Cancer (AJCC) groupings recommend use both TNM and Serum tumor markers for staging.[7]

TNM classification

Primary tumor (T)

TX- Tumor cannot be assessed

T0- No evidence of primary tumor (after radical orchiectomy)

T1-Tumor is limited to the testis and epidemic without vascular invasion

T2-Tumor limited to the testis and epidemic with vascular invasion or to the tunica vaginalis

T3- Tumor invaded the spermatic cord

T4- Tumor invades the scrotum

Lymph nodes (N)

NX- Regional lymph nodes cannot be assessed

N0- No regional lymph nodes

N1- Enlarged regional lymph nodes <2 cm in dimension

N2-Lymph nodes 2-5cmm in dimension

N3- Lymph nodes > 5 cm in dimension

Distant metastasis (M)

MX-Distant metastasis cannot be assessed

M0- No distant metastasis

M1-Non-regional nodal or pulmonary metastasis

Staging according to the level of Tumour marker

Sx indicates tumor markers unavailable or not done. S0 indicates tumor markers are within normal limit. Following table indicates other S categories.[8]

Final staging

- Stage I-pT1–4, N0, M0, SX
- Stage IA-pT1, N0, M0, S0
- Stage IB-T2-4, N0, M0, S0
- Stage IS-Any pT/Tx, N0, M0, S1–3
- Stage II-Any pT/Tx, N1–3, M0, SX
- Stage IIA-Any pT/Tx, N1, M0, S0-1
- Stage IIB-Any pT/Tx, N2, M0, S0-1
- Stage IIC-Any pT/Tx, N3, M0, S0-1
- Stage III-Any pT/Tx, any N, M1, SX
- Stage IIIA-Any pT/Tx, any N, M1, S0-1
- Stage IIIB-Any pT/Tx, N1–3, M0-1, S2
- Stage IIIC-Any pT/Tx, N1–3, M0-1, S3

Risk classification

Good- risk non-seminoma

- Testicular or retroperitoneal primary tumor, and
- Non-pulmonary visceral metastases, and
- Good markers-S1

Table-III

Stages	LDH	AFP (ng/ml)	HCG (mIU/ml)
S1	<1.5 times than normal	< 1000	< 5 000
S2	1.5-10 times than normal	1 000-10 000	5 000-50 000
S3	>10 times than normal	>10 000	>50 000

Table III is presenting the stages of tumor and the level of tumor markers present in each stage.

Intermediate- risk non-seminoma

- Testicular or retroperitoneal primary tumor, and
- Non- pulmonary visceral metastases,
- Intermediate marker-S2

Poor risk non-seminoma

- Mediastinal primary, or
- No pulmonary visceral metastases, or
- Poor markers-S3:

Good-risk seminoma

- Any primary site, and
- No non-pulmonary visceral metastases, and
- Marker-S1

Intermediate-risk seminoma

- Any primary site, and
- Non-pulmonary visceral metastases, and
- Marker-S1

Poor-risk seminoma

No patients are classified as poor prognosis9

Treatment

Initial therapy is selected according to AJCC stage group; risk stratification (good, intermediate, or poor risk), as per the guidelines of the International Germ Cell Cancer Collaborative Group 7; and histology (seminoma versus nonseminoma). [8,9]

Current guidelines from the National Comprehensive Cancer Network (NCCN) and the National Cancer Institute recommend treatment approach keyed to AJCC staging. These treatment groups are as follows:

Initial therapy consists of radical orchiectomy via inguinal approach. (Fig-9)

Seminoma management

Stage I

Clinical stage I seminoma have a very high cure rate. Cure can sometimes be achieved by radical inguinal orchiectomy alone. Options after orchiectomy include active surveillance, adjuvant chemotherapy, and adjuvant radiation therapy. Median time to relapse in patients who do not receive adjuvant treatment is 12 months but relapse can occur even beyond 5 years.

Active surveillance is recommended for patients with horseshoe or pelvic kidney or inflammatory bowel disease and for those who have received prior radiotherapy. Surveillance can also be offered to selected patients with T1 or T2 disease. Surveillance consists of a history and physical exam and measurement of AFP and hCG every 3 to 4 months for the first 3 years, every 6 months for years 4 to 7, then annually up to year 10. A CT scan of the abdomen and pelvis is recommended at each visit and a chest x-ray at alternate visits. It is essential that patients maintain strict adherence to the surveillance program for at least 10 years.

Adjuvant radiation therapy consists of delivery of 20-30 Gy to the infradiaphragmatic area, including th para-aortic lymph nodes and in some cases the ipsilateral ileoinguinal nodes. According to surveillance data, the overall incidence of disease failure without radiation therapy is 15% to 27%, with median of 20%. With radiation therapy, failure rates were 2% to 5%, with a median of 3%.

Adjuvant chemotherapy with a single dose of carboplatin is currently recommended as an alternative to radiation therapy. In a randomized study in 1,477 patients, after a median follow-up of 4 years there was no difference in relapse-free survival between patients receiving single-dose carboplatin and those receiving radiation therapy.[10] Five-year follow-up in 1,148 patients from this trial showed relapse-free rates of 96% for the radiation arm and 94.7% for the carboplatin arm. However, there were 15 new germ cell tumors in the radiation therapy arm versus two in the carboplatin arm, giving a hazard radio of 0.22 (95% CI 0.05, 0.95 p = 0.33). Acute toxicity such as lethargy and days missed from work is less with carboplatin than with radiation therapy.

Stage-II

Active surveillance is not an option. These patients receive adjuvant chemotherapy or radiation therapy

Radiation therapy: 35-40Gy is administered to the infradiaphragmatic area, including the para-aortic and ipsilateral iliac lymph nodes. Mediastinal radiation is not recommended.

Adjuvant chemotherapy: Four courses of chemotherapy with etoposide and cisplatin (EP) may be given.11

Stage-III

Seminoma stage IIC and III, good risk: Either four cycles of EP or three cycles of bleomycin, etoposide, and cisplatin (BEP)

- Seminoma stage IIC and III, intermediate risk: Four cycles of BEP

Nonseminoma management

Stage I

After radical inguinal orchiectomy, treatment options are active surveillance or chemotherapy. Retroperitoneal lymph node dissection (RPLND) is used to guide chemotherapy; the number of positive nodes present in the sample determines the number of chemotherapy cycles given. Open nerve-sparing RPLND is preferred over laparoscopic RPLND. RPLND has multiple complications of with (RPLND), including retrograde ejaculation.

Stage-II

Recommended treatment varies according to the results of tumor marker assays and CT scan.

Nonseminoma with normal tumor markers: open nerve-sparing RPLND or chemotherapy, either EP for 4 cycles or BEP for 3 cycles.

Stage-III

- Nonseminoma stage IIIA good risk: 95% of patients are cured with chemotherapy, either EP for 4 cycles or BEP for 3 cycles.
- Nonseminoma stage IIIB intermediate risk: BEP for 4 cycles is given; the cure rate is 70%.
- Nonseminoma stage IIIB poor risk: Enrollment in clinical trials is preferred. Chemotherapy with 4 cycles with BEP can be considered but fewer than 50% of patients will experience a durable complete response. In patients who cannot tolerate BEP because of pneumonitis from the bleomycin component, VIP (etoposide [VePesid], ifosfamide, mesna, cisplatin [Platinol-AQ]) is recommended.

Surgery for residual disease

Surgical resection is recommended for patients with residual disease after chemotherapy.[12] Laparoscopic LN dissection is recommended for stage 1 and 2 disease.[13] Retroperitoneal lymph node dissection (RPLND) should clear the region of residual disease. Open nerve-sparing RPLND is preferred over laparoscopic RPLND. Patients in whom RPLND reveals viable cancer, post chemotherapy residual masses are treated with subsequent chemotherapy.[13,14] Open nerve-sparing RPLND has multiple complications, including retrograde ejaculation.

Prognosis

Good-prognosis nonseminoma): 5-year survival is 90%.[15]

Good-prognosis seminoma (90% of seminomas): 5-year survival is 85%

Intermediate-prognosis nonseminoma: 5-year survival is 80%

Intermediate-prognosis seminoma: 5-year survival is 70%

Poor-prognosis nonseminoma: 5-year survival is 70%

Poor-prognosis s seminoma: No seminoma patients are classified as poor prognosis.

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