TESTICULAR CANCER

General Overview

- Testicular germ cell tumors are divided into seminoma's and non-seminoma's. The latter consist of a mixture of histological subtypes (embryonal carcinoma, yolk sac, choriocarcinoma, teratoma)
- Diagnosis is usually made after auto-palpation of testicular swelling
- Peak incidence between 20-30 years for non-seminoma and between 30-40 years for seminoma
- The main risk factor is aberrant testicular development (e.g. cryptorchidism, hypospadia)
- Treatment is given with curative intent and cure rates are high, even in the metastatic setting

Staging (AJCC Version 8) and Prognosis

- Physical exam (incl scrotum, all nodal regions, breast), bilateral testicular ultrasound, CT thorax-abdomen, tumor markers (alpha-foetoprotein, beta-hCG, LDH), sperm banking
- Orchidectomy (if high suspicion of benign lesion: discuss enucleation with frozen section)
- Tumor markers post-operatively (take variable half-life into account. In case of favorable marker decline, measure regularly until at least 2 consecutive normal markers).
- MRI brain in case of IGCCCG poor-prognosis, multiple lung metastases or beta-hCG >5000 IU/l
- In case BEP (bleomycin-etoposide-cisplatin) chemotherapy is indicated: spirometry, audiometry, sperm banking, port-a-cath
- For pts 18-35 years: contact AYA nurse to organize personalized patient trajectory

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed[1] **T0**: No evidence of primary tumor **Tis**: Intratubular germ cell neoplasia+ **T1**: Limited to testis and epididymis without vascular/lymphatic invasion; may invade tunica albuginea but not tunica vaginalis* **T2**: Limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis** **T3**: Tumour invades spermatic cord with or without vascular/lymphatic invasion** **T4**: Tumour invades scrotum with or without vascular/lymphatic invasion	**Nx**: LN cannot be assessed **N0**: no regional LN **N1**: M+ with a LN mass 2 cm or less or multiple LN (none more than 2cm) **N2**: M+ with a LN mass > 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour **N3**: LN mass > 5 cm in greatest dimension	**M0**: no distant M+ **M1**: distant M+ ** **M1a**: non regional LN or lung M+ **M1b**: distant M+ other than non regional LN and lung M+

LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.
1 Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is assessed in the radical orchidectomy specimen; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.
+ The current "Carcinoma in situ" nomenclature is replaced by GCNIS.

Update: March 2024

** AJCC eighth edition subdivides T1 Pure Seminoma by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension*
*** AJCC eighth edition considers the hilar soft tissue invasion and epididymal invasion as pT2, while the discontinuous involvement of the spermatic cord is considered as pM1 .*

Serum Tumor markers (pre chemotherapy)	***LDH (U/L)***	***hCG (mIU/ml)***	***AFP (ng/mL)***
SX: *not available*			
S1:	<1.5 x ULN and	*<5000 and*	*<1000*
S2:	1.5 – 10 x ULNC or	*5000 – 50.000 or*	*1000 – 10000*
S3	>10 x ULN or	*> 50000*	*>10000*

Prognostic groups for testicular cancer (UICC, 2016, 8th edn.)

Table based on EAU guidelines for testicular cancer (2023)

Stage grouping	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

A prognostic calculator for metastatic non-seminomas can be consulted at https://eortc.shinyapps.io/IGCCCG-Update/

Update: March 2024

Treatment localized (N0) testicular germ cell tumors

- Germ cell neoplasia in situ: 50% 5-year risk of progression to testis carcinoma. Treat with orchidectomy if contralateral testis is normal. Alternative in solitary testis: active surveillance or radiotherapy. (Petersen *et al,* J Clin Oncol 2002; Dieckman *et al*, Ann Oncol 2013)
- Discuss recurrence rates, acute and long term toxicity and follow up schedule for both surveillance and adjuvant chemotherapy
- Stage I seminoma: orchidectomy + surveillance.
    - Single cycle of adjuvant carboplatin AUC 7 is possible in patients with risk factors who do not wish to undergo surveillance. (Oliver et al, J Clin Oncol 2011)
- Stage IA non-seminoma (pT1): orchidectomy + surveillance (Kollmannsberger *et al,* J Clin Oncol 2015; Groll *et al*, Crit Rev Oncol Hematol 2007)
- Single cycle of adjuvant BEP is possible in patients who do not wish to undergo surveillance
- Stage IB (pT2-pT4) non-seminoma: orchidectomy + single cycle adjuvant BEP (Albers *et al*, J Clin Oncol 2008; Tandstad *et a*l, Ann Oncol 2014)
    - Surveillance is possible in patients who do not wish to undergo chemotherapy
    - Retroperitoneal lymph node dissection is not standard. Only for post-pubertal teratoma or patients who do not accept surveillance and cannot receive chemotherapy.

Treatment N+ and M+ testicular germ cell tumors

- Clinical stage I with persistently elevated markers after orchidectomy: repeat ultrasound of contralateral testis and CT thorax-abdomen at 4 weeks and treat as metastatic non-seminoma.
    - ➢ Only in case of stable marginally elevated markers, monitoring until further marker rise or progression on imaging is permitted.

Seminoma:

- Stage IIA/B: 3 cycles of BEP (Culine, Ann Oncol 2007; Giannatempo et al, Ann Oncol 2015)
    - ➢ If contra-indication for bleomycin: 4 cycles of EP (de Wit et al, J Clin Oncol 1997)
    - ➢ If contra-indication for BEP or EP: radiotherapy
    - ➢ If retroperitoneal LN <2cm and normal markers: repeat imaging (CT or FDG-PET-CT) and markers after six weeks. Treat only in case of progressive LN, marker rise or positive biopsy
- Stage ≥IIC with IGCCCG good prognosis: 3 cycles of BEP (Bokemeyer et al, Br J Cancer 2004)
- Stage ≥IIC with IGCCCG intermediate prognosis: 4 cycles of BEP (EAU guidelines 2023)
    - ➢ If contra-indication for bleomycin: 4xVIP (etoposide, ifosfamide, cisplatin)

Non-seminoma:

- Stage IIA with normal markers: nerve-sparing retroperitoneal lymph node dissection. (Neuenschwander, Eur Urol Focus 2022)
    - ➢ If <2cm and normal markers: repeat imaging and markers after six weeks. Treat in case of persistent or progressive lymph node enlargement or marker rise.
- Stage IIA with elevated markers or stage IIB, with IGCCCG good prognosis: 3 cycles of BEP (Mead et al, Clin Oncol 1997; de Wit et al, J Clin Oncol 1997)
- IGCCCG intermediate prognosis: 4 cycles of BEP (de Wit et al, Br J Cancer 1998)

Update: March 2024

- IGCCCG poor prognosis: 4 cycles of BEP

- Before and during chemotherapy:
  - Prescribe prophylactic LMWH during chemotherapy
  - Measure markers every cycle. Measure them on C1d5 as well (to detect increase due to tumor lysis rather than progression)
  - In case of 4 cycles: CT thorax-abdomen after 2 cycles
  - Lung spirometry before starting bleomycin, but only upon clinical indication afterwards. Perform chest auscultation and anamnesis for respiratory complaints before bleomycin.
  - Give bleomycin warning card. Lifelong contra-indication for pure oxygen unless life-threatening circumstances (bleomycin).
  - In smokers, refer urgently to smoking cessation consultation and follow up

Follow up after 1st line treatment

- CT thorax-abdomen and tumor markers 2-4 weeks after the last cycle of BEP
  - If residual mass (>1cm) with normal or normalizing markers: surgical resection
  - If residual mass without normalizing markers: tumor board individualized discussion (2nd line chemotherapy, radiation or resection)
- Follow up to be organized by urology for surgical patients and by medical oncology after BEP.
- Physical exam incl palpation of contralateral testis at every follow up.
- Consider follow up echography of contralateral testis in case of clinical abnormalities or microcalcifications
- Survivorship care:
  - Screen for testosterone deficiency.
  - After BEP:
    - Lifelong cessation of smoking and cannabis use (bleomycin).
    - Lifelong contra-indication for pure oxygen unless life-threatening circumstances (bleomycin). Give bleomycin warning card.
    - Lifelong strict follow-up and control of cardiovascular risk factors. Yearly measurement of cardiovascular risk factors (lipids, cholesterol, glycemia, blood pressure, weight)
    - Avoid noise exposure (cisplatin)

Follow-up Localized RCC

Follow-up schedules follow the ESMO expert consensus recommendations (Honecker et al, Ann Oncol 2018)

Seminoma stage I (active surveillance or after adjuvant carboplatin/radiotherapy):

Exam	Year 1	Year 2	Year 3	Year 4 & 5
Tumor markers	2x	2x	2x	1x
Abdominal MR (or CT)	2x	2x	1x at 36 months	1x at 60 months

Non-seminoma stage I (active surveillance):

Exam	Year 1	Year 2	Year 3	Year 4 & 5
Tumor markers	4x	4x	2x	2x
Chest X-ray	2x	2x	At 36 months if LVI+	At 60 months if LVI+
Abdominal MR (or CT)	2x	2x	At 36 months	At 60 months

After BEP, with normal markers:

Exam	Year 1	Year 2	Year 3	Year 4 & 5
Tumor markers	4x	4x	2x	2x
Chest X-ray	2x	1x	1x	1x
Chest CT *Only if lung metastases*	2x	At 24 m	At 36 months	At 60 months
Abdominal MR (or CT)	2x	At 24 m	At 36 months	At 60 months

What's new ?

- The SAKK 01/10 single arm phase 2 trial showed favorable outcomes after single dose carboplatin followed by involved-node radiotherapy in stage IIA and IIB seminoma, thus proposing a possible de-escalation of both chemo- and radiotherapy. Further de-escalation studies are ongoing, before these strategies are ready for standard practice. (Papachristofilou et al, Lancet Oncol. 2022)

Update: March 2024