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COLLEGIUM MEDICUM

Testicular cancer

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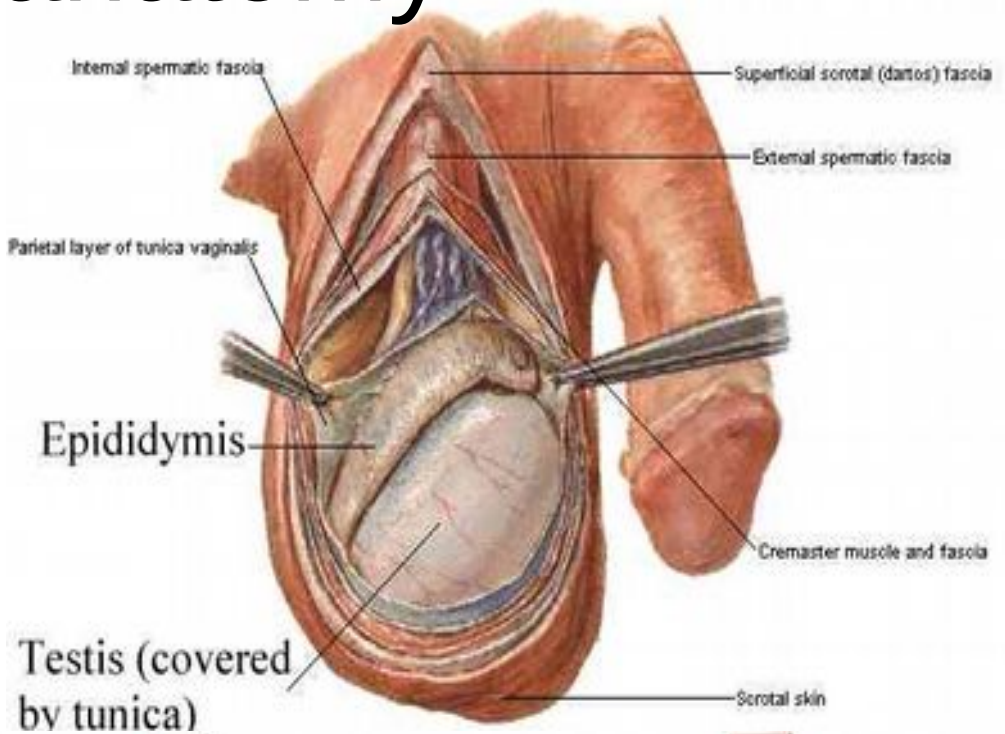
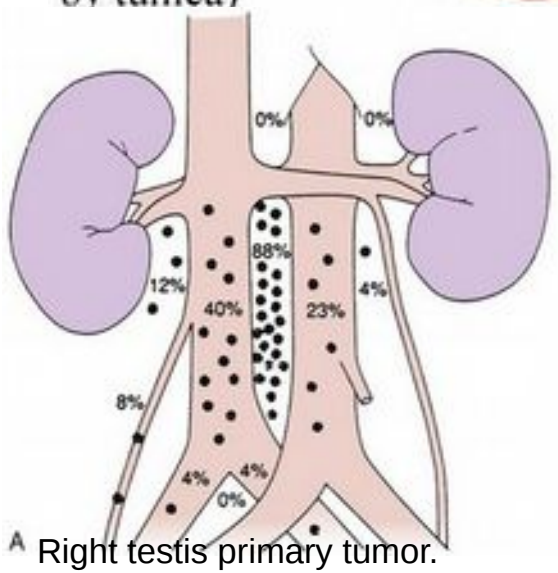
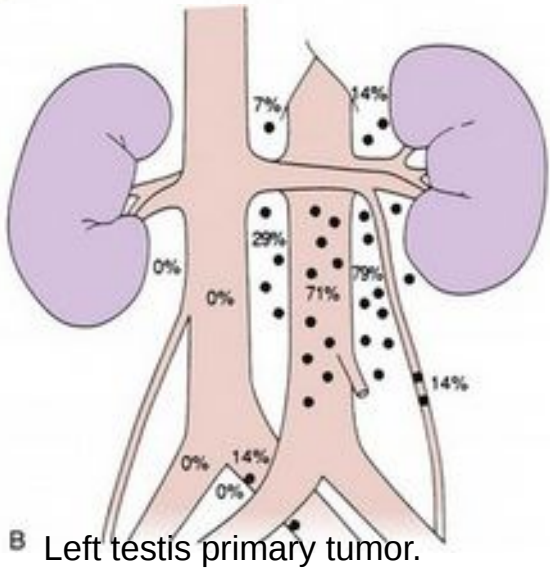
Testes anatomy

- lies obliquely within the scrotum suspended by the spermatic cord
- typically left testis situated slightly lower than the right
- typical size:
  - 3-4 cm craniocaudal axis
  - 2-3 cm transverse axis
  - 1,5-2 cm saggital axis
- Weight ~10-15g





A Right testis primary tumor.

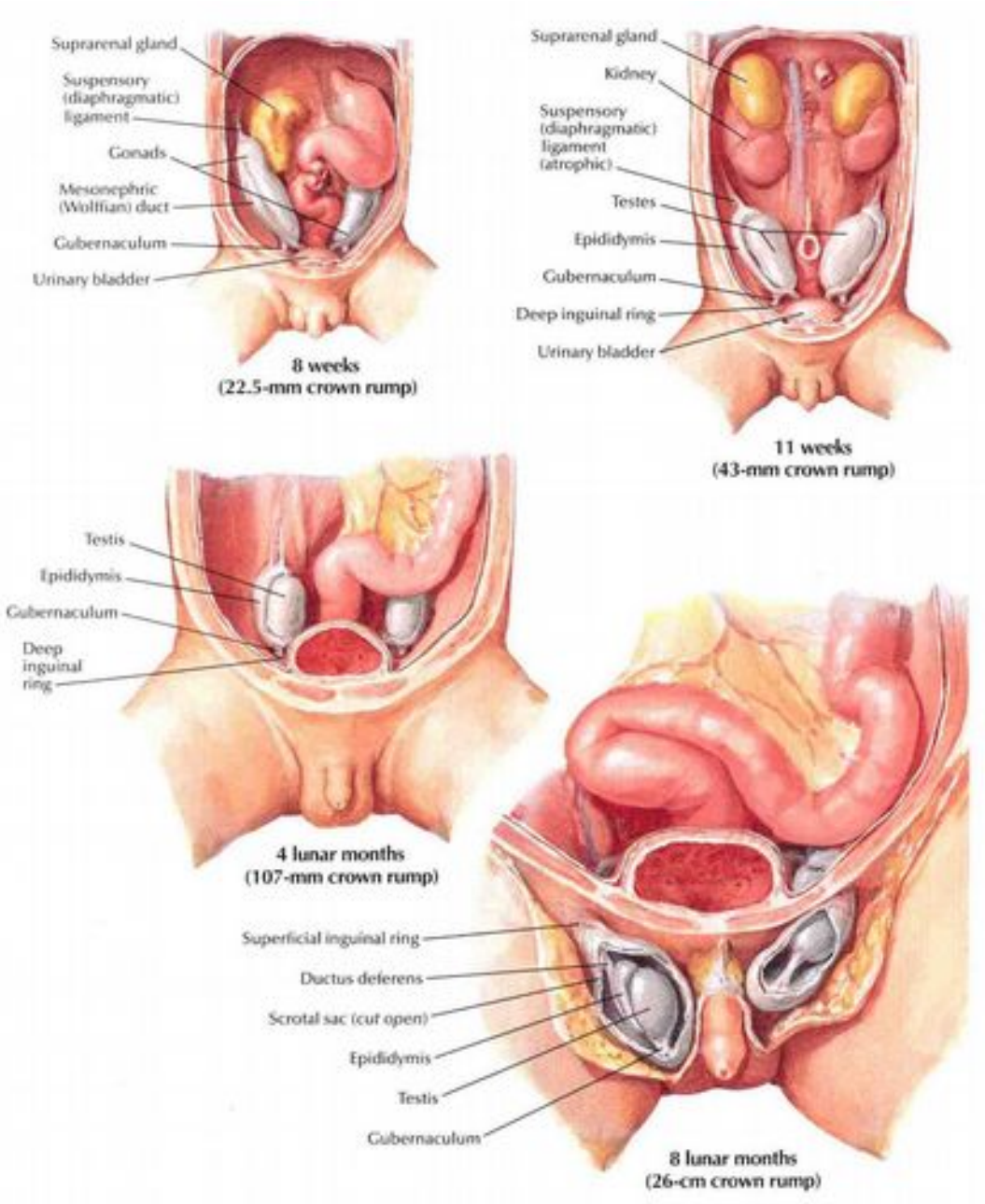


B Left testis primary tumor.

Distribution of retroperitoneal lymph node metastases in early-stage germ cell tumors.

Testes development and descent

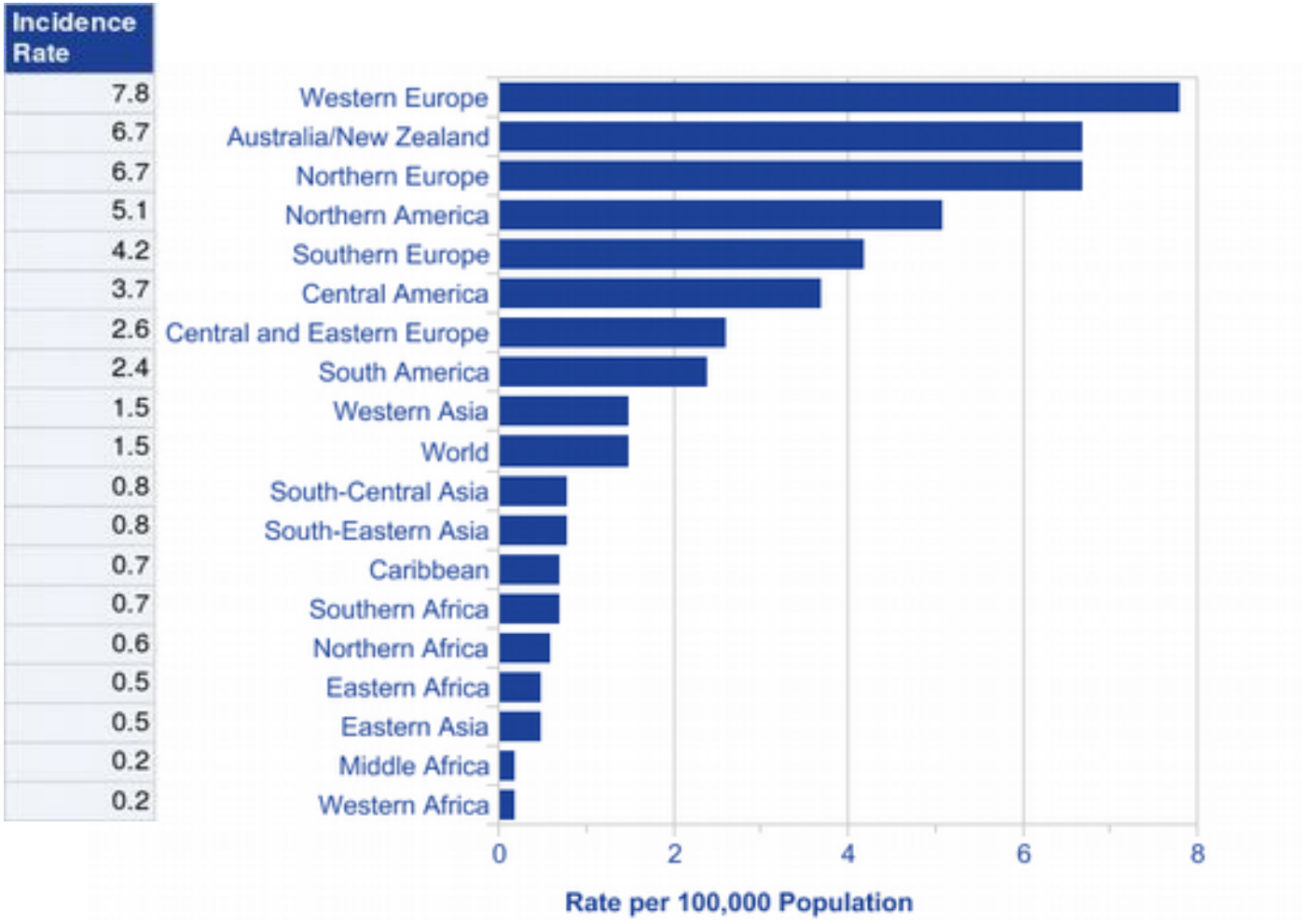
- Develops at T10-T12 segments in retro-abdominal space from so called genital ridge
- Begin to descend in 2nd month of intrauterine life
  - 3rd month reach iliac fossa
  - 4th -6th month deep inguinal ring
  - 7th month inguinal canal
  - 8th month: superficial inguinal ring
  - 9th month: scrotum
- Can give rise to ectopic testicular tissue along the descent path



Testicular cancer – risk factors

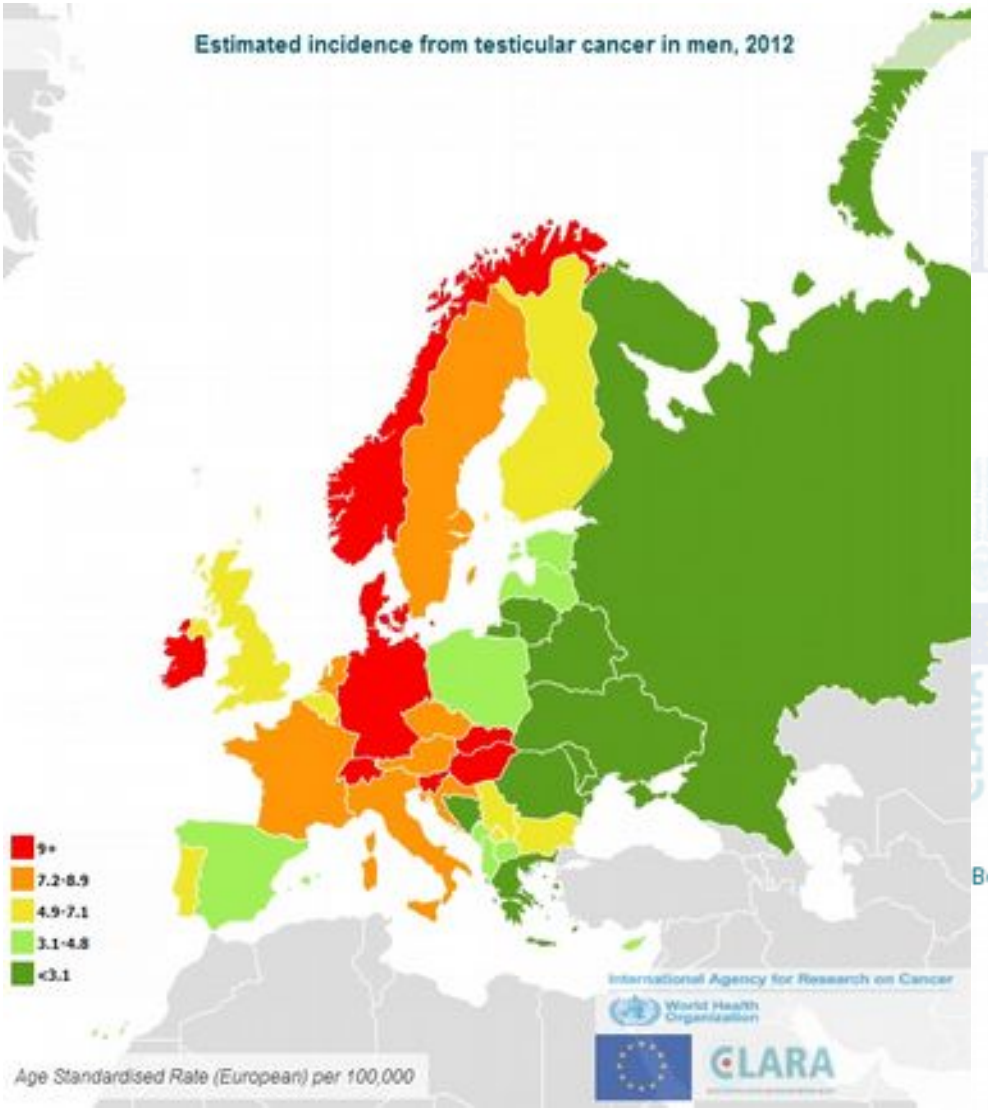
- Relative risk by ethnicity
  - Caucasian RR 1,0
  - Hispanic RR 0,9 – 0,4
  - Asian RR 0,3
  - African RR 0,2
- Congenital syndromes:
  - Down syndrome
  - Klinifelter syndrome
  - true hermaphroditism
  - ichthyosis
  - „prune belly” (Eagle-Barrett-Obrinsky) syndrome
- Previous history of:
  - mumps orchitis
  - cryptorchidism (especially untreated)
  - inguinal hernia
  - contralateral testicular cancer
  - intratubular germ cell neoplasia (ITGCN) a precursor lesion
- Enviromental factors
  - western lifestyle
  - marijuana use
  - estrogen exposure

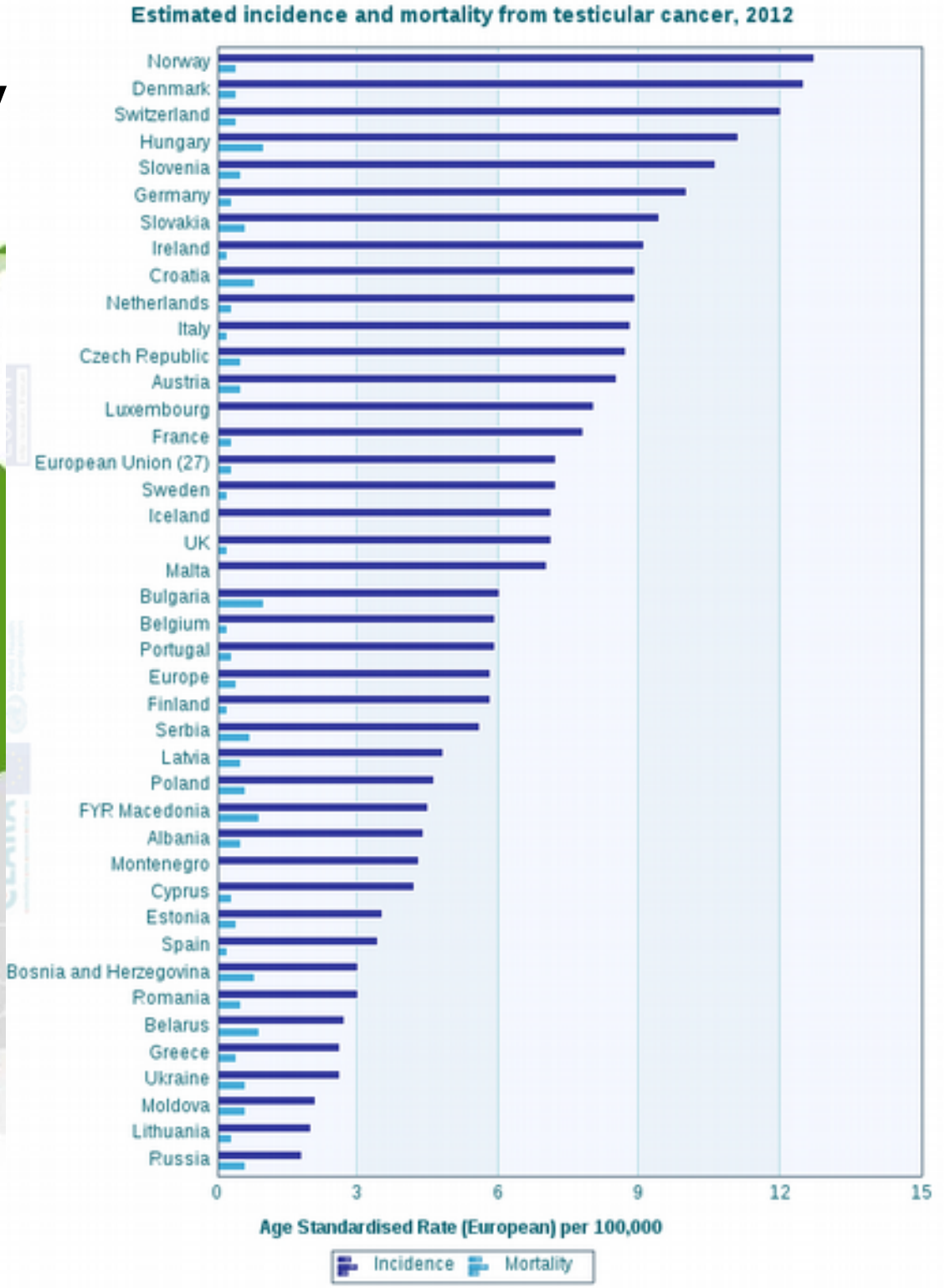
Testicular cancer incidence worldwide



Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10

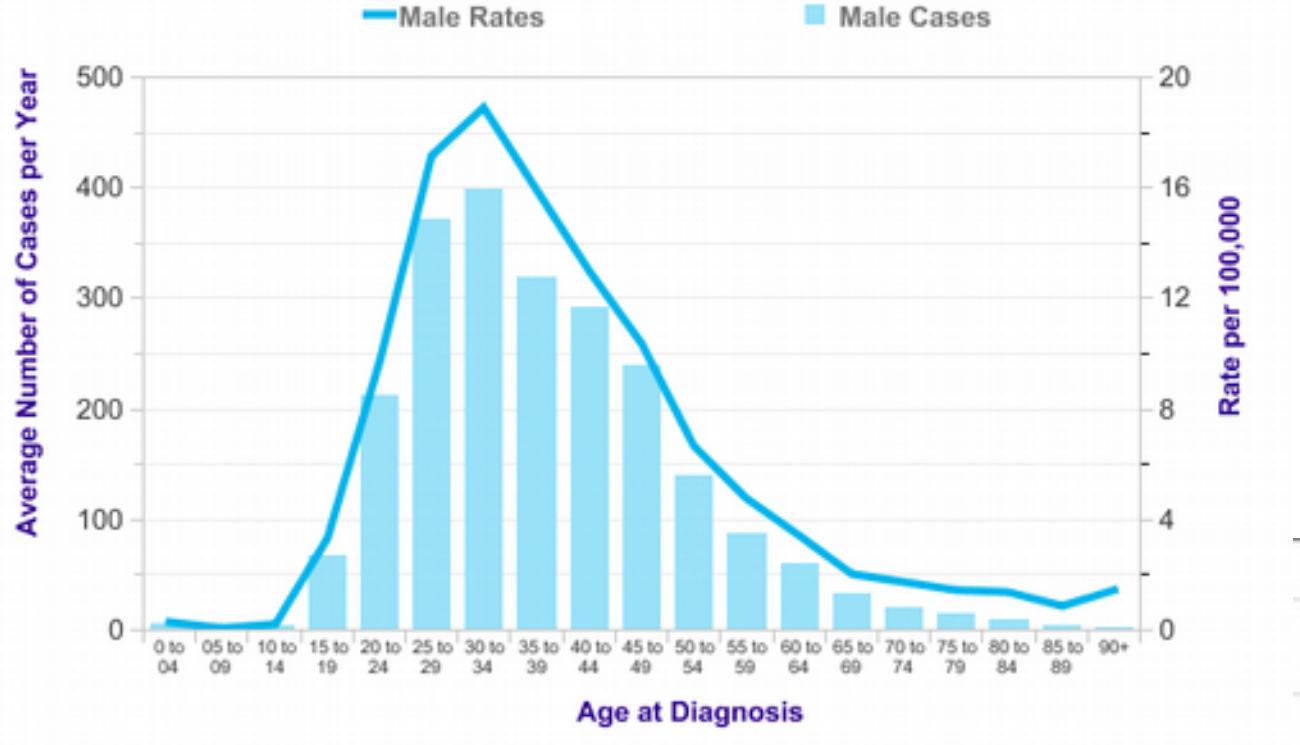
Incidence and mortality
European perspective





Based on: Cancer Research UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/testicular-cancer/incidence#heading-One, Accessed OCT 2016.

Testicular cancer – incidence by age



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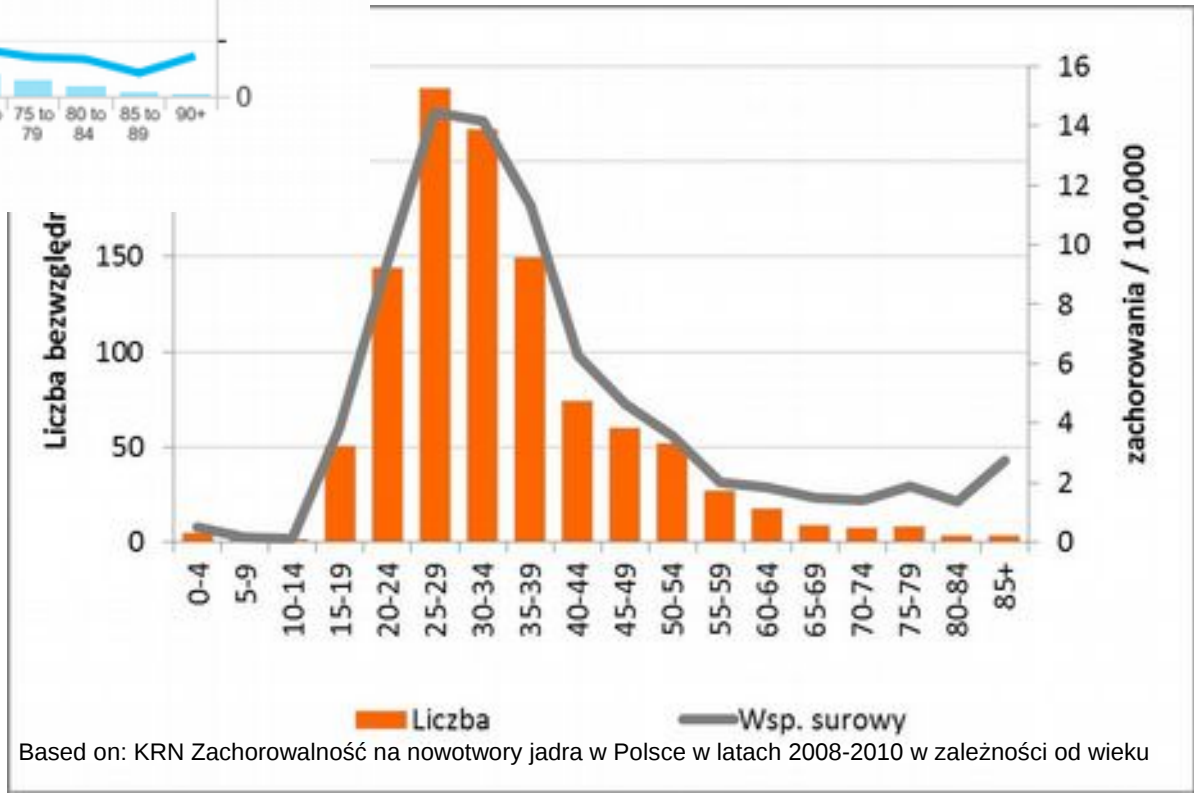
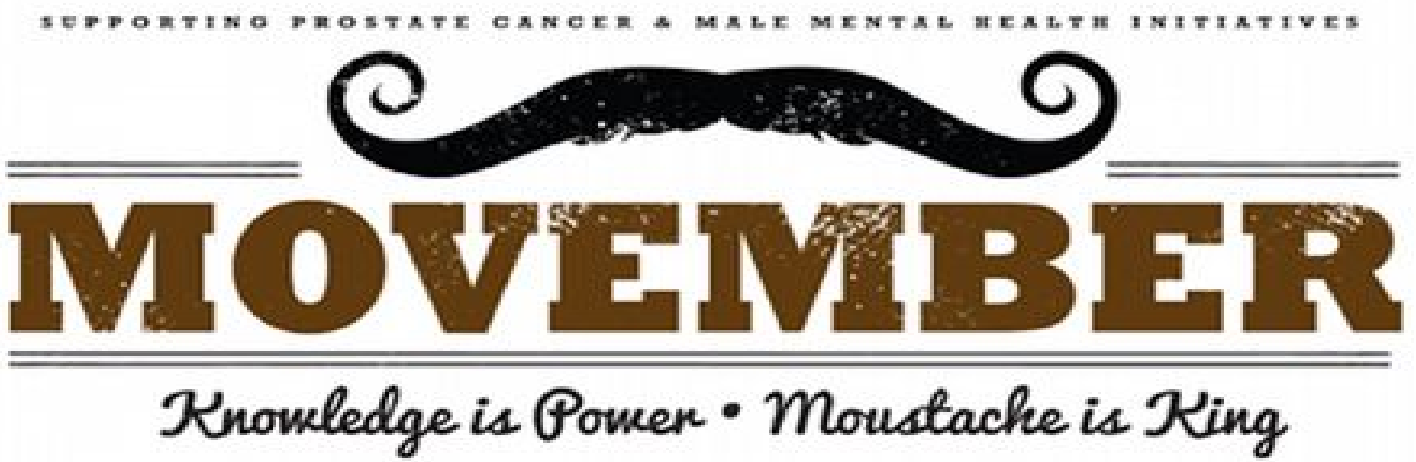


Based on: KRN Zachorowalność na nowotwory jadra w Polsce w latach 2008-2010 w zależności od wieku

Testicular cancer – symptoms

Palpable testicular tumor

- pain
- swelling
- sexual dysfunctions
- hematospermia
- abdominal mass
- distant metastases
- abnormal laboratory results



Testicular cancer – pathology

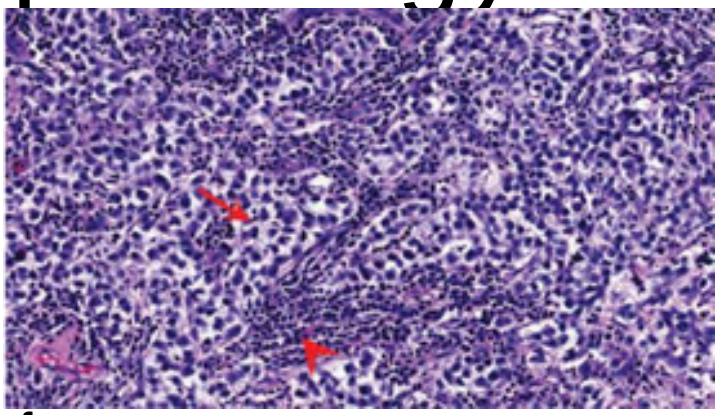
- Germ Cell Tumors (95%)
  - Seminoma
  - Embryonal carcinoma
  - Yolk sac tumor
  - Trophoblastic tumors
    - Choriocarcinoma
    - Other
  - Teratoma
    - Dermoid cyst
    - Monodermal teratoma
    - Teratoma with somatic type malignancies
  - mixed (very common)

- Non germ-cell histologies (5%)
  - Lymphoma
  - Other (<1%)

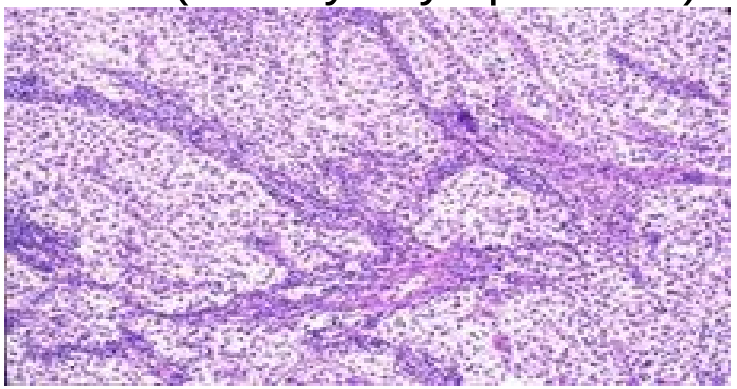
- Clinical classification
  - Seminoma (35-40%)
  - Non-seminoma (55-60%) (incl. mixed histologies)

  - Non-germ cell

Testicular cancer – pathology



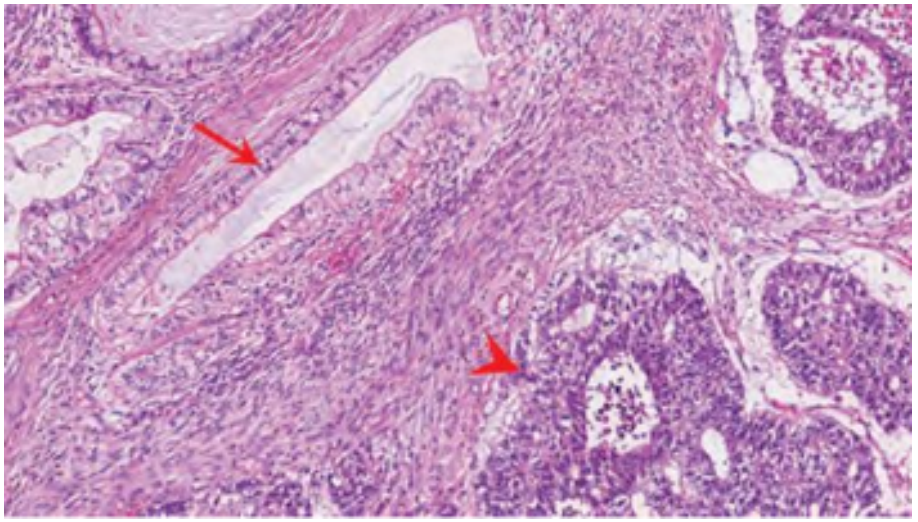
- Seminoma
  - the most common single histology
  - right > left testis
  - typically 4th and 5th decade; never seen in infancy
  - patients present with painless testicular mass
  - as much as 30 % have metastases at presentation (usually asymptomatic)
  - serum alpha fetoprotein is rarely elevated
  - Beta HCG elevated in ~30% of patients

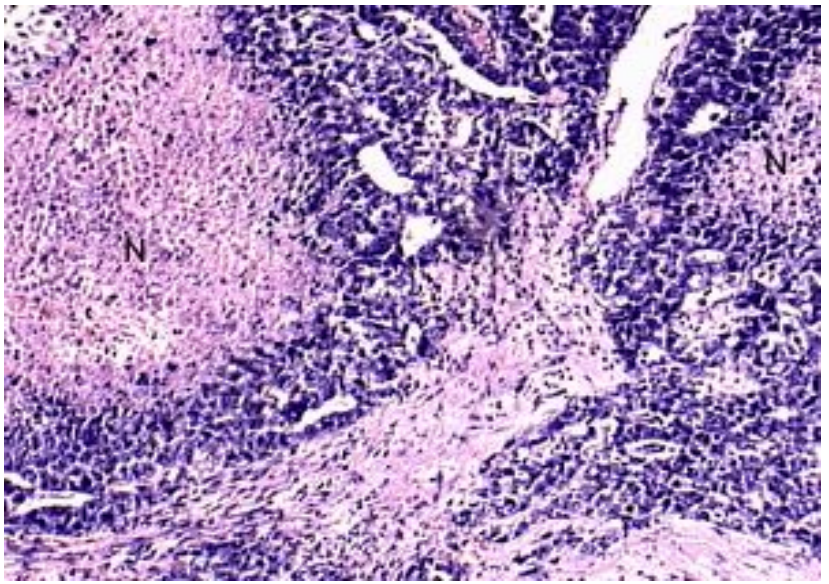


- Subtypes
  - classical (80%)
  - Anaplastic (5-10%) - agressive, poor prognosis
  - Spermatocytic (~10%) - indolent, low metastatic potenctial, good prognosis

Testicular cancer – pathology

- Embryonal carcinoma
  - most undifferentiated type of germ cell tumor
  - present (solo or as component) in ~90% of non-seminoma germ-cell tumors
  - serum AFP elevated in ~30% and B-HCG in 20% of cases
  - ~60% cases with non-elevated AFP and B-HCG - role of LDH
  - highly agressive, frequently metastasizes and/or invades cord structures

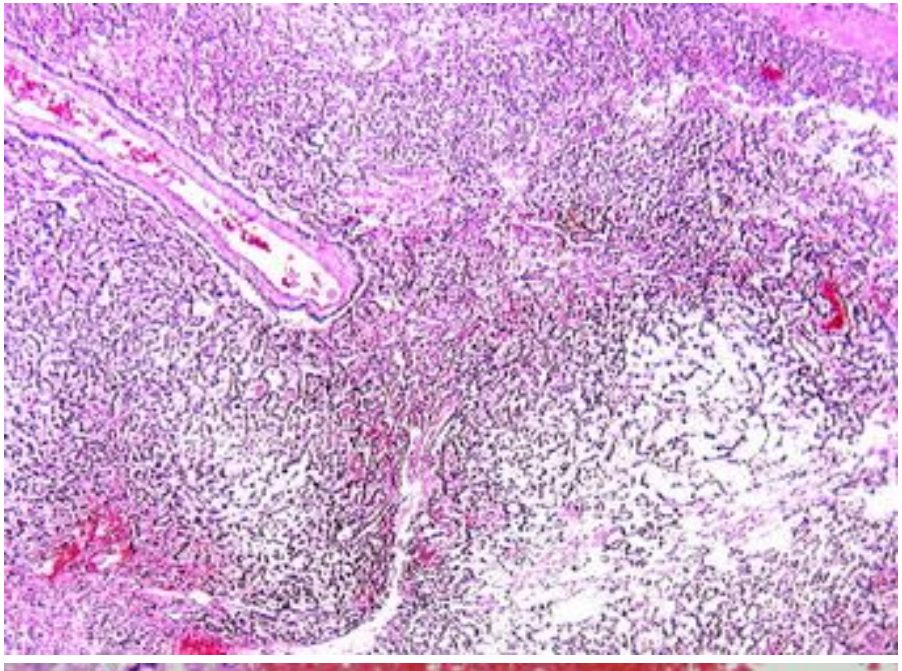


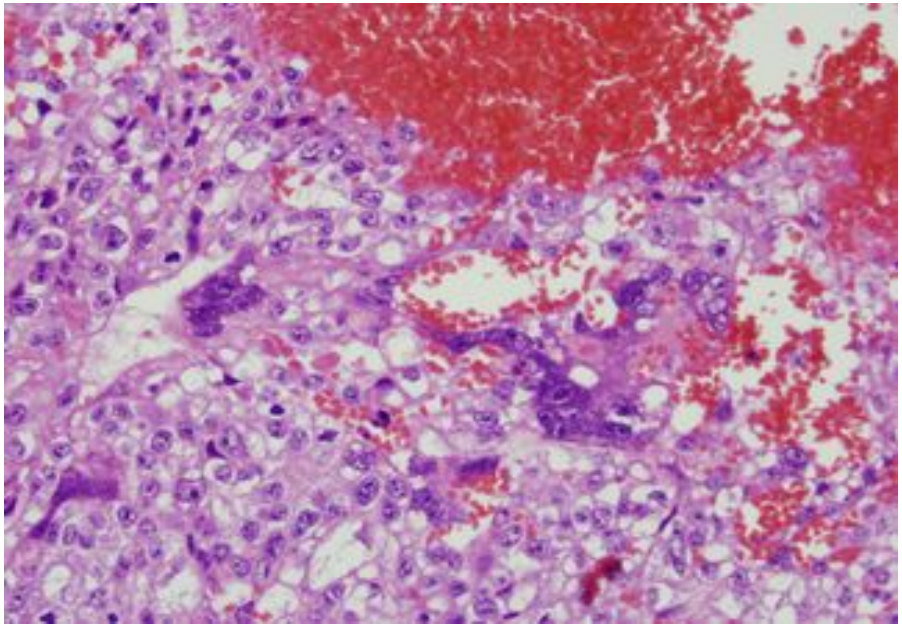


Testicular cancer – pathology

- Yolk Sac Tumor
  - most common germ cell tumor in children
  - typically as a part of mixed GCT (sole component in ~2%).
  - Typically elevated AFP

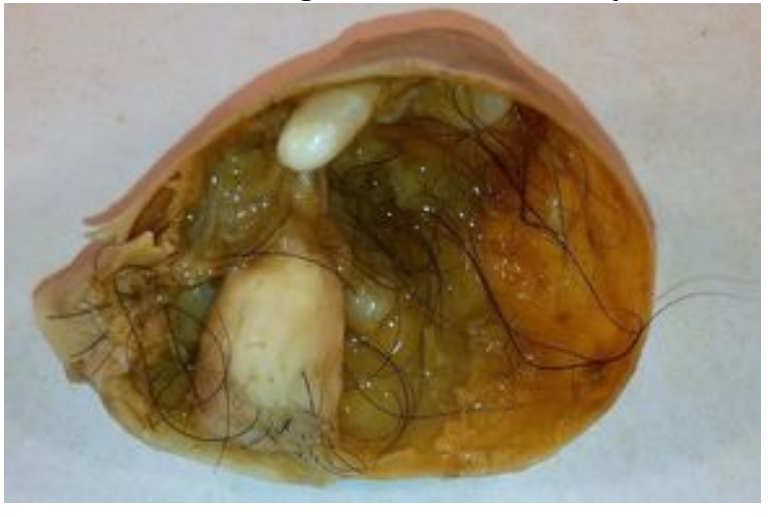
- Choriocarinoma
  - rare very aggressive
  - early distant metastases (lungs, brain)
  - Primary lesion very often subclinical, witohut testicular mass
  - Frequent intratumor bleeding
  - Typically elevated B-HCG

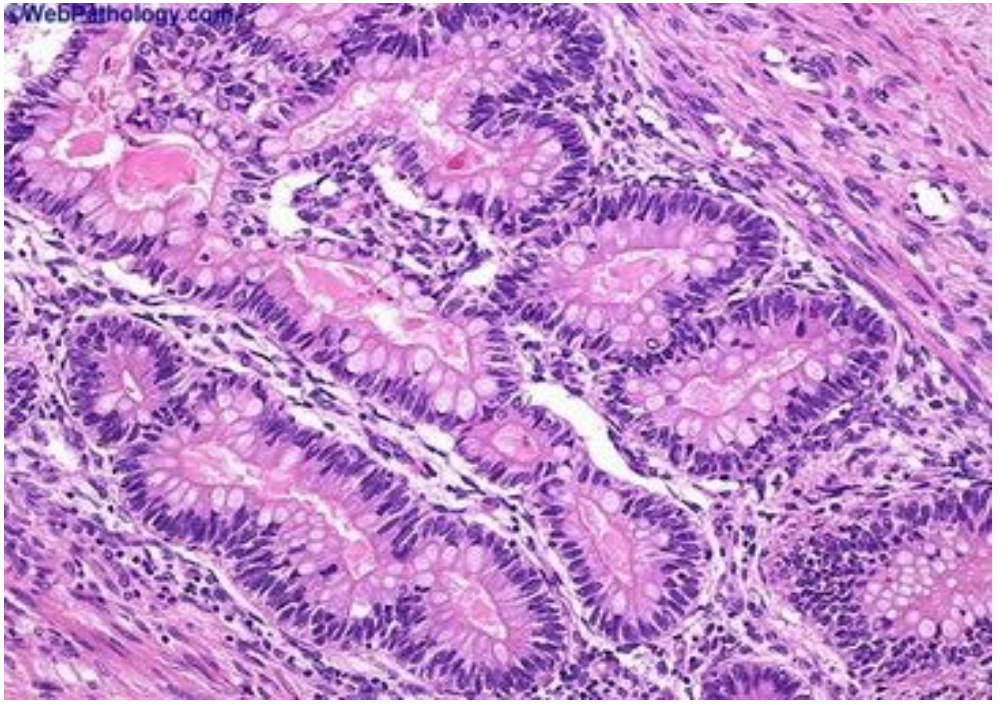




Testicular cancer – pathology

- Teratoma
  - Contain all three germ layers with varying degree of diffrentiation
  - Highly differentiated tissues can be present (ie. hair, teeth, cartilage)
  - in pure form in pediatric patients only
  - in adults – frequent (~45%) as a component of mixed germ cell tumors
  - Normal serum markers or mildly elevated AFP
  - relatively lower chmosensitivity (can relapse as sole component after chemo)
  - Subtypes:
    - mature – low metastatic potential
    - immature – higher metastatic potential



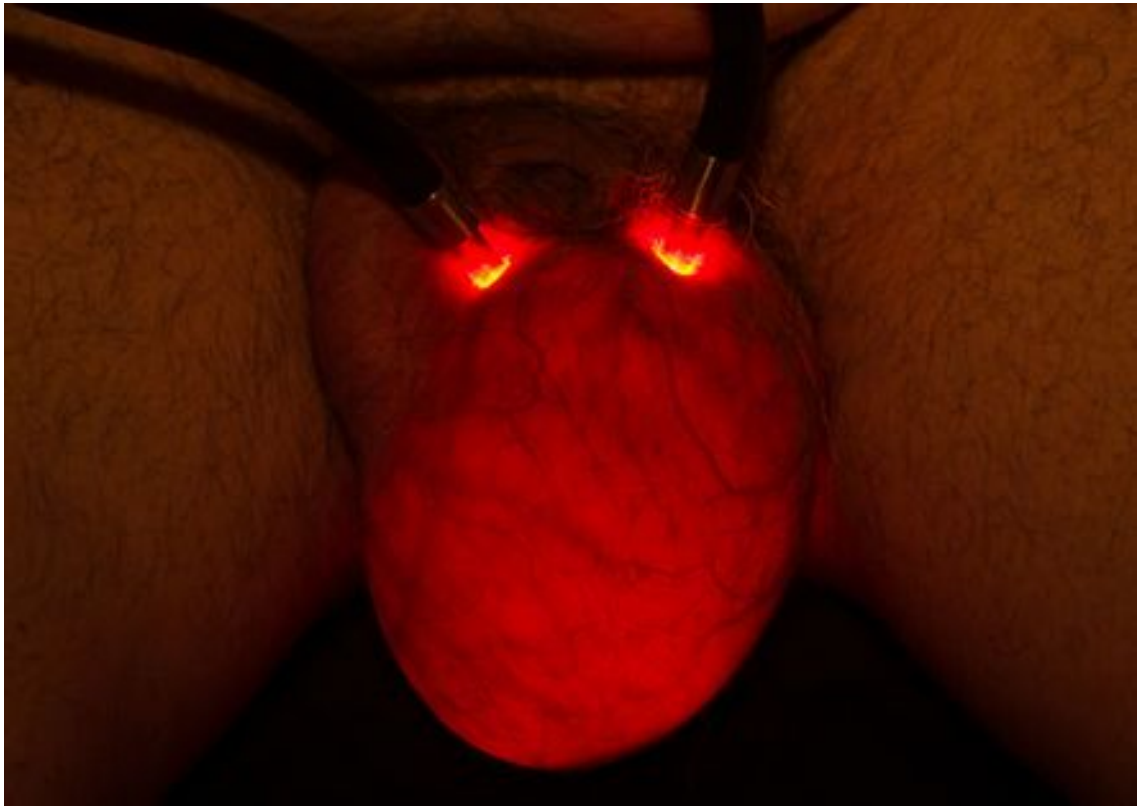


Testicular cancer – pathology

- Tumors from interstitial cells (rare)
  - Leydig cells tumors
    - Produce androgens – precocious puberty in boys but gynecomastia and decreased libido in adults (peripheral conversion to estrogens)
  - Sertoli cell tumors
    - Estrogen production - gynecomastia and decreased libido
    - 90% benign
  - Gonadoblastoma
    - Mixed germ cell/ intesrstitial cell histology
    - Exclusively in patients with disgenetic gonads and intersex syndromes
    - high risk of bilateral tumors

Testicular cancer – workup

Axiom to remember:
„Any solid, firm testicular mass, that cannot be trans-illuminated, should be regarded as malignant unless proven otherwise.”

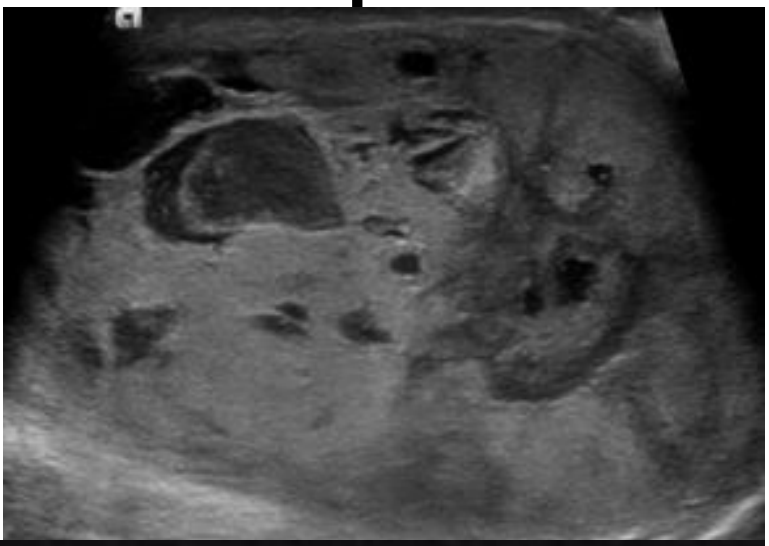


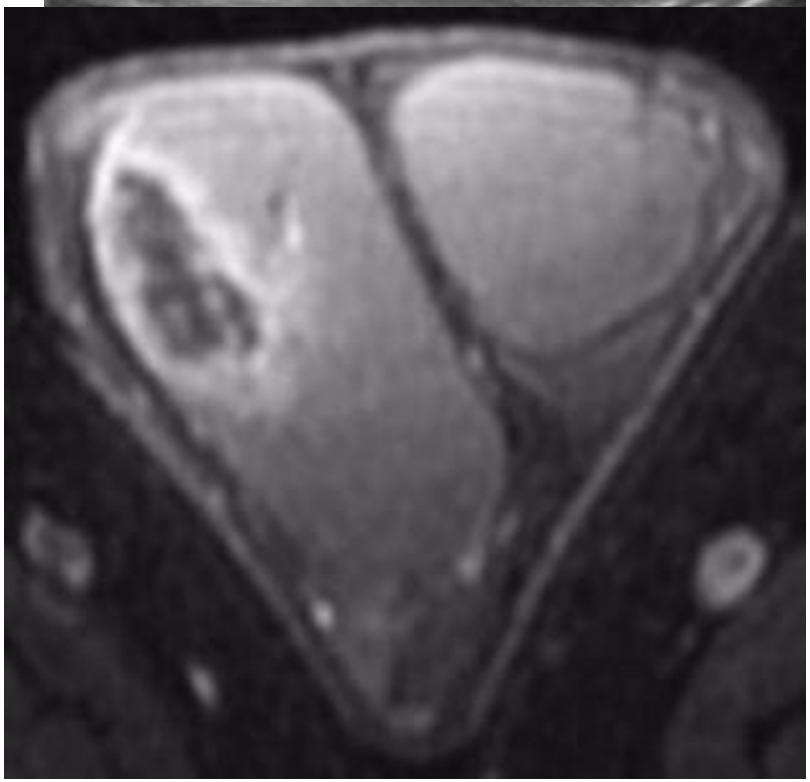
Transiluminated hydrocele

Testicular cancer – workup

Patient presenting with testicular tumor

- Testicular ultrasound
  - well established standard for testicular mass assessment.
  - Will confirm/exclude malignancy in majority of cases (near 100% sensitivity and 98-100% specificity).
  - At least 7,5Mhz linear transducer with color Doppler option required
- MRI +C
  - if USG nonconclusive (~1,5% cases)
- Biopsy – only in extragonadal mid-line tumors of suspected germ-cell origin





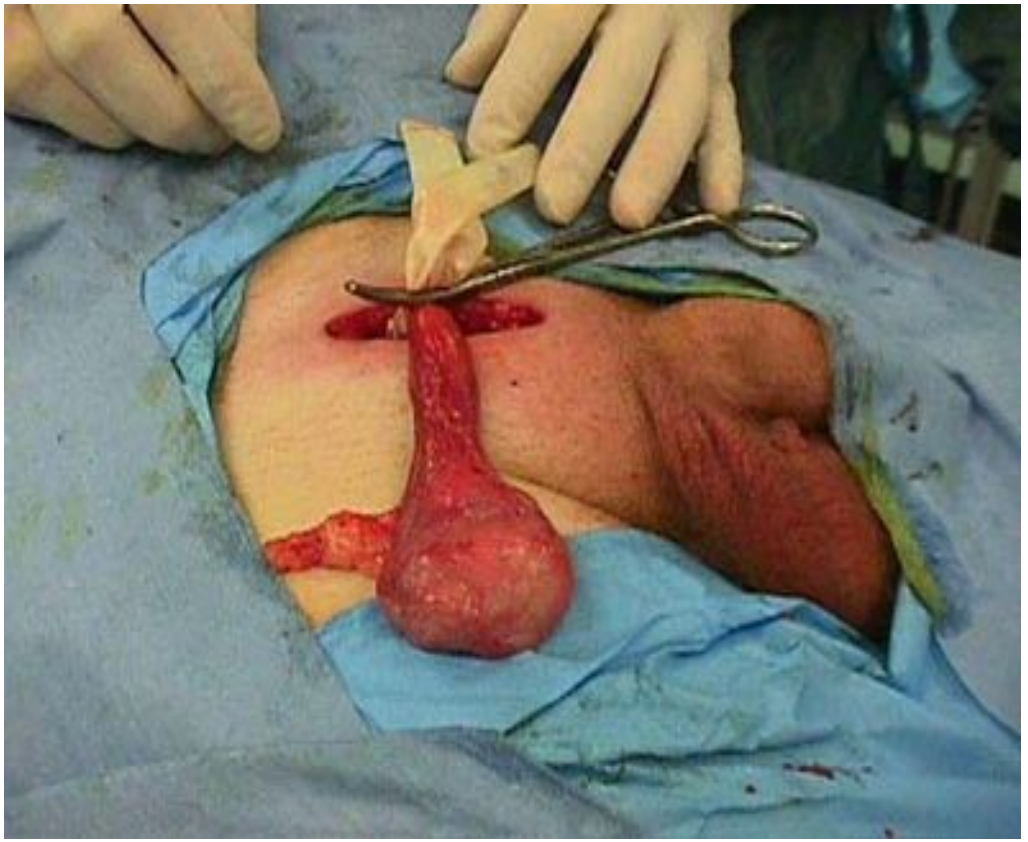
Testicular cancer – workup

Patient with testicular malignancy confirmed on imaging

- abdominal ultrasound and chest X-ray
  - Preliminary assessment of tumor burden before surgical treatment
- laboratory studies
  - CBC, LFT, RFT
  - circulating biomarkers (AFP, b-HCG, LDH) as baseline before the surgery

Testicular cancer – surgery

- Orchiectomy including testicular cord, through inguinal incision without rupturing testicular capsule :
  - never through scrotal access (significantly higher rate of local reccurences)
  - standard first-line therapeutic intervention unless extremly high metastatic burden mandates urgent chemotherapy
  - confirms the diagnosis
  - defines cancer subtype
  - defines T stage
  - is curative in early stages
  - consider intraoperative H-P assessment
  - organ sparing strategies feasible in experienced centres (rare).



Testicular cancer – postoperative workup

Patient with histologicly confirmed cancer

- CT scan of the abdomen and pelvis is mandatory.
- thoracic CT should be carried out in non-seminomas
- thoracic CT can be omitted in seminoma patients without infradiaphragmatic metastases.
- MRI of the central nervous system
  - in advanced stages,
  - in choriocarcinoma/high HCG,
  - cerebral symptoms.
- positron emission tomography (PET) scanning does not contribute to initial staging

Adapted from: Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. J. Oldenburg1, S. D. Fosså1, J. Nuver2, A. Heidenreich3, H-J Schmoll4, C. Bokemeyer5, A. Horwich6, J. Beyer7 & V. Kataja8, on behalf of the ESMO Guidelines Working Group; Annals of Oncology 24 (Supplement 6): vi125–vi132, 2013

Testicular cancer – postoperative workup

Patient with histologicly confirmed cancer

- tumour markers (AFP, HCG, LDH) should be followed until normalisation or lack of further decrease.
  - HCG t½ is up to 3 days
  - AFP t½ is 5–7 days
  - the patient is considered marker positive (S1-3) only if AFP, HCG and LDH fail to normalize after the operation (ie. Abnormal AFP befor orchiectomy is not consider S+)
- Serum levels of total testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) should be determined.
- Semen analysis and sperm banking should be discussed with all patients.

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Staging

Definition of TNM

TNM Category	Description
Primary Tumor (T)	
pTX	Primary tumor cannot be assessed.
pT0	No evidence of primary tumor (e.g., histologic scar in testis).
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion. Tumor may invade into the tunica albuginea but not the tunica vaginalis.
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion or tumor extending through the tunica albuginea with involvement of the tunica vaginalis.
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion.
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion.
Note: Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.	
Regional Lymph Nodes (N)	
Clinical	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes; none >2 cm in greatest dimension.
N2	Metastasis with a lymph node mass >2 cm but not >5 cm in greatest dimension, or multiple lymph nodes, any one mass >2 cm but not >5 cm cm in greatest dimension.
N3	Metastasis with a lymph node mass >5 cm in greatest dimension.
Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed.
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and ≤5 nodes positive; none >2 cm in greatest dimension.
pN2	Metastasis with a lymph node mass >2 cm but not >5 cm in greatest dimension, or >5 nodes positive, none >5 cm, or evidence of extranodal extension of tumor.
pN3	Metastasis with a lymph node mass >5 cm in greatest dimension.
Distant Metastases (M)	
M0	No distant metastasis.
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastases
M1b	Distant metastasis other than to nonregional lymph nodes and lungs
Serum Tumor Markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 × N[a] **AND** hCG (mIU/mL) <5,000 **AND** AFP (ng/mL) <1,000
S2	LDH 1.5–10 × N **OR** hCG (mIU/mL) 5,000–50,000 **OR** AFP (ng/mL) 1,000–10,000
S3	LDH >10 × N **OR** hCG (mIU/mL) >50,000 **OR** AFP (ng/mL) >10,000

Stage Grouping

Group	T	N	M	S[a]
Stage 0	pTis	N0	M0	S0
Stage I	pT1–4	N0	M0	SX
IA	pT1	N0	M0	S0
IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS	Any pT/Tx	N0	M0	S1–3
Stage II	Any pT/Tx	N1-3	M0	SX
IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1	SX
IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

Germ Cell Tumor Risk Classification

Risk Group	Seminoma	Nonseminoma
Good	Any hCG Any LDH Nonpulmonary visceral metastases absent Any primary site	AFP <1,000 ng/mL hCG <5,000 mIU/mL LDH <1.5 × ULN Nonpulmonary visceral metastases absent Gonadal or retroperitoneal primary site
Intermediate	Nonpulmonary visceral metastases present Any hCG Any LDH Any primary site	AFP 1,000–10,000 ng/mL hCG 5,000–50,000 mIU/mL LDH 1.5–10.0 × ULN Nonpulmonary visceral metastases absent Gonadal or retroperitoneal primary site
Poor	Does not exist	Mediastinal primary site Nonpulmonary visceral metastases present (e.g., bone, liver, brain) AFP >10,000 ng/mL hCG >50,000 mIU/mL LDH >10 × ULN

Testicular cancer – postoperative therapeutic options

- Surveillance - number of different protocols:
  - physical and biomarkers every 3-4 months and less often after 2-3 years
  - abdominal (CT preferred) and chest imaging every 3-6 months and less often after 2-3 years
  - PET if CT ambiguous
- Adjuvant radiotherapy on regional LNs (20-36Gy).

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Testicular cancer – postoperative therapeutic options

- Lymphadenectomy
  - burdensome
  - provides additional staging information
- Adjuvant chemotherapy
  - Platinium derivatives
  - Polytherapy preferred

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Testicular cancer – most common CT regimens

BEP[a]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	100 mg/m^2	Day 1–5
Bleomycin	30 mg	Day 1, 8,
EP[b]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	100 mg/m^2	Day 1–5
VIP/PEI[c]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	75 mg/m^2	Day 1–5
Ifosfamide	1.2 g	Day 1–5
TIP[d]	(Repeat cycles every 3 weeks)	
Paclitaxel	250 mg/m^2	Day 1
Cisplatin	25 mg/m^2	Day 2–5
Ifosfamide	1.5 g	Day 2–5

VeIP[e]	(Repeat cycles every 3 weeks)	
Vinblastine	0.11 mg/kg	Day 1 + 2
Ifosfamide	1.2 g/m^2	Day 1–5
Cisplatin	20 mg/m^2	Day 1–5
TI-CE[f]	(TI cycles 1–2 every 2 weeks)	
Paclitaxel	200 mg/m^2	Day 1
Ifosfamide	2.0 g	Day 2–4
	(CE cycles 3–5 every 3 weeks)	
Carboplatin	AUC = 7	Day 1–3
Etoposide	400 mg/m^2	Day 1–3
CE[g]	(Two cycles, may be preceded by VeIP)	
Carboplatin	700 mg/m^2	Day 1
Etoposide	750 mg/m^2	Day 1–3

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	Stage I	Stage IIA	Stage IIB/IIC/III
First line	Low risk* Preferred : • Surveillance Alternatively : ▪ Carboplatin x 1 (AUC 7) ▪ Radiotherapy (20 Gy) High risk# Preferred: • Surveillance • Carboplatin x 1 (AUC 7) Alternatively: • Radiotherapy (20 Gy)	▪ BEPx3 (or EPx4) ▪ Radiotherapy	• BEPx3-4 (VIPx3-4)
Residual disease	n/a	Observation Consider biopsy or resection of lesion > 3 cm, particularly if PET positive	
Relapse	Post-surveillance/carboplatin ▪ Localised: Radiotherapy ▪ Otherwise: BEPx3-4 Post-radiotherapy ▪ BEPx3 (EPx4)	Salvage chemotherapy In localised lesions: consider radiotherapy Surgery in case of a single resectable lesion	

*Low risk: absence of rete testis invasion and tumour <4 cm
#High risk: rete testis invasion or tumour ≥4 cm

Standard treatment strategies for seminoma.

Adapted from: Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. J. Oldenburg1, S. D. Fosså1, J. Nuver2, A. Heidenreich3, H-J Schmoll4, C. Bokemeyer5, A. Horwich6, J. Beyer7 & V. Kataja8, on behalf of the ESMO Guidelines Working Group; Annals of Oncology 24 (Supplement 6): vi125–vi132, 2013

	Stage I	Stage IIAIII		
		Good	Intermediate	Poor
First line	Vascular invasion present Preferred: • Surveillance Alternatively: ▪ 1-2xBEP ▪ RPLND (rarely) Vascular invasion absent Preferred: ▪ 1-2xBEP ▪ Surveillance Alternatively: ▪ RPLND (rarely)	▪ BEPx3 (EPx4) ▪ RPLND (if marker negative stage IIA)	▪ BEPx4 ▪ VIPx4	▪ BEPx4 ▪ VIPx4
Residual disease	n/a	Resection in case of lesion > 1 cm Observation in case of lesion < 1 cm		
Relapse	Post-surveillance or post-RPLND: ▪ BEPx3-4 Surgery in case of a single resectable lesion Post-chemotherapy: ▪ Salvage chemotherapy Surgery in case of a single resectable lesion	Salvage chemotherapy Surgery in case of a single resectable lesion		

Standard treatment strategies for non-seminoma.

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Testicular cancer – post-tratment

- Imaging assessment
  - If no complete response – schedule PET-CT (reactive/fibrotic lesions versus residual neoplasm)
  - If PET positive – refractor disease – second line (salvage) treatment
- Surveillance - number of different protocols:
  - physical and biomarkers every 3-4 months and less often after 2-3 years
  - abdominal (CT preferred) and chest imaging every 3-6 months and less often after 2-3 years
  - PET if CT ambiguous
- Screening for independent and treatment related malignancies (when feasible)
- Assessing and managing late treatment toxicities (ie. pulmonary fibrosisis after bleomycin or hearing loss after platinum salts).
- Reproductive counselling

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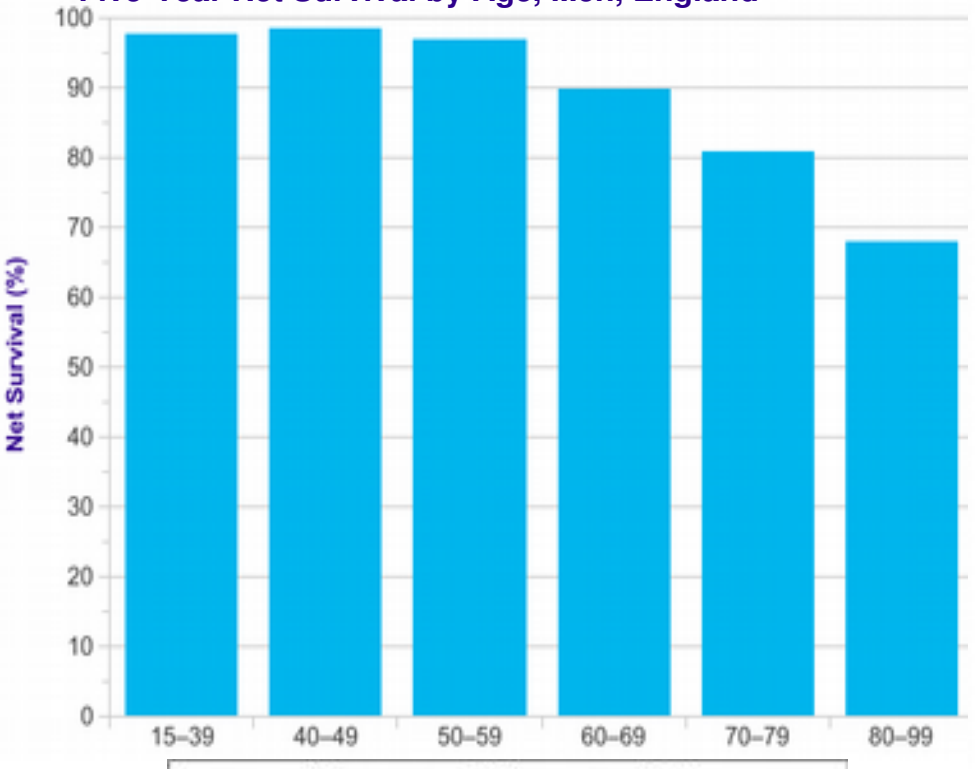
Testicular cancer – relapse

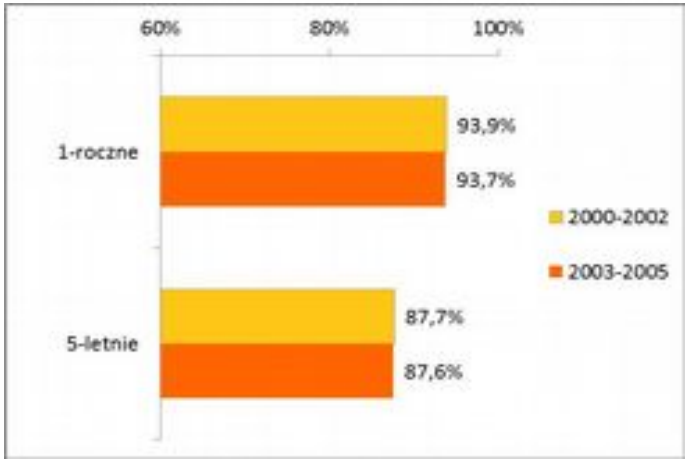
- differential – relapse vs second primary
- restaging (as post-orchiectomy workup)
- treatment choice considerations:
  - surgery:
    - localized/ oligometastatic reccurence
    - teratoma component in primary (often chemoresistant)
    - uncertain whether reccurrence or non-malignant lesion
  - Radiotherapy
    - localized/ oligometastatic reccurence
    - Chemorefreactory tumor restricted to lymph nodes
  - Second line chemotherapy
    - Regimen usually different from one usde primarily
    - Consider high-dose chemotherapy with auto-HSCT

Testicular cancer – prognosis

Testicular Cancer (C62): 2009-2013

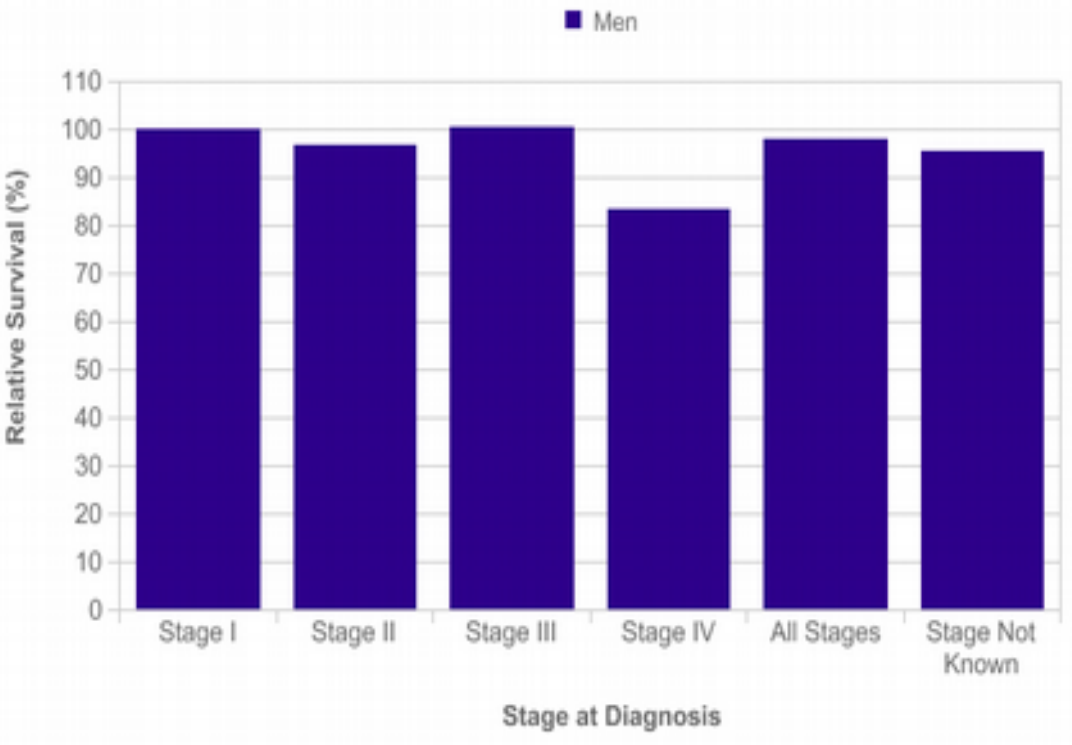
Five-Year Net Survival by Age, Men, England





Testicular Cancer (C62): 2006-2010

One-Year Relative Survival (%) by Stage, Adults Aged 15-99



Favourable prognosis, even in metastatic setting

Based on: Cancer Research UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/testicular-cancer/incidence#heading-One, Accessed OCT 2016.

KRN : Wskaźniki 1-rocznych i 5-letnich przeżyć względnych u chorych na nowotwory jadra w Polsce.

Testicular cancer

Questions?

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Thank You

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