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Follow-up in testicular cancer

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Follow-up in testicular cancer

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FONDAZIONE PIEMONTESE PER LA RICERCA SUL CANCRO ONLUS

ISTITUTO DI CANDIOLO

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Disclosures

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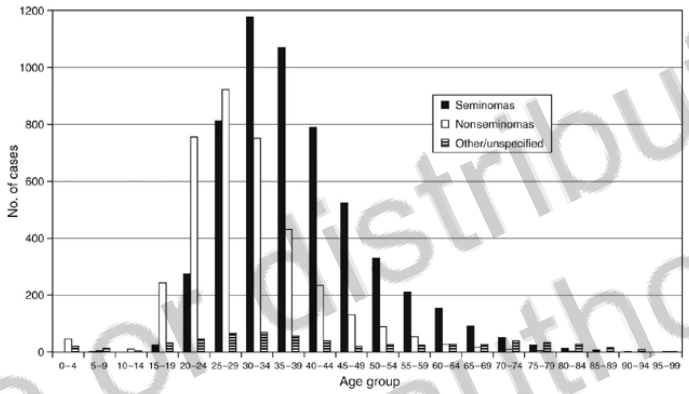
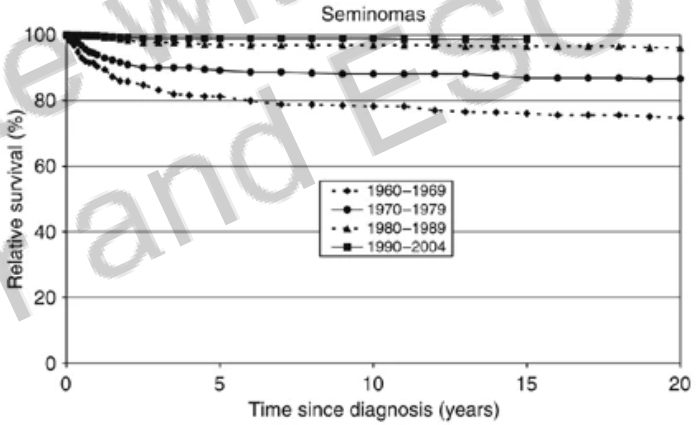
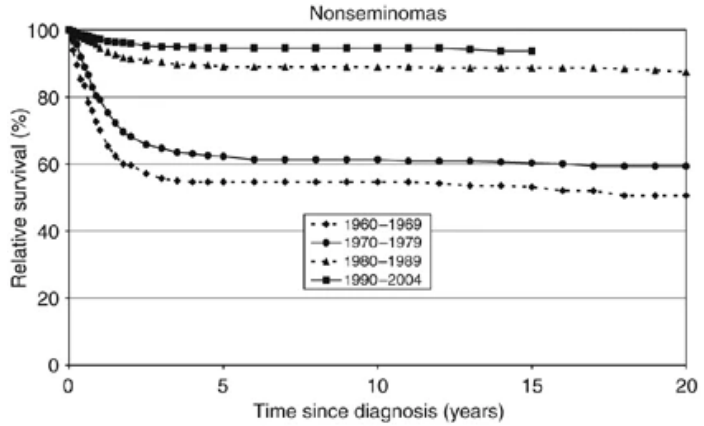
Testicular cancer: facts and figures

- The most common malignancy in **young males**, between **16 and 34 years** (increasing incidence)
- About **50% seminomas**
- **80-85% stage I** disease





- The paradigm of a **curable neoplasm**
- Almost all patients become **long-term survivors**
- **Relapses** and **long-term effects** of treatments are of upmost importance for the **follow-up**



Horwich A et al ***Lancet*** *2006*
Robinson D et al Br J Cancer 2007

Outline

- Relapse risk
- Treatment-related long-term effects
- Surveillance and follow-up recommendations
- Management of treatment-related effects

Risk of relapse in early stage disease

Stage and histology	Risk factor (RF)	Risk of relapse	Cure rate	References
Stage I Seminoma	***Tumor size* (?)** ***Rete testis invasion* (?)**	After #1 Carbo AUC7: 4-5% Surveillance: 15-20% - without RFs: 4-6% - 1-2 RFs: 15.9-31% Usually within 3 years	**≥ 99%**	*Warde et al J Clin Oncol 2002* *Mortensen et al Eur Urol 2014* *Tandstad et al Ann Oncol 2016* *Zengerling et al Urol Oncol 2018* *Boormans et al Eur Urol 2018*
Stage I Non-seminoma	**Vascular invasion (VI)** **Embryonal carcinoma**	After #1 BEP (or RPLND): <5% Surveillance: ≈ 30% - VI (-): 15% - VI (+): 50%	**≈ 99%**	*Albers et al J Clin Oncol 2003* *Nicolai N et al Eur Urol 2010* *Cohn-Cedermark et al Andrology 2014*
Stage II A/B Seminoma	**LN size (2 cm) and no.**	- RT or #3 BEP: 5%	**>97-98%**	*Giannatempo et al Ann Oncol 2015*
Stage II A/B Non-seminoma	**Serum markers (m)**	- RPLND/#2BEP or #3-4 BEP: 7-11% - If m-, Surveillance (or RPLND): 10% - If m+: #3-4 BEP: 11%	**≈ 97-98%**	*Weissbach et al Eur Urol 2000*

Prognosis has improved in stage IIC/III

Analysis on 12,135 pts, 9,677 Non-Se and 2,458 Se, treated with platinum-based CT between 1990-2013

Seminoma

Good Prognosis	Intermediate Prognosis	Poor Prognosis
· Any primary site · No non-pulmonary visceral metastases · Normal AFP, any hCG, any LDH *90% of seminomas* *5-year PFS 82%* *5-year OS 86%*	. Any primary site . *Non-pulmonary visceral metastases* . Normal AFP, any hCG, any LDH *10% of seminomas* *5-year PFS 67%* *5-year OS 72%*	No patients classified as poor prognosis

Non Seminoma

Good Prognosis	Intermediate Prognosis	Poor Prognosis
. Testis/retroperitoneal primary . No non-pulmonary visceral metastases . Good markers all of: AFP < 1.000 ng/ml hCG < 5.000 IU/L LDH < 1,5 x upper limit of normal *56% of non-seminomas* *5-year PFS 89%* *5-year OS 92%*	. Testis/retroperitoneal primary . No non-pulmonary visceral metastases . Intermediate markers any of: *AFP ≥ 1.000* and ≤ 10.000 ng/ml or *hCG ≥ 5.000* and ≤ 50.000 IU/L or *LDH ≥ 1,5* x N and ≤ 10 x N *28% of non-seminomas* *5-year PFS 75%* *5-year OS 80%*	· *Mediastinal primary* · *Non-pulmonary visceral metastases* · Poor markers any of: AFP > 10.000 ng/ml or hCG > 50.000 IU/L or LDH > 10 x upper limit of normal *14% of all GCTs* *16% of non-seminomas* *5-year PFS 41%* *5-year OS 48%*

Analysis on 5202 non-Se and 660 Se pts treated with platinum-based CT between 1975-1990 IGCCCG, JCO 1997

IGCCCG	5-year PFS 1997	5-year PFS Update	5-year OS 1997	5-year OS Update
Good	89% (87 - 91%)	90% (89 - 91%)	91% (89 - 93%)	**96% (95 - 96%)**
Interm.	75% (71 - 79%)	77% (75 - 79%)	79% (75 - 83%)	**88% (87 - 90%)**
Poor	41% (35 - 47%)	**54% (52 - 56%)**	48% (42 - 54%)	**67% (65 - 69%)**

Parameter	Estimate	SE	DF	P-value
Age (years) by 1 y	0.020	0.004	1	<.0001
Lung mets	0.465	0.090	1	<.0001
LDH >2.5xUNL	0.564	0.108	1	<.0001

Online IGCCCG calculator available at: https://www.eortc.org/IGCCCG-Update

9,531 pts to update IGCCCG estimates on contemporary data
4,903 pts to build and validated new prognostic model

***Risk factors**:*

- *Histology (non-seminoma)*
- *Primary site (extragonadal/mediastinal)*
- *Visceral non-pulmonary metastases*
- *Serum tumour markers (STMs) levels*

Gillessen et al J Clin Oncol 2021

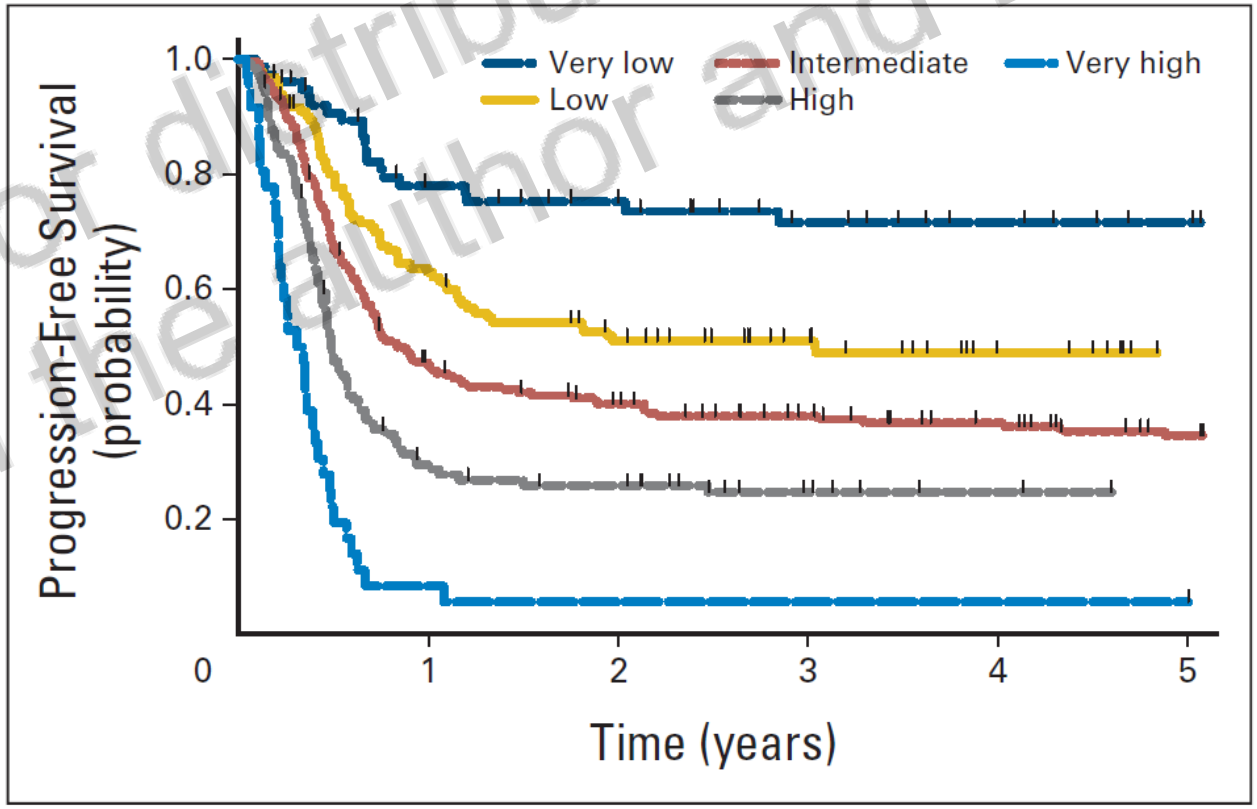
Prognosis in relapsed/refractory disease

The International Prognostic Study Group (IPSG) score on analysis on 1,984 patients with GCT who progressed after at least 3 cisplatin-based cycles and were treated with cisplatin-based conventional-dose or carboplatin-based high-dose salvage chemotherapy

Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma

	Score Points				
Parameter	0	1	2	3	Score
Primary site	Gonadal	Extragonadal	—	Mediastinal nonseminoma	
Prior response	CR/PRm−	PRm+/SD	PD	—	
PFI, months	> 3	≤ 3	—	—	
AFP salvage	Normal	≤ 1,000	> 1,000	—	
HCG salvage	≤ 1,000	> 1,000	—	—	
LBB	No	Yes	—	—	
Score sum (values from 0 to 10)					
Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3					
Add histology score points: pure seminoma = −1; nonseminoma or mixed tumors = 0					
Final prognostic score (−1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)					

Abbreviations: CR, complete remission; PRm−, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease; PD, progressive disease; PFI, progression-free interval; AFP, alpha fetoprotein; HCG, human chorionic gonadotrophin; LBB, liver, bone, brain metastases.

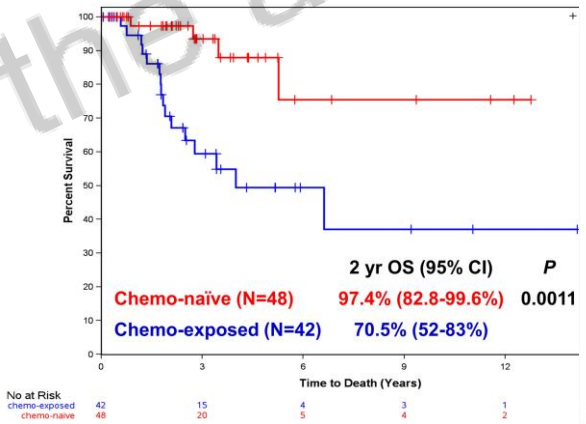


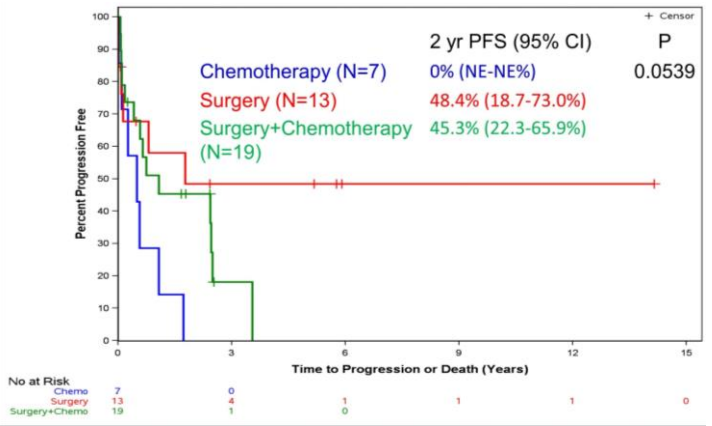
International Prognostic Study Group et al J Clin Oncol 2010

Late relapses – Indiana University series

- 90 patients (1993-2000)
- ~ **1.5-3% late relapses**, **up to 72% diagnosis with symptoms**, up to 40% markers or imaging
- Median FU: 3.02 years (from relapse)
- 20/83 chemo-naïve
- **43/49 CR with surgery**
- **6/32 CR with chemotherapy (4 chemo-naïve)**
- late relapses should be managed **primarily with surgery** (if feasible), **salvage chemotherapy is generally ineffective**
- **follow-up over 5 years** or patient education on signs / symptoms?

	Chemo-naïve Seminoma N=26	Chemo-exposed Seminoma N=3	Chemo-naïve NSGCT N=22	Chemo-exposed NSGCT N=39
2-5 years	22 (84.6%)	3 (100%)	18 (81.8%)	18 (46.1%)
>5 years	4 (15.4%)	0	4 (18.1%)	21 (53.8%)

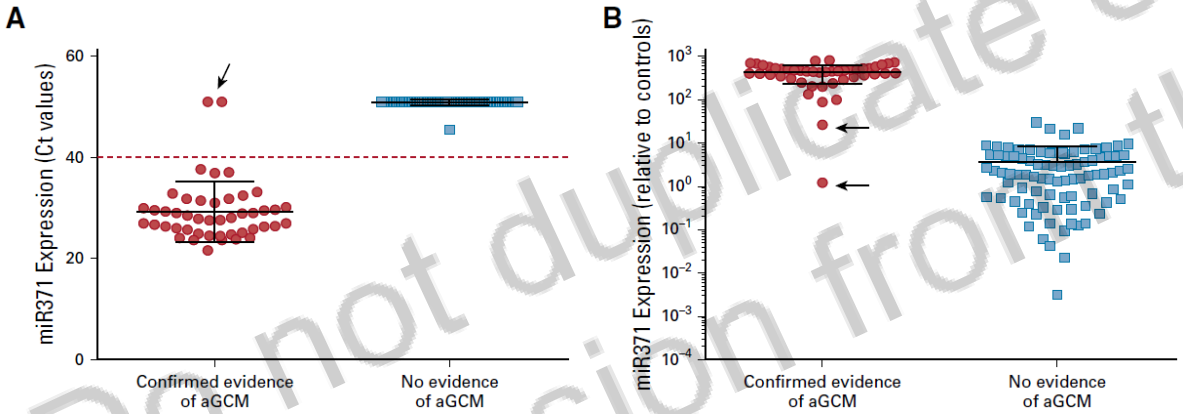


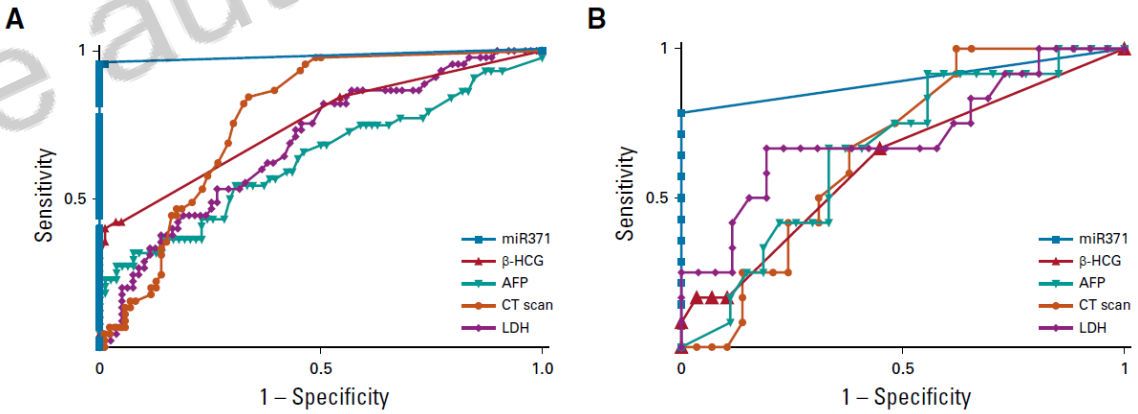


Richardson NH et al ASCO 2021

Early identification of relapse: novel biomarkers

- **miRNA-371** is expressed in plasma of patients with clear evidence of active germ cell malignancy (aGCM)
- **ROC curves** show the high specificity and positive predictive value of miRNA 371 and confirm it **overperforms** compared to **CT imaging** and **serum tumour markers**





Nappi et al J Clin Oncol 2019
Dieckmann et al J Clin Oncol 2019

Long-term effects of treatments

Type	Causes	Effects	References
Secondary malignancies	Radiotherapy (field [subdiaphragmatic] and dose-dependent) Chemotherapy (etoposide and cisplatin dose-dependent)	Leukemia and solid tumours: RR=1.8-2.21 Leukemias: 2% cumulative risk if etoposide >2000mg/mq (>4 BEP) Gastrointestinal cancer risk by 53% with each additional 100 mg/m2 of cisplatin-based Cht Risk remains after 20-30 years No added risks by CT scans	*Travis et al J Natl Cancer Inst 1997 & 2000* *Kollmannsberger et al J Clin Oncol 1998* *Travis et al J Natl Cancer Inst 2005* *van den Belt-Dusebout et al J Clin Oncol 2007* *De Gonzalez eta al Lancet Oncol 2011* *Van Walraven et al J Clin Oncol 2011* *Fung et al J Clin Oncol 2013* *Vidal et al Ann Oncol 2014* *Hauptman et al Br J Cancer 2015 & 2016* *Kier et al JAMA Oncol 2016* *Groot et al J Clin Oncol 2018* *Baciarello G et al ASCO Proc 2017*
Cardiovascular (hypertension, ischemic heart disease)	Chemotherapy Radiotherapy Tumour volume (VTEs)	Age-adj OR of hypertension: 1.29 for RT, 1.63 for cisplatin at ≤ 850 and 2.32 >850 mg 6% IHD event after cisplatin	*Sagstuen et al J Clin Oncol 2005* *van den Belt-Dusebout et al. J Clin Oncol 2007* *Fossa et al J Natl Cancer Inst 2007* *Srikanthan et al J Clin Oncol 2015* *Fung et al J Clin Oncol 2015* *Groot et al Cancer 2020*
Metabolic syndrome	Chemotherapy Tumour (hypogonadism?)	Dose-dependent for cisplatin, bleomycin, etoposide	*Haugnes HS et al Ann Oncol 2007*

Long-term effects of treatments

Type	Causes	Effects	References
Infertility **Hypogonadism** **Sexual disfunction** **Aging**	Chemotherapy (ifosfamide) Surgery Tumour (contralateral risk)	30% reduction in paternity Premature hormonal and physiologic aging Accelerated cellular senescence, reduced telomere length, epigenetic modifications, somatic mutations, and mitochondrial DNA infidelity	*Fossa et al J Natl Cancer Inst 2007* *Fossa et al J Clin Oncol 2009* *Sprauten et al J Clin Oncol 2014* *Ness et al J Clin Oncol 2018*
Renal and pulmonary	Chemotherapy (cisplatin and bleomycin)	Stable after acute phase Pulmonary limited but at risk lung surgery, embolism, smoking and IGCCCG poor	*Lauritsen et al J Clin Oncol 2016* *Chovanec et al Ann Oncol 2017*
Neurologic	Chemotherapy (cisplatin and/or taxanes)	6% overall: ototoxicity (22%), parhestesias (29%), Raynaud's (39%)	*Fossa et al J Natl Cancer Inst 2010* *Fung et al J Natl Compr Canc Netw 2019*
Anxiety and depression	Chemotherapy ? Disease	Anxiety 20% TC survivors vs. 12.5% general population 7.9%-9.7% depression (? general population)	*Smith et al Psychooncology 2018* *Dahl et al. J Clin Oncol 2005* *Vehling S et al Gen Hosp Psychiatry 2016* *Hellesness et al J Clin Oncol 2021*

Non-testicular cancer (TC) mortality

- **23-40% excess non-TC mortality** vs general population (1975 onward) related to cisplatin-based Cht (**PBCT**) and **RT** ≥ 20 Gy, not after surgery
- **Younger survivors < 20 years**, 2.27-fold significantly increased risk
- **Cumulative mortality** of **9.6% 25 years after treatment**

Causes of non-TC mortality:

- **Secondary malignancies:** most important (43% excess after PBCT, 59% after RT), likely not significant after Carboplatin
- **Cardiovascular disease: within the first year** (60% excess mortality, 2.1-fold risk of IHD mortality after PBCT)
- **Suicide risk 20% increase** 1.65-fold excess after PBCT
- **Others: infections/surgery, genitourinary diseases/PBCT, digestive diseases/RT**

Fung et al J Clin Oncol 2021

Long-term effects of treatments: genetic susceptibility

- Germline mutations associated with cisplatin-related:
- **Pulmonary toxicity** (BLMH)
- **Neuropathy** (GSTP1 and RPRD1B)
- **Ototoxicity** (megalin, COMT, TPMT, and ACYP2);
- Hearing loss (WFS1)
- Tinnitus (OTOS)

Table 1. Genetic susceptibility to the late complications of treatment in testicular cancer survivors (TCSs): an overview*

First author, year (ref.)	Population	Study design	Treatment regimen(s)	Endpoint	Genetic marker (gene)†	Major findings
Oldenburg, 2007 (139)	Norwegian TCS treated 1980–1994 (n = 238)	Retrospective cross-sectional; long-term toxicities assessed via Scale for Chemotherapy-Induced Neurotoxicity, 1998–2002	BEP, 44%; CVB, 44%; 100% exposed to cisplatin-based therapy (median cum. dose = 397 mg/m²); 95% exposed to bleomycin (median cum. dose = 145 mg/m²)	Neurotoxicity	Glutathione *S*-transferase (*GSTP1*)	*GSTP1* genotype G-G vs A-G or A-A: finger paresthesias (OR = 0.46, 95% CI = 0.22 to 0.96), toe paresthesias (OR = 0.42, 95% CI = 0.20 to 0.88), and for tinnitus (OR = 0.33, 95% CI = 0.14 to 0.74)
Oldenburg, 2007 (140)	Norwegian TCS treated 1980–1994 (n = 173)	Retrospective cross-sectional; hearing impairment assessed with audiometric testing, 1998–2001	BEP, 44%; CVB, 44%; 100% given cisplatin-based therapy (median cum. dose = 397 mg/m²); 95% given bleomycin (median cum. dose = 145 mg/m²)	Ototoxicity	Glutathione *S*-transferase (*GSTP1*)	*GSTP1* genotype A-A vs G-G: hearing impairment (OR = 3.82, 95% CI = 1.12 to 13.98). *GSTPI* genotype A-A vs A-G: hearing impairment (OR = 4.25, 95% CI = 1.26 to 14.38)
Nuver, 2005 (136)	Consecutive nonseminomatous TC patients treated at University Hospital Groningen, the Netherlands, 1977–2003 (n = 340)	Retrospective cohort; data on bleomycin-induced pulmonary toxicity derived from medical records	All patients received bleomycin-containing regimen (median cum. dose = 270 mg)	Pulmonary toxicity	Bleomycin hydrolase (*BLMH*)	*BLMH* genotype not associated with either development of BIP or changes in pulmonary function tests
de Haas, 2008 (141)	See Nuver, 2005 (136) (subset, n = 304)	Retrospective cohort; data on vital status, last follow-up date, and cause of death derived from medical records and general practitioner files	All patients received a bleomycin- and platinum-containing regimen (median bleomycin cum. dose by genotype: 270 mg [A/A], 270 mg [A/G], and 360 mg [G/G]; median cisplatin cum. dose by genotype: 400 mg/m² [A/A], 400 mg/m² [A/G], and 400 mg/m² [G/G])	Overall survival	Bleomycin hydrolase (*BLMH*)	*BLMH* SNP A1450G had a statistically significant effect on TC-related survival (for G-G vs A-A, HR = 4.97, 95% CI = 2.17 to 11.39) and on early relapse (16% with a genotype of G-G relapsed at <2 y vs 9% with A-A who relapsed at <2 y; *P* = .19)

Travis et al J Natl Cancer Inst 2010
Fung et al J Natl Compr Canc Netw 2019

Long-term effects of treatments: genetic susceptibility

- **However:**
- Data still **not validated** for clinical use
- **Expensive tests** and need of **specialised labs**
- Often not eventually helpful due to the **necessity of treatments** to guarantee the cure rate

Table 1 (continued).

First author, year (ref.)	Population	Study design	Treatment regimen(s)	Endpoint	Genetic marker (gene)†	Major findings
Peters, 2000 (142)	German patients with testicular germ cell tumor, osteosarcoma, neuroblastoma, and brain tumor; diagnosed 1991–1996 (n = 20 with ototoxicity, n = 19 without hearing loss)	Nested case–control; hearing impairment assessed via audiogram	100% given cisplatin-based therapy; (median cum. dose = 429 mg/m² in group with ototoxicity; 422 mg/m² in group without hearing loss)	Ototoxicity	Glutathione *S*-transferase (*GSTM3*)	*GSTM3**B allele was protective for ototoxicity; allele frequency (0.025 in ototoxicity group vs 0.18 in group with normal hearing) (χ^2 = 5.37; *P* = .02)
Peters, 2003 (143)	See Peters, 2000 (142)	See Peters, 2000 (142)	See Peters, 2000 (142)	Ototoxicity	Mitochondrial DNA sequence variations	Haplotype J (defined by a *Nla*III site gain at position 4216 and by site losses at positions 13704 *Bst*NI and 16065 *Hin*fI) frequency in ototoxicity group was 0.25 vs 0.05 in group with normal hearing (χ^2 = 2.9; *P* = .08)
Riedemann, 2008 (144)	See Peters, 2000 (142); 50 additional patients (25 with ototoxicity, 25 without hearing loss)	See Peters, 2000 (142)	100% given cisplatin-based therapy (mean cum. dose = 425 mg/m² in group with ototoxicity and 434 mg/m² in group without hearing loss)	Ototoxicity	Megalin (*LRP2*)	rs4668123 was not associated with genotype and ototoxicity; rs2075252 had an A-allele frequency in the ototoxicity group of 0.32 vs an A-allele frequency in group with normal hearing of 0.14 (χ^2 = 5.83; *P* < .02; OR = 3.45, 95% CI = 1.11 to 11.2)

* BEP, bleomycin, etoposide, and cisplatin; BIP, bleomycin-induced pneumonitis; CI = confidence interval; cum. = cumulative; CVB, cisplatin, vinblastine, and bleomycin; HR = hazard ratio; OR = odds ratio; ref. = reference; SNP = single-nucleotide polymorphism; TC, testicular cancer.

† Entrez Gene identification is in parenthesis.

Travis et al J Natl Cancer Inst 2010
Fung et al J Natl Compr Canc Netw 2019

Surveillance and Follow-up: definition

- **No standard definition**, often considered as interchangeable, but some Authors suggest:

- **Surveillance** is intended to reach an **early diagnosis of relapse**, with the term ***active*** indicating an alternative option to treatment.

- **Follow-up** aims at detecting **medium-** and **long-term consequences** of treatment

- So far, there is **no strong evidence** supporting the **modalities** and **timing** of **examinations** useful for these two clinical aspects but some **practical guidelines,** besides specific active surveillance protocols for stage I, have been reported over the latest decades (other than NCCN, EAU and ESMO guidelines) considering different **risk factors**, **radiological examination type** and **timing**, **follow-up intensity and duration**

Beyer et al Ann Oncol 2013
Banna et al Cr Rev Oncol Haematol 2019
Chovanec et al Nat Rev Urol 2016

UK guidelines for the follow-up: seminoma

- **Seven scenarios** by **stages** and **treatments**
- **Seminoma stage I active surveillance**:
- **n.5 CT scans:** every 6m for 2ys, then yearly for 5ys

Note:

- **CT** scans of **abdomen only** (unless pelvis at high risk)
- **CXR** instead of CT
- After 5y: yearly until **10 years**, clinical and markers
- **Late effects** assessed at 2, 5 and 10 years

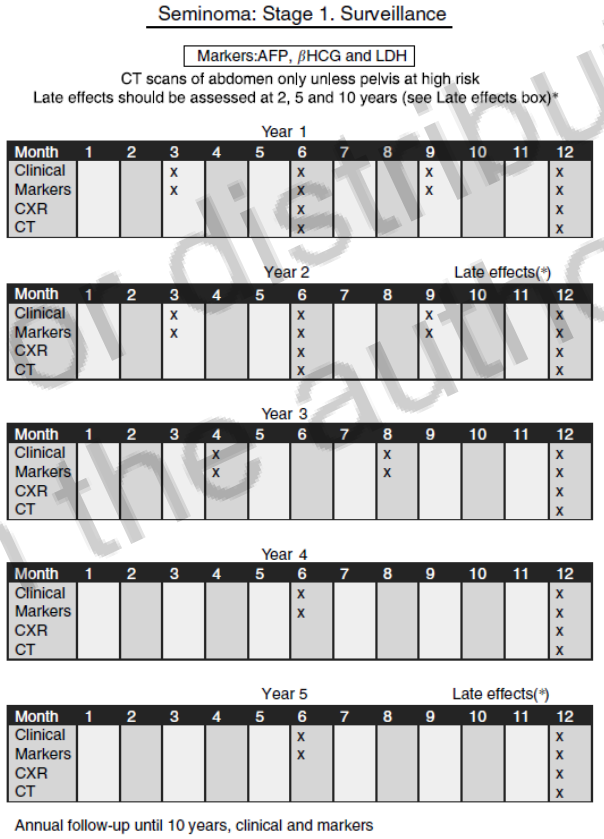
(*) Late effects

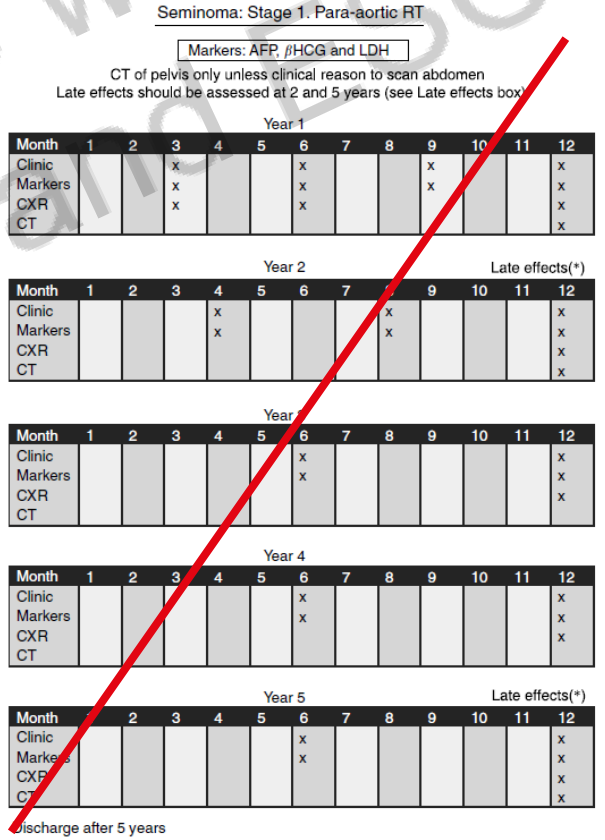
Clinical examination including blood pressure measurement, height and weight

Urea + electrolytes, fasting cholesterol (HDL and LDL), trigylcerides, fasting glucose

Hormone profile (FSH, LH and testosterone)

van As et al Br J Cancer 2008





- Advise not smoking and paying attention to their body weight
- Especially after 5 years of follow-up investigate suspicions of heart and/or kidney disease
- Advise all nationwide developed screening programs

UK guidelines for the follow-up: seminoma

- **Seminoma stage I single-agent carboplatin**:
- **n.3 CT** scans: years 1, 2 and 5

- **Seminoma stage IIa/b carboplatin/radiotherapy**:
- **n.4 CT scans**: 2 year 1, 1 year 2, 1 year 5

- For both:
- **CT scan** of **abdomen only** (unless pelvis at high risk)
- **CXR** instead of CT
- After 5y: yearly until **10 years**, clinical and markers
- **Late effects** assessed at **2**, **5** and **10 years**

Seminoma: Stage 1. Single-agent carboplatin

Markers: AFP, βHCG and LDH

CT of abdomen only unless pelvis at high risk
Late effects should be assessed at 2, 5 and 10 years (see Late effects box)*

Year 1

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical	x		x			x			x			x
Markers	x		x			x			x			x
CXR						x						x
CT												x

Year 2 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical				x				x				x
Markers				x				x				x
CXR												x
CT												x

Year 3

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												

Year 4

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												

Year 5 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												x

Annual follow-up until 10 years, clinical and markers

Seminoma: Stages IIa/b. Carboplatin and radiotherapy

Markers: AFP, βHCG and LDH

CT scans should be abdomen only unless pelvis at high risk
Late effects should be assessed at 2, 5 and 10 years (see Late effects box)*

Year 1

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical			x			x			x			x
Markers			x			x			x			x
CXR			x			x						x
CT			x									x

Year 2 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical				x				x				x
Markers				x				x				x
CXR												x
CT												x

Year 3

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												

Year 4

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												

Year 5 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												x

Annual follow-up until 10 years, clinical and markers

van As et al Br J Cancer 2008

UK guidelines for the follow-up: non-seminoma

- **Non-seminoma stage I surveillance**:
- **n.3 CT** scans: 2 year 1, 1 year 2

- **Non-seminoma stage I adjuvant chemotherapy: carboplatin/radiotherapy**:
- **n.1 CT** scan: 1 year 1

- For both:
- **CT scan** of **abdomen only** (unless pelvis at high risk)
- **CXR** instead of CT
- **Late effects** assessed at **2** and **5 years**
- **Complete at 5ys**

Table I Time course of relapse in surveillance of stage I nonseminoma

Reference	Patients	Relapses	Cumulative relapses Year 1 (%)	Year 2(%)	Year 3(%)
MRC, Read *et al* (1992)	373	100 (27%)	80	92	100
Atsu *et al* (2003)	132	32 (24%)	87	100	100
Daugaard *et al* (2003)	301	86 (29%)	80	89	95
Divrik *et al* (2006)	211	66 (31%)	79	95	—
Drury A Royal Marsden, unpublished)	478	115 (24%)	80	90	97

van As et al Br J Cancer 2008

Nonseminoma germ cell tumour: Stage 1. Surveillance

Markers: AFP, βHCG and LDH

CT scans should be of abdomen only unless pelvis at high risk
Late effects should be assessed at 2 and 5 years (See Late effects box)*

Year 1

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical	x		x		x		x		x		x	x
Markers	x	x	x	x	x	x	x	x	x	x	x	x
CXR	x		x		x		x		x		x	x
CT abdo			x									

Year 2 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical			x			x			x			x
Markers			x			x			x			x
CXR			x			x			x			x
CT abdo												x

Year 3

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical				x				x				x
Markers				x				x				x
CXR				x				x				x
CT												

Year 4

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR						x						x
CT												

Year 5 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR						x						x
CT												

Nonseminoma germ cell tumour: Stage 1. Adjuvant chemotherapy

Markers: AFP, βHCG and LDH

CT scan should be of abdomen only unless pelvis at high risk
Late effects should be assessed at 2 and 5 years (See Late effects box)*

Year 1

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical	x		x			x			x			x
Markers	x		x			x			x			x
CXR			x			x						x
CT abdc						x						

Year 2 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinica				x				x				x
Marker				x				x				x
CXR												x
CT												

Year 3

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinica						x						x
Marker						x						x
CXR												x
CT												

Year 4

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinica						x						x
Marker						x						x
CXR												x
CT												

Year 5 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinica						x						x
Marker						x						x
CXR												x
CT												

UK guidelines for the follow-up: non-seminoma

- **Non-seminoma & seminoma stage IIc-III post-ChT**:
- **n.1 CT** scan (after CR): year 5

- Note:
- **CT scan** of **abdomen only** (unless pelvis at high risk)
- **CXR** instead of CT
- **Seminoma complete at 5ys**
- **Non-seminoma** continue up to **10ys** with yearly CXR, then biannually without CXR
- **Late effects** assessed at **2, 5** and **10 years**

NSGCT and seminoma: Stages IIc–IV. Post chemotherapy

Markers: AFP, βHCG and LDH

CT until CR with or without surgery, frequency determined by MDT

Late effects should be assessed at 2,5 and 10 years (See Late effects box)*

Year 1

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical		x		x		x		x		x		x
Markers		x		x		x		x		x		x
CXR				x				x				x
CT												

Year 2 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical				x				x				x
Markers				x				x				x
CXR				x				x				x
CT												

Year 3

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												

Year 4

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												

Year 5 — Late effects(*)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Clinical						x						x
Markers						x						x
CXR												x
CT												x

Discharge seminoma patients at 5 years

For NSGCT patients, follow up annually until 10 years and then biannually. Stop performing CXRs at 10 years

van As et al Br J Cancer 2008

Active surveillance for clinical stage I disease: several strategies

Table 1 | Comparison of active surveillance strategies

Strategy	Year 1	Year 2	Year 3	Year 4	Year 5	After year 5
Indiana University						
Abdominal CT scan with or without pelvic CT scan	Every 4 months	Every 6 months	Annually	Annually	Annually	None
History, clinical examination, AFP, and hCG	Every 4 months	Every 4 months	Every 4 months	Every 4 months	Every 4 months	Annually
ESMO						
No specific modality recommended	Recommendations for the follow-up schedule need to be adapted according to national and institutional requirements					
EAU						
Abdominopelvic CT scan	Every 6 months	Every 6 months	At 36 and 60 months	At 36 and 60 months	At 36 and 60 months	None
Clinical examination, tumour markers	Every 4 months	Every 4 months	Annually	Annually	Annually	NA
Chest radiography	Every 6 months	Every 6 months	None	None	None	None
NCCN						
Abdominal CT scan with or without pelvic CT scan	At 3, 6 and 12 months	Every 6–12 months	Every 6–12 months	Every 12–24 months	Every 12–24 months	NA
Chest radiography	As clinically indicated, consider chest CT scan in symptomatic patients					
History and clinical examination, serum markers optional	Every 3–6 months	Every 6–12 months	Every 6–12 months	Annually	Annually	Annually

Table 1 | Comparison of active surveillance strategies

Strategy	Year 1	Year 2	Year 3	Year 4	Year 5	After year 5
MD Anderson Cancer Center						
Abdominal CT scan	Every 6 months	Every 6 months	Every 6 months	Annually up to 10 years	Annually up to 10 years	Annually up to 10 years
Chest radiography	At alternate visits	At alternate visits	At alternate visits	At alternate visits	At alternate visits	At alternate visits
History, clinical examination, AFP, hCG and LDH	Every 3 months	Every 3 months	Every 4 months	Every 6 months in years 4–7, then annually up to 10 years	Every 6 months in years 4–7, then annually up to 10 years	Every 6 months in years 4–7, then annually up to 10 years
Switzerland and Germany 2010 consensus						
Abdominal CT scan	Every 6 months	Every 6 months	None	None	None	None
Chest radiography	Every 6 months	Every 6 months	Annually	Annually	Annually	None
Abdominal ultrasonography	At months 3 and 9	At months 3 and 9	Every 6 months	Annually	Annually	None
Ultrasonography of contralateral testis	Annually up to 10 years	Annually up to 10 years	Annually up to 10 years	Annually up to 10 years	Annually up to 10 years	Annually up to 10 years
History, clinical examination, AFP, hCG and LDH	Every 3 months	Every 3 months	Every 6 months	Every 6 months	Every 6 months	Annually

AFP, α-fetoprotein; EAU, European Association of Urology; ESMO, European Society for Medical Oncology; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network

Chovanec et al Nat Rev Urol 2016

Active surveillance for clinical stage I non-seminoma: Danish guidelines

- **n.4 CT scans** but **frequent serum tumour markers**
- 30.6% relapse at 5 years: **50% if VI+** vs 12% without
- Most of **early relapses** (80% with 1st year) detected by **increased markers**, late relapses by CT scan
- **94.4%** relapses **IGCCCG good prognosis**
- **Late relapses** after 5 years: **0.5%**

Table 4. Suggestion for a Follow-Up Program for Patients With Stage I NSGCC

	Month																				
Program Element	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	30	36	42	48	54	60
CT scan				x				x				x						x				x
Tumor markers	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination		x		x		x		x		x		x	x	x	x	x	x	x	x	x	x	x
Free and total testosterone, LH, FSH		x										x				x						x

Abbreviations: CT, computed tomography; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NSGCC, nonseminoma germ cell cancer.

Daugaard et al J Clin Oncol 2014

Active surveillance for clinical stage I disease: Canadian guidelines

- **n.6 CT scans** for **non-seminoma** and **n.7** for **seminoma**, but **less frequent serum tumour markers**
- Relapse: 19% non-seminoma, 13% seminoma
- Most relapse within 2/3 years (90% non-seminoma and 92% seminoma)
- Mostly detected **by CT scan** vs STM in **seminoma** (87/3%), but **similarly or better by STM depending** on **VI** in **non-seminoma**: 48/38% in VI(-) and 41/61% in **VI(+)**
- **90% non-seminoma and 99% seminoma** relapses **IGCCCG good prognosis**

Table 4. Authors' Recommendations for Surveillance Schedules Based on the Observed Patterns of Relapse and the Authors' Expert Opinion

	Frequency (months)			
Year	Physical Examination	Tumor Marker*	Chest X-Ray	CT/MRI Abdomen†
CSI-NONSEM				
Year 1	2	2	4, 8, 12	4, 8, 12
Year 2	3	3	18, 24	18, 24
Year 3	6	6	—	36‡
Year 4	6	6	—	—
Year 5	6	6	—	60‡
CSI-SEM				
Year 1	3	3	6, 12	6, 12
Year 2	6	6	18, 24	18, 24
Year 3	6	6	—	30, 36
Year 4	6	6	—	—
Year 5	6	6	—	60‡

Abbreviations: CSI-NONSEM, clinical stage I nonseminoma; CSI-SEM, clinical stage I seminoma; CT, computed tomography, MRI, magnetic resonance imaging.
*Alpha fetoprotein/human choriogonadotropin (lactate dehydrogenase is of questionable benefit in stage I).[22]
†MRI only in experienced centers.
‡Proposed by several authors.

Kollmannsberger et al J Clin Oncol 2014

Follow-up and surveillance: recommendations from Italian consensus

- Promoted by AIOM and IGG:
- 42 experts
- 14 scientific societies
- 3 survivors

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Recommendations for surveillance and follow-up of men with testicular germ cell tumors: a multidisciplinary consensus conference by the Italian Germ cell cancer Group and the Associazione Italiana di Oncologia Medica☆

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[e] SIRM - Società Italiana di Radiologia Medica, Italy
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[g] AIRO - Associazione Italiana di Radioterapia Oncologica, Italy
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[i] SIUrO - Società Italiana di Urologia Oncologica, Italy
[j] FAVO - Federazione Italiana delle Associazioni di Volontariato in Oncologia, Italy
[k] AIMN - Associazione Italiana Medicina Nucleare e Imaging Molecolare, Italy
[l] SIMI - Società Italiana Medicina Interna, Italy
[m] FIMMG - Federazione Italiana Medici di Medicina Generale, Italy
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Banna et al Cr Rev Oncol Haematol 2019

Stage I Seminoma – 5-year surveillance and follow-up

Note:

- **Risk-adapted**:
- **H - High-risk** patients (15-30% risk of relapse): tumor size (≥4 cm) and / or invasion of the rete testis, no adjuvant therapy
- **L - Low-risk** (5%): no risk factors, or any adjuvant therapy
- Use of **abdomen-pelvis MRI without contrast** (instead of abdomen-pelvis CT with contrast), **US** only when CT or MRI not foreseen
- **2 abdomen imaging** alone **in low risk** x 5 years
- **Metabolism** including andrology every 2-3 years
- **Psychological counseling**: at least once at the beginning and in case of signs of psychosocial distress and / or a reduction in the perceived quality of life during the follow-up

Table 1
5-year surveillance and follow-up for the stage I Seminoma.

Month	6th	12th
1 st year		
Physical examination and markers (AFP, bHCG e LDH)	all	all
Abdominal imaging (CT with contrast or MRI without contrast)[a]	only H	all
Testicular ultrasound	–	all
2nd Year		
Physical examination and markers (AFP, bHCG e LDH)	all	all
Abdominal imaging (CT with contrast or MRI without contrast)[a]	only H	all
Testicular ultrasound	–	all
FSH, LH, testosterone	–	all
3rd year		
Physical examination and markers (AFP, bHCG e LDH)	all	all
Abdominal imaging (CT with contrast or MRI without contrast)[a]	–	only H
Testicular ultrasound	–	all
4th year		
Physical examination and markers (AFP, bHCG e LDH)	alll	all
Abdominal imaging (CT with contrast or MRI without contrast)[a]	–	only H
Testicular ultrasound	–	all
5th year		
Physical examination and markers (AFP, bHCG e LDH)	all	all
Abdominal imaging (CT with contrast or MRI without contrast)[a]	–	only H
Testicular ultrasound	–	all
FSH, LH, testosterone	–	all
Other:		
Psycological[b]	–	–
Metabolism[c]	–	–
Visits[d]	–	–

[a] Ultrasound only when a CT or MRI is not foreseen.
[b] In all cases, at least once at the beginning of follow-up and in cases presenting symptoms of psychosocial distress and/or reduction of perceived quality of life during the follow-up.
[c] Including blood lipids, glucose, creatinine, vitamin D, FSH, LH, testosterone, BMI and blood pressure: every 2–3 years in the first 5–10 years, after 10 years on the basis of personal anamnesis.
[d] Including andrology, internal medicine, cardiology, nephrology, ORL (+/- audiometric tests), pneumological (+/- respiratory tests) consulting: if symptoms, clinical or laboratory abnormalities, risk factors including PEB for 3–4 cycles and/or radiotherapy, desire of paternity (andrology and semen analysis).

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Stage I Non-seminoma: 5-year surveillance and follow-up

Note:

- **Risk-adapted**:
- **H - High-risk patients** (50% risk of relapse): presence of VI, no adjuvant therapy;
- **I - Intermediate risk** (15%): absence of VI invasion, no adjuvant therapy;
- **L - Low-risk** (<5%): after treatment with #1 PEB (or RPLND).
- Use of **abdomen-pelvis MRI without contrast** (instead of abdomen-pelvis CT with contras), better **CXR** of chest CT, US only when CT or MRI not foreseen
- **Max 8 CT / MRI abdomen-pelvis** with contrast in high-risk x 5 years
- **Psychological counseling**: at least once at the beginning of the follow-up and in case of signs of psychosocial distress and / or a reduction in the perceived quality of life during the follow-up.

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Table 2
5-year surveillance and follow-up for the stage I Nonseminoma.

Month	4th	6th	8th	12th
1 st Year				
Physical examination and markers (AFP, bHCG e LDH)	all	–	all	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray better than CT) imaging	only H	only I-L	only H	all
Testicular ultrasound	–	–	–	all
2nd Year				
Physical examination and markers (AFP, bHCG e LDH)	all	–	all	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray better than CT) imaging	–	all	–	only H-I
Testicular ultrasound	–	–	–	all
FSH, LH, testosterone	–	–	–	all
3rd Year				
Physical examination and markers (AFP, bHCG e LDH)	–	all	–	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray better than CT) imaging	–	only H	–	only H-I
Testicular ultrasound	–	–	–	all
4th Year				
Physical examination and markers (AFP, bHCG e LDH)	–	all	–	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray better than CT) imaging	–	–	–	only H
Testicular ultrasound	–	–	–	all
5th Year				
Physical examination and markers (AFP, bHCG e LDH)	–	all	–	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray better than CT) imaging	–	–	–	only H
Testicular ultrasound	–	–	–	all
FSH, LH, testosterone	–	–	–	all
Other:				
Psycological[b]	–	–	–	–
Metabolism[c]	–	–	–	–
Visits[d]	–	–	–	–

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PEB, cisplatin, etoposide, bleomycin.
[a] Ultrasound only when a CT or MRI is not foreseen.
[b] At least once at the beginning of follow-up and in cases presenting symptoms of psychosocial distress and/or reduction of perceived quality of life during the follow-up.
[c] Including blood lipids, glucose, creatinine, vitamin D, FSH, LH, testosterone, BMI and blood pressure: every 2–3 years in the first 5–10 years, after 10 years on the basis of personal anamnesis.
[d] Including andrology, internal medicine, cardiology, nephrology, ORL (+/- audiometric tests), pneumological (+/- respiratory tests) consulting: if symptoms, clinical or laboratory abnormalities, risk factors including PEB for 3–4 cycles and/or radiotherapy, desire of paternity (andrology and semen analysis).

Advanced disease in remission after treatment: 5-year surveillance and follow-up

Note:

- **Risk adapted**:
- **H - High-risk patients** (> 45% risk of relapse/progression): “poor-risk” according to the IGCCCG classification at the first line of treatment or relapsed / refractory not “very low risk” according to IPFSG (95% of patients)
- **I - Intermediate risk** (25-30%): "intermediate-risk" according to the IGCCCG classification at the first line of treatment or relapsed / refractory "very low risk" according to IPFSG;
- **L - Low-risk patients** (<15%): “good-risk” according to the IGCCG classification at the first line of treatment.
- **Use of abdomen-pelvis MRI without contrast** instead of abdomen-pelvis CT with contrast and better **chest x-ray** or **low-dose CT** or contrast CT

Banna et al Cr Rev Oncol Haematol 2019

Table 3
5-year surveillance and follow-up for the advanced disease in remission after treatment.

Month	4th	6th	8th	12th
1 st Year				
Physical examination and markers (AFP, bHCG e LDH)	only H	all	only H	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray or low-dose CT or CT with contrast)[b] and other imaging examinations based on the sites of advanced disease	only H	only I-L	only H	all
Testicular ultrasound	–	–	–	all
2nd Year				
Physical examination and markers (AFP, bHCG e LDH)	only H	all	only H	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray or low-dose CT or CT with contrast)[b] and other imaging examinations based on the sites of advanced disease	only H	only I-L	only H	all
Testicular ultrasound	–	–	–	all
FSH, LH, testosterone	–	–	–	all
3rd Year				
Physical examination and markers (AFP, bHCG e LDH)	–	all	–	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray or low-dose CT or CT with contrast)[b] and other imaging examinations based on the sites of advanced disease	–	only H-I	–	all
Testicular ultrasound	–	–	–	all
4th Year				
Physical examination and markers (AFP, bHCG e LDH)	–	all	–	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray or low-dose CT or CT with contrast)[b] and other imaging examinations based on the sites of advanced disease	–	only H-I	–	all
Testicular ultrasound	–	–	–	all
5th Year				
Physical examination and markers (AFP, bHCG e LDH)	–	all	–	all
Abdominal (CT with contrast or MRI without contrast)[a] and thoracic (X-ray or low-dose CT or CT with contrast)[b] and other imaging examinations based on the sites of advanced disease	–	only H-I	–	all
Testicular ultrasound	–	–	–	all
FSH, LH, testosterone	–	–	–	all
Other:				
Psycological[c]	–	–	–	–
Metabolism[d]	–	–	–	–
Visits[e]	–	–	–	–

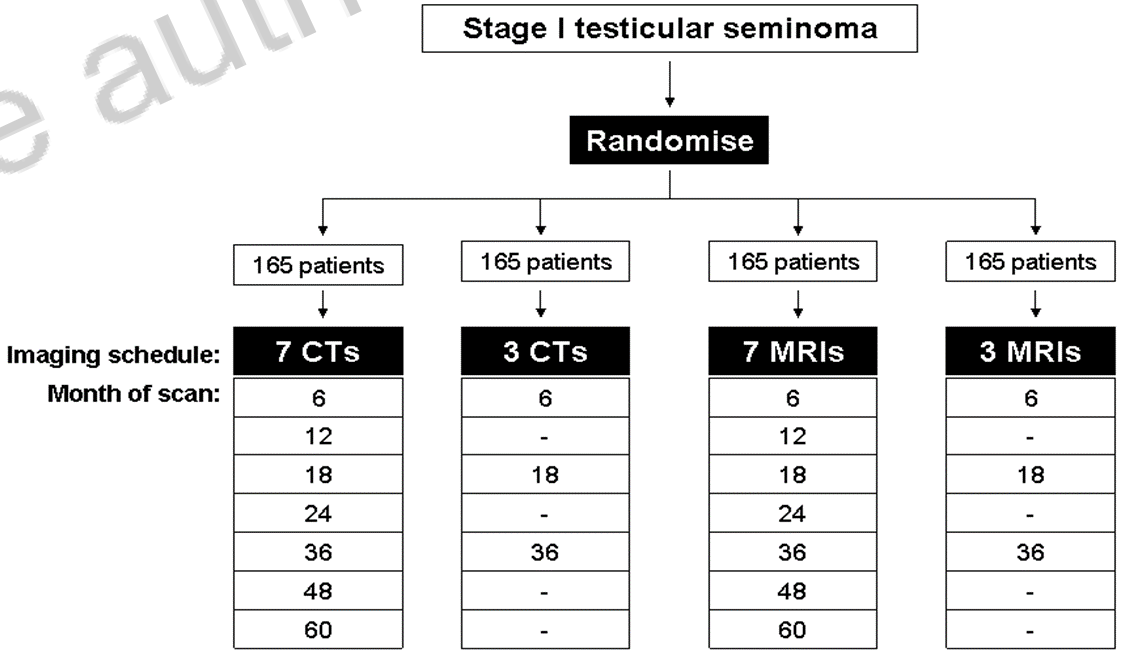
[a] Ultrasound only when a CT or MRI is not foreseen.
[b] If a risk of thoracic relapse is estimated (i.e. > 5%).
[c] In all cases, at least once at the beginning of follow-up and in cases presenting symptoms of psychosocial distress and/or reduction of perceived quality of life during the follow-up.
[d] Including blood lipids, glucose, creatinine, vitamin D, FSH, LH, testosterone, BMI and blood pressure: every 2–3 years in the first 5–10 years, after 10 years on the basis of personal anamnesis.
[e] Including andrology, internal medicine, cardiology, nephrology, ORL (+/- audiometric tests), pneumological (+/- respiratory tests) consulting: if symptoms, clinical or laboratory abnormalities, risk factors including PEB for 3–4 cycles and/or radiotherapy, desire of paternity (andrology and semen analysis).

Radiological imaging

- Ph-3-R **TRISST study** in **stage I seminoma**: non-inferiority for both comparisons i.e. **imaging frequency** (7 vs 3) and modality (MRI vs. CT). **MRI should be recommended**
- **Abdominopelvic US** might be preferred **after 3 years of FU**
- Use of **low-dose CT**: device type and imaging protocols to be periodically updated
- Low-dose **model–based iterative reconstruction**: 67% reduction in Rx dose
- **Contralateral testis US**: 3-4% risk at 15 years

TRISST

Trial of Imaging and Schedule in Seminoma Testis



Joffe at al ASCO GU 2021
Baciarello et al ASCO GU 2017
Salminen E at al Anticancer Res
Murphy KP et al Eur J Radiol Open 2016
Wanderas et al Eur J Cancer 1997

Management of treatment-related complications

- Aim to **reduce treatment burden**
- Administer **intense hydration** with **cisplatin**
- Assess/monitor **pulmonary function** (bleomycin)
- Discuss **sperm cryopreservation**
- Implement effective **coping strategies**
- Monitor **hormonal status** (replace testosterone)
- Advise to adhere to **national screening** guidelines
- Counsel about **CVD risk-factor modification**
- Avoid **smoking**, **sympathomimetic**, **ototoxic drugs**
- Prescribe **duloxetine** for **pain management**

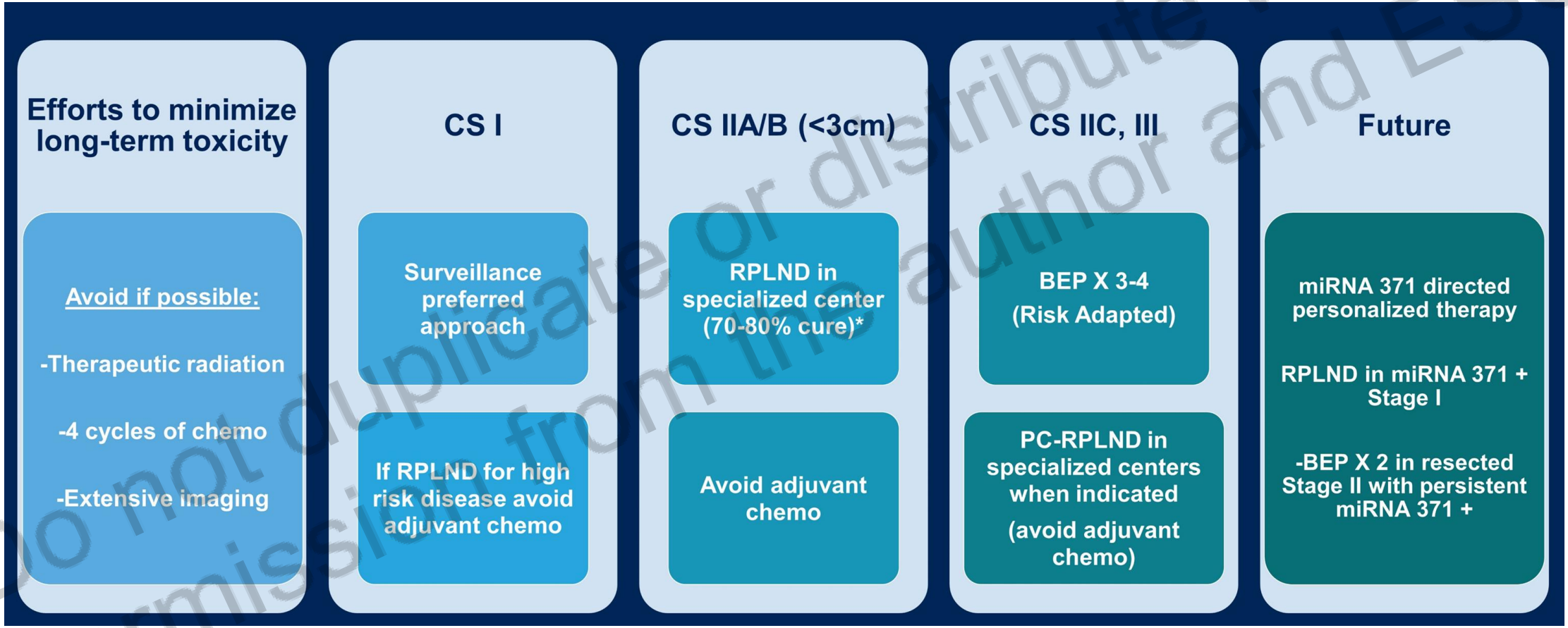
eTable 1. Recommended Management Options for Treatment-Related Complications

Treatment-Related Complications	Recommended Management
Second malignant neoplasms	• Healthcare providers should advise TCS to adhere to national cancer screening guidelines applicable to the general population[6] • Every effort should be made to reduce the amount of cytotoxic exposure needed to successfully treat the cancer
CVD	• No established evidence-based CVD screening recommendations exist specifically for TCS • Healthcare providers should counsel TCS about CVD risk-factor modification, advising adherence to guidelines[7] for the general population
Raynaud phenomenon	• Raynaud phenomenon–associated symptoms can be prevented by avoidance of cold and other aggravating factors, including smoking, sympathomimetic drugs, and selected treatments for either attention-deficit/hyperactivity disorder or migraine headaches[8]
Ototoxicity	• Although there are no effective pharmacotherapies to prevent or treat cisplatin-related ototoxicity, TCS should minimize noise exposure and avoid other ototoxic agents.
Neurotoxicity	• ASCO clinical practice guidelines for CIPN[9] recommend duloxetine for management of pain, because there are no effective agents available to prevent or treat CIPN
Nephrotoxicity	• During cisplatin-based chemotherapy, healthcare providers should avoid nephrotoxic drugs[10] and administer intense hydration[11] to minimize the degree of renal damage
Pulmonary toxicity	• Before initiation of any bleomycin-containing chemotherapy regimen, healthcare providers should perform a detailed patient history, including consideration of age, smoking status, and preexisting lung disease, and consider baseline pulmonary function • Healthcare providers should also withhold bleomycin at the earliest clinical signs or symptoms of bleomycin-induced pulmonary toxicities during chemotherapy
Hypogonadism	• Healthcare providers should routinely evaluate TCS for hypogonadism symptoms and assess hormonal status accordingly • Decisions to administer testosterone replacement therapy should be based on clinical symptoms of hypogonadism, and referrals to endocrinologists should be considered for challenging cases[10]
Infertility	• The ASCO clinical practice guideline for fertility preservation[12] recommends referral of patients with cancer to appropriate reproductive specialists if clinically indicated; sperm cryopreservation remains a standard fertility preservation practice before treatment initiation for interested patients with TC
Cognitive impairment	• Because subjective cognitive complaints may reflect the effects of underlying anxiety and depression that are prevalent in TCS,[13] implementation of effective coping strategies should be considered
Chronic CRT	• Exercise and psychologic interventions should be considered

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; CRT, cancer-related fatigue; CVD, cardiovascular disease; TC, testicular cancer; TCS, testicular cancer survivors.

Fung et al J Natl Compr Canc Netw 2019

Possible improvements in the general management of patients with testicular cancer



Hellesnes ASCO 2021

Lesson from the SARS-CoV2 pandemic

ESMO recommendations[1]:

- given the high cure rate with oncological treatments, even in advanced disease, and being GCTs prevalent in the young population, the indication for curative oncological treatment should be guaranteed and priority unless relevant comorbidities

Survey of 3 cooperative groups (Italian, European and Canadian) during the pandemic[2]:

- **preference for surveillance in stages I**;
- **bleomycin should not be omitted** (i.e., 3 PEB cycles better than 4 EP cycles);
- surgery or radiotherapy (where indicated) must not be delayed (also for residue);
- G-CSF recommended as primary PEB prophylaxis during the pandemic

[1]*ESMO guidelines during COVID-19 pandemic. Available at https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic*
[2]*Nappi e al The Oncologist 2020*

Take-home messages

- Follow-up and surveillance for testicular cancer start with **careful assessment**, **appropriate treatment** and **counselling**
- **Evidence** on modalities and timing of examinations is **limited but** following **clinical recommendations** would result in **optimising risk-benefit ratios** for **individual patients**, while **ensuring economic use** of **resources**
- **Open issues**: **length of follow-up** and **surveillance**, **examinations** (clinical, instrumental and lab), **professionals** to be involved
- **Precision-medicin approaches** with **novel biomarkers** (like miRNA-371) and **genetic variants** (i.e. germline mutations) will likely help to **reduce treatment burden, develop risk-based**, **targeted prevention** and **intervention** through the identification of testicular cancer (risk) and acute or long-term adverse events
- A **longitudinal cohort study following survivors** for life to examine **morbidity** and **latency trends** of late adverse outcomes according to treatment types is needed

Thanks!

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ASSOCIAZIONE ITALIANA TUMORE DEL TESTICOLO

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