

Review

# Cisplatin Resistance in Testicular Germ Cell Tumors: Current Challenges from Various Perspectives

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**Table S1.** Summary of some recent studies exploring cisplatin resistance in tumor models other than testicular germ cell tumors.

Tumor Model	Main Mechanism	Main Findings	Reference
Bladder Cancer	Uptake/Efflux/Detoxification, DNA repair, apoptosis, epigenetics, growth factors	Details the impact of extrinsic and intrinsic apoptosis pathways. Details epigenetic regulation of these pathways.	Broad review in [1]
Epithelial (i.e. non-GCT) Ovarian Cancer	DNA repair	Alterations of HR, NER, BER and MMR contribute to cisplatin sensitivity/resistance. Mutations in HR genes as biomarkers of response to PARPis	Broad review in [2]
	TLS	Overexpression of DNA polymerase eta contributes to cisplatin resistance	[3]
Lung cancer (SCLC)	Apoptosis	Sensitivity to cisplatin correlates with Bcl-2/Bim ratio. The BH3-mimetic ABT-263 sensitizes tumor cells to cisplatin and radiation	[4]
Lung cancer (NSCLC)	Epigenetics	Silencing the lncRNA UCA1 sensitizes tumor cells to cisplatin	[5]
	TLS	Overexpression of DNA polymerase eta predicts survival after treatment with cisplatin	[6]
Esophageal cancer	Epigenetics	miR-338-5p promoted cisplatin sensitivity in tumor cells, by targeting <i>FERMT2</i>	[7]
Head and neck cancer	Autophagy and microenvironment	CAFs contribute to cisplatin resistance by activating autophagy	[8]
Gastric cancer	EMT	The transcription factor eIF5A2 regulates cisplatin resistance by promoting EMT	[9]
Colorectal cancer	Apoptosis, inflammatory cytokines	The pro-inflammatory cytokine IL-17 promotes cisplatin resistance. Regulates apoptotic players Bax, Bcl-2	[10]
Breast cancer	p53 and inflammatory cytokines	The <i>TP63</i> isoform $\Delta$ NP63 $\alpha$ (which counteracts p53 by promoting pro-survival signals) is induced by IL-1 $\beta$ and downregulates <i>ATM</i> , contributing to cisplatin resistance	[11]
Cervical cancer	Efflux, DNA repair, apoptosis, epigenetics, EMT, activation of stress response chaperones	Multifactorial perspective. Includes overview of several agents (including natural compounds) that antagonize cisplatin resistance	Broad review in [12]

Abbreviations: BER – base excision repair; CAF – cancer-associated fibroblast; EMT – epithelial-to-mesenchymal transition; HR – homologous recombination; lncRNA – long non-coding RNA; MMR –

mismatch repair; NER – nucleotide excision repair; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer; TLS – translesion synthesis.

**Table S2.** Review of the literature regarding growing teratoma syndrome with testicular origin.

Number of Patients	Age	Pre-CT Histology	Testicular Tumor laterality	Pre-CT Tumor size (cm)	Staging	Presentation	TM Before CT	Topography and Size of GTS Masses	Treatments Performed	Complications	Patient Outcome / Follow-up (months)	Relevant Details	Author (Ref.)
1	20y	Metastases: imTE	Left	Testis: 10x7x8; Metastases: N/A ("entire abdomen and pelvis + neck")	N/A; IGCCCG good risk	Testicular mass + abdominal distension + leg swelling (DVT)	Elevated	"Entire abdomen and pelvis" + neck (8cm)	3BEP→Orchiectomy along with radical Resection + LND	Seroma (resolved)	ANED (8)	Orchiectomy only after CT	Nassiri, 2019 [13]
1	19y	Testis: mixed	Left	N/A	III (lung metastases)	Testicular mass + constitutional symptoms	N/A	Lung + hilar, N/A	Orchiectomy→3BEP+3TIP→2 Resections	None	ANED (12)	-	Tanaka, 2018 [14]
22	Median 28y (IQR 22-34)	Testis: 16 Mixed, 2 EC, 2 YST, 2 TE	N/A	Testis: median 4.8 (IQR 1.9-9.4)	16 II, 5 III, 1 N/A	N/A	Elevated	Median 6 (IQR 4-12.2)	Orchiectomy→CT→RPLND	Adjunctive surgeries (n=4); rapid growth needing CT interruption (n=1); grade III/IV post-operative complications (n=4)	Disease relapse (n=2); DFD (n=1; 9 after RPLND); median 25 (IQR 8-47)	Only patients undergoing post-CT RPLND	Paffenholz and Pfister, 2018 [15]

1	36y	Testis: TE with ST cells	Left	Testis: 2; paratracheal nodes: 1; lombo-aortic nodes: 2	pT1	Testicular pain	Elevated $\beta$ -HCG	Abdominal, 4.5; Mediastinal: 2; Cervical: 5	Orchiectomy→2BEP→RPLND→3 Resections	Horner syndrome	Disease relapse (GTS 3, 6, 8 after RPLND); ANED (48)	-	Priod, 2017 [16]
1	PT:47y; GTS: 51y	Testis: Mixed (YST, mTE, EC)	N/A	Testis: 10	I	Shortness of breath	Normal	Abdominal (19x18)+ Chest (14x12)+ Thigh (16x10)	Orchiectomy→BEP+VIP→RPLND+2 Resections	None	Disease relapse (GTS 48 after orchiectomy); ANED (24)	-	Gange, 2016 [17]
2	PT: 23y; GTS: 24y	Testis: Mixed (TE, CH, EC)	Right	N/A	T2 (IIC); IGCCCG intermediate	N/A	N/A	Abdominal, 21	Orchiectomy→4BEP→Resection	None	Disease relapse (GTS 12 after orchiectomy); ANED (10)	-	Scavuzzo, 2014 [18]
	28y	Testis: Mixed (TE, EC)	Left	III A			Elevated AFP, LDH and $\beta$ -HCG	Abdominal, 30	Orchiectomy→3BEP→Resection		Disease relapse (GTS 6 after orchiectomy); ANED (8)		
1	27y	N/A	Left	N/A	N/A	N/A	N/A	Abdominal, cardiac (right ventricle)	CT→Orchiectomy→2 Resections	Mild tricuspid regurgitation	ANED (24)	Orchiectomy only after CT; tricuspid valve	Roubelakis, 2014 [19]

												repair technique after tumor excision	
15	Median 23y (range: 16-39)	Testis: NS in 12, SE in 2, "hemorrhagic mass" in 1	N/A	N/A	8 II, 7 III	N/A	N/A	Retroperitoneal, median 7 (range 4-25); non- retroperitoneal in 4	Orchiectomy→CT→RPLND	2 major (Clavien ≥III); 5 additional procedures performed	ANED (8, range 1-64)	mTE in only 40% patients at orchiotomy	Lee, 2014 [20]

**Abbreviations:** AFP: alpha fetoprotein; ANED: alive with no evidence of disease; β-HCG: human chorionic gonadotropin subunit β; CH: choriocarcinoma; CT: chemotherapy; DFD: died from disease; DVT – deep venous thrombosis; EC: embryonal carcinoma; GTS – growing teratoma syndrome; IGCCCG: International Germ Cell Cancer Collaborative Group; imTE: immature teratoma; IQR: interquartile range; LDH: lactate dehydrogenase; LND: lymph-node dissection; mTE: mature teratoma; N/A – not available; NS – non-seminoma; PT: primary tumor; RPLND: retroperitoneal lymph-node dissection; SE – seminoma; TM: tumor markers; YST: yolk sac tumor

Table S3 – Review of the literature regarding growing teratoma syndrome with ovarian origin.

Patient s (N)	Age	Histology (and Grade of NmTE)	Ovarian tumor laterality	Pre-CT Tumor Size (cm)	Staging	Presentation	TM Before CT	Topography and Size of GTS Mass (cm)	Treatments Performed	Complications	Patient Outcome / Follow-up After Last Treatment (months)	Relevant Details	Author (Ref.)
2	21y	Ovary: Mixed	Left	13x7	N/A	Abdominal distension	Elevated AFP	Adnexal, 35x20	3BEP→Resection	None	ANED (24)	-	Saba, 2018 [21]
	23y	Ovary: Mixed (imTE + YST)	Right	N/A		N/A	N/A	Adnexal, 7x4	3BEP→Resection	None	ANED (6)		
1	PT: 35y; GTS: 57y	Ovary: imTE	N/A	N/A	N/A	Asymptomatic	Normal	Pelvic + Hepatic (recurrence)	TH+BSO→5MTX/VP16→Resection	None	GTS 264 after 1 <sup>st</sup> treatment; ANED (18)	Somatic-type malignancy in liver metastasis (follicular carcinoma) 22 years after primary tumor resection	Shannon, 2017 [22]
1	12y	Ovary: imTE, grade III	Right	Pelvic implants: 3.5x1.5; chest implants: 2x1; diaphragm implants: 2.5	FIGO IIC	Abdominal distension with mass, weight loss	Elevated AFP	Pelvic, 9x8; peritoneal implant next to liver: 7x7	Right SO→4BEP→Resection→Experimental protocol (temozolomide + tretinoin + sorafenib)	None	“Without new tumor growths”	Rupture of primary tumor and seeding	Rentea, 2017 [23]
1	13y	Ovary: imTE (grade II);	Right	N/A	N/A	Abdominal distension	Elevated AFP	Abdominal (peri-	Right SO→Left SO +	None	Disease relapse (3 after right SO; 2	Patient was initially	Johnson,

		pelvic mass: imTE + mTE					and LDH	hepatic/spl enic)	TH→4BEP+2EP →Resection		weeks after CT); ANED (30)	under- staged (IA)	2017 [24]
1	14y	Ovaries: mTE (left) + imTE grade III (right)	Bilateral	12-13	IA	Abdominal distension and pelvic pain	Elevate d AFP	Liver, 5x4; left ovary: 6x4	Right SO + Left cystectomy→4E P→ 2 Resections	None	GTS 6 and 15 after SO; ANED (11)	-	Yakut , 2016 [25]
6	Median 24 (range 17-38)	Ovaries: only imTE patients included (grade III, n=5; grade I, n=1)	N/A	N/A	IA (n=1); IIIA (n=2); IIIC (n=1); IV (n=2, liver and small bowel)	Pelvic pain and bloating	N/A	Pelvic + Abdominal (all patients); mediastina l (n=1); 16- 23	Surgery→4BEP/ EP→1 to 4 additional resections (complete resections in 5/6 patients)	None	GTS (median 20 after surgery, range 8-42; median 12 after CT, range 2-48); recurrence of GTS (n=3, 12-132 after 1 <sup>st</sup> GTS episode); ANED (n=5, median 90, range 24-166) and AWD (n=1)	Crude incidence of GTS = 40% (6/15 patients with imTE receiving CT); disease stage associated with GTS risk	Nguy en, 2016 [26]
1	PT: 16y; GTS: 25y	Ovary: imTE	Right	Ovary: 40x25	N/A	Abdominal distension and pain	N/A	Abdominal , 29x24	Right O→4BEP→ Resection	None	GTS 108 after O; ANED (14)	Successful pregnancy	Li S, 2016 [27]
1	PT: 14y; GTS: 24y	Ovary: imTE, grade II	Right	N/A	N/A	Abdominal pain	N/A	Abdominal (liver + spleen), 19x16	Right O→ 3BEP → Resection	None	GTS 120 after O; ANED (6)	-	Li X, 2016 [28]
1	10y	Ovaries/pelv ic: imTE (biopsy)	N/A	N/A	N/A	Abdominal distension and pain	Elevate d AFP	Abdominal , N/A	4BEP→Resectio n	None	ANED (6)	-	Katari a, 2016 [29]
1	37y	Ovary: imTE, grade III; pelvic recurrence: imTE + mTE	Left	N/A	N/A	N/A	Elevate d AFP	Abdominal /pelvic + Liver, N/A	Left SO→ Resection →4BEP→ Resection	None	Disease relapse (4 after SO); GTS 9 after SO; ANED (10)	-	Soufi, 2015 [30]

1	PT: 20y; GTS: 21y	Ovary: imTE, grade III	Left	Ovary: 17; peritoneal implants: 0.5	FIGO IIIB	Abdominal distension	Elevate d AFP	Abdominal , 5	Left SO→3BEP→ Resection (laparoscopic)	None	GTS 17 after SO; ANED (12)	Residual disease in SO; immature glial peritoneal implants	Shiget a, 2015 [31]
1	15y	Ovary: imTE, grade III	Left	Ovary: 25; implants: 8 and 5	N/A	Abdominal pain and asthenia	Elevate d AFP	Retro- hepatic (12), cardiophre nic, pelvic (8)	Left SO→BEP+5TIP → Resections	None	ANED (N/A)	<i>Gliomatosis peritonei</i>	Portill a, 2015 [32]
1	15y	Ovary: imTE	Left	Ovarian/ Pelvic: 20x12; Peritoneal implants (7x6) and peri- hepatic (8x6)	FIGO III	Abdominal distension and pain	Elevate d AFP	Peritoneal implants (7x3) and peri- hepatic (12x8)	Left SO→3BEP+5TIP → Resection	None	Disease progression (23 days after SO); ANED (5)	<i>Gliomatosis peritonei</i>	Ocam ica, 2015 [33]
2	27y	Ovary: imTE, grade III	Left	Ovary: 19x15	IA	Abdominal and back pain	Norma l	Pelvic, N/A	Left SO→3BEP+4EP → Resection → Surveillance	None	Disease relapse (8 after first resection); AWD (8)	<i>Gliomatosis peritonei</i> ; viable pregnancy during treatment (after CT)	Merar d, 2015 [34]
	22y	Ovary: imTE, grade II	Right	Ovary: 20x12	IIB	Neurologic / behavioral symptoms and abdominal distension	Elevate d AFP	Liver (1 <sup>st</sup> , 3.5); colon, pouch of Douglas and left ovary (2 <sup>nd</sup> , 2)	Right SO→4BEP→ Resection→2BE P→ 2 Resections	Infertility	GTS 5 after SO; 2 after liver resection; “few months” after 2 <sup>nd</sup> resection; ANED (108)	<i>Paraneopla stic syndrome (anti- NMDA receptor encephaliti</i>	





													AFP – true case?	
1	PT: 29y; GTS: 30y	Ovary: “immature germ cell tumor”	Right	Ovary: 6x5.5	N/A	Abdominal pain and distension	Elevated AFP and $\beta$ HCG	Liver and lung	Right SO→3BEP	None	GTS 12 after SO; ANED	-	Panda, 2014 [37]	
1	PT: 12y; GTS: 30	Ovary: imTE	N/A	N/A	N+ (lymph nodes)	Abdominal mass, respiratory distress	N/A	Abdominal/pelvic, 40	TH+BSO→CT (incomplete)→Resection	Massive blood loss, respiratory complications	GTS 216 after surgery; ANED	-	Ohashi, 2014 [38]	
5	PT: 20y (range 13-17)	Ovary: imTE (n=3) and YST (n=2)	N/A	N/A	III (n=2) and I (n=2)	N/A	Elevated AFP in all	Abdominal/pelvic (n=3), ovarian (n=2); 2.2-6.4, 3.3, 5.5	Surgery→BEP→Surgery	None	GTS 29 after surgery (range 5-83); ANED or insufficient FUp	4/5 were asymptomatic at time of GTS diagnosis	Han, 2014 [39]	
1	4y	Ovary: mixed (YST, TE, Dysg)	Left	17	N/A	Abdominal swelling, vomiting	Elevated AFP and $\beta$ HCG	Retroperitoneal (multiple implants)	Resection→CT→Multiple resections	None	Disease relapse (4 after 1 <sup>st</sup> resection, 7 after 2 <sup>nd</sup> resection; 5 after 3 <sup>rd</sup> resection); ANED	-	Daher, 2014 [40]	

**Abbreviations:** AFP: alpha fetoprotein; ANED: alive with no evidence of disease; AWD: alive with disease;  $\beta$ -HCG: human chorionic gonadotropin subunit  $\beta$ ; CT: chemotherapy; DFD: died from disease; DWD: died with disease; Dysg: dysgerminoma; FUp: follow-up; GTS – growing teratoma syndrome; imTE: immature teratoma; LDH: lactate dehydrogenase; mTE: mature teratoma; N/A – not available; O: oophorectomy; PT: primary tumor; SO: salpingo-oophorectomy; TH: total hysterectomy; TM: tumor markers; YST: yolk sac tumor

**Table S4.** – Review of the literature regarding growing teratoma syndrome with extragonadal origin.

Number of patients	Age	Primary Tumor Location	Primary Tumor Histology	Pre-CT Tumor Size (cm)	Staging	Presentation	TM Before CT	Topography and Size of GTS Masses	Treatments Performed	Complications	Patient Outcome / Follow-up after Last Treatment (months)	Relevant Details	Author (Ref.)
3 (♂)	24y	Med	imTE	13×13×16	N/A	Respiratory symptoms, chest pain	Elevated (S3)	Med, 12×15×19	3BEP→Resection	None	ANED (28)	-	Sachdeva et al, 2019 [41]
	21y		mTE	23×13×13			Elevated	Med, 25×18×15	3BEP+2EP→Resection	None	ANED (24)		
	22y		imTE	N/A			Elevated	Med, 16×14×13	3BEP→2 resections	None	Disease relapse (7); ANED (16 after 2 <sup>nd</sup> resection)		
1 (♂)	1m	Sacr	mTE	N/A	N/A	Detected in fetal US	N/A	Sacr, N/A	Resection→CT→Resection	Spinal cord compression	ANED (N/A)	-	Sertbas et al, 2019 [42]
1 (♂)	26y	Med	Mixed (SE, YST, TE)	N/A	N/A	Dyspnea, orthopnea and fever	Elevated	Med, 14×10	3BEP→2 resections	Massive bleeding (incomplete first resection)	Disease relapse (~12 after 1 <sup>st</sup> resection); DFD (3 after 2 <sup>nd</sup> resection)	Somatic-type malignancy in 2 <sup>nd</sup> resection: angiosarcoma	Matsuoka et al, 2019 [43]
1 (♂)	PT: 23y;	Cranial (pineal)	N/A (biopsy non-)	N/A	N/A	Headache, nausea,	Normal	Cranial, 2×1.5	RT→Resection	None	Disease relapse (108 after	No CT, but RT – true GTS?	Khoo B et al, 2017 [44]

	GTS: 32y		diagnostic )			poor balance					RT); ANED			
1 (♂)	PT: 51y; GTS: 69y	Med	mTE (first two resections)	5, 8 and 10×9	N/A	Mass	Normal in first two resections; elevated AFP and βHCG (third resection)	Med, 15×13	Resections at 51, 59 and 69 years→3BEP→ Resection	Severe respiratory distress needing mechanical ventilation	Disease relapse (96 after 1 <sup>st</sup> resection and 120 after 2 <sup>nd</sup> resection); ANED (54)	-	Hakiri et al, 2017 [45]	
1 (♂)	37y	RP	Mixed (imTE, YST)	16 + 8	cT× N1 M1b S3 (IIC)	Abdomina l distension and pain, weight loss	Elevated AFP, βHCG and LDH (S3)	Abdominal/p elvic, 10×8	Resection→4BEP → Resection	Severe myelodyspl asia secondary to therapy	DFD (5)	Klinefelter syndrome patient	Konheim , 2017 [46]	
1 (♂)	5y	Cranial (pineal)	mTE (biopsy)	N/A	N/A	Gaze paresis and headache	Elevated AFP	Cranial, N/A	“Cisplatin-based CT” → Resections (incomplete) → interferonα-2b → Palbociclib → Thermoablations	Neurologic symptoms, central venous sinus thrombosis, respiratory distress	AWD (30 after diagnosis)	Experimental drug Palbociclib (CDK inhibitor)	Schultz, 2015 [47]	
1 (♂)	13y	Cranial (pineal)	Germinom a (biopsy)	3.3	N/A	Headache, gaze palsy and vomiting	Normal	Cranial, N/A	Open biopsy→3EP→RT → Resection →RT	None	Disease progressi on under CT (at 2 <sup>nd</sup> course); ANED (9)	Biopsy not representative (mixed tumor?); report of another case of enlarging mTE, but not treated with CT	Oya, 2014 [48]	

											(expanding definition?)		
2 (67)	12y	Cranial (pineal)	N/A	N/A	N/A	Headache, double vision	Elevated AFP (serum and CSF)	Cranial	Carboplatin/etoposide and ifosfamide/etoposide → partial resection → RT → M multiple resections along with chemotherapy → Final total resection and submyeloablative CT	None	Disease progression under CT after partial resection; ANED (36 after final treatment)	Successive partial resections; rhabdomyosarcoma in one of resections (somatic malignancy)	Glass, 2014 [49]
	7y	Cranial (pineal)	N/A	N/A	N/A	Diplopia, Parinaud's syndrome	Elevated AFP and β-HCG	Cranial	CT → partial resection → RT → R resection	Precocious puberty; hemorrhage	DFD (4.5 after surgery)	"somatic malignancy in the form of carcinoma" at the second resection	

**Abbreviations:** AFP: alpha fetoprotein; ANED: alive with no evidence of disease; AWD: alive with disease; β-HCG: human chorionic gonadotropin subunit β; CSF: cerebral spinal fluid; CT: chemotherapy; DFD: died from disease; GTS – growing teratoma syndrome; imTE: immature teratoma; LDH: lactate dehydrogenase; Med: mediastinal; mTE: mature teratoma; N/A – not available; PT: primary tumor; RT: radiotherapy; RP: retroperitoneal; Sacr: sacral; SE – seminoma; TM: tumor markers; US: ultrasound; YST: yolk sac tumor

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