

Patients with Differences of Sex Development and the Development of Gonadal Malignancy: Risk Stratification and Long-Term Outcomes

*Jacqueline Morin MD¹, Leslie Peard MD¹,
Timothy Vanadurongvan MD², Jonathan Walker MD²,
M. Irfan Donmez MD², Ali M. Ziada MD¹ & Amanda F. Saltzman MD¹*

¹University of Kentucky Department of Urology, Lexington, KY

²University of Colorado, Department of Surgery, Division of Urology, Denver, CO

Introduction

- Some patients with DSD are known to be at increased risk for pre-malignant GCNIS/Gb and invasive GCTs
- Current management often involves early gonadectomy
 - Guaranteed infertility and hypogonadism
 - Prevention of potential future gonadal GCT
- Natural history of timing of these events is unknown
- Long-term oncologic outcomes are unknown

Objectives

1. To validate a previously described malignancy risk stratification system¹
2. To determine likelihood of finding Gb or GCT at the time of gonadal surgery
3. To describe long-term oncologic outcomes for patients with DSD and Gb or invasive GCT

¹Cools *et al.*, 2006, Looijenga *et. al.* 2007

Methods

- Systematic PubMed review to identify patients (PRISMA)
 - Included patients with DSD diagnosis + gonadal surgery + pathology reported
- Recorded information on:
 - DSD diagnosis, karyotype, age at surgery, pathologic diagnosis, treatment, follow up, recurrence, survival
- Grouped patients and report trends using descriptive non-parametric methods:
 - Risk class¹
 - Pathologic diagnosis
- Evaluated the rates of finding Gb or GCT at gonadal surgery and compared RFS and OS using the Kaplan-Meier method and log-rank testing

¹Cools *et al.*, 2006, Looijenga *et. al.* 2007

Risk Classification System¹

Table 3. Risk of type-II germinal cell tumors (GCTs) in the various categories of disorders of sex development (DSD) patients, classified into high-, intermediate-, low- and no-risk groups.

Risk group	Disorder	Malignancy risk (%)	Recommended action	Studies (n)	Patients (n)
High	GD ^a (+Y) ^b intra-abdominal	15–35	Gonadectomy ^c	12	>350
	PAIS non-scrotal	50	Gonadectomy ^c	2	24
	Frasier	60	Gonadectomy ^c	1	15
	Denys–Drash (+Y)	40	Gonadectomy ^c	1	5
Intermediate	Turner (+Y)	12	Gonadectomy ^c	11	43
	17 β -HSD	28	Monitor	2	7
	GD (+Y) ^c	Unknown	Biopsy ^d and irradiation?	0	0
	PAIS scrotal gonad	Unknown	Biopsy ^d and irradiation?	0	0
Low	CAIS	2	Biopsy ^d and ???	2	55
	Ovotestis DSD	3	Testis tissue removal?	3	426
	Turner (– Y)	1	None	11	557
No (?)	5 α -reductase	0	Unresolved	1	3
	Leydig cell hypoplasia	0	Unresolved	2	

CAIS, complete androgen insensitivity syndrome; 17 β -HSD, 17 β -hydroxysteroid dehydrogenase deficiency; PAIS, partial androgen insensitivity syndrome.

^a Gonadal dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete).

^b GBY region positive, including the *TSPY* gene.

^c At time of diagnosis.

^d At puberty, allowing investigation of at least 30 seminiferous tubules, with diagnosis preferably based on OCT3/4 immunohistochemistry.

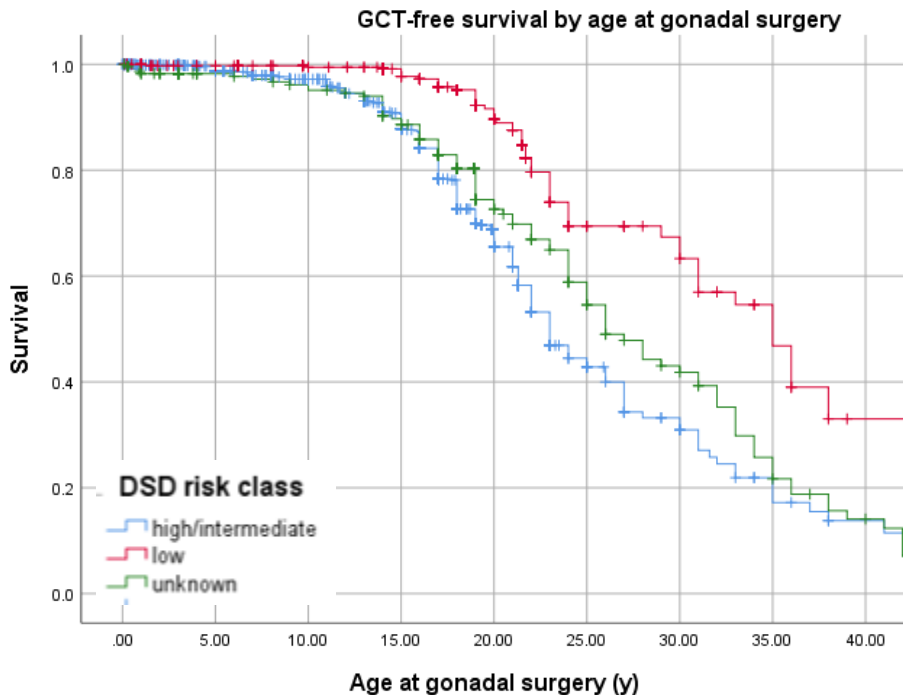
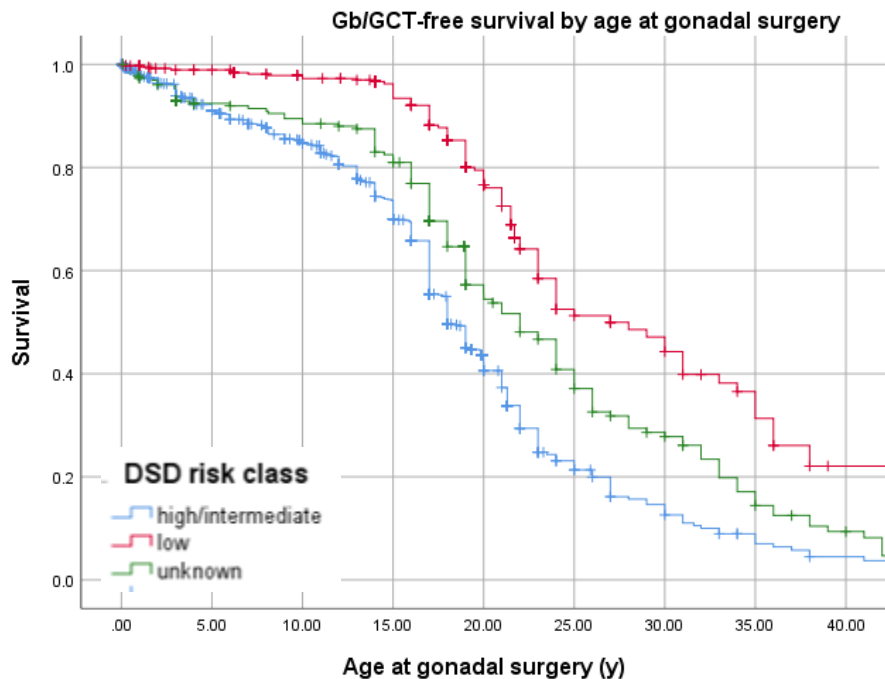
Results

- 386 articles, 2037 patients (range 1951-2017)
- Median age at surgery 17 y (IQR 11-20 y)
- Median follow up 60 mos (IQR 30-68.1 mos)

Risk class	n (%)	No Gb/GCT	Gb	GCT	Median age at surgery (IQR)
All patients	2037 (100%)	61%	18.1%	11.9%	17 y (11-20 y)
High/intermediate	1175 (58%)	54.6%	23.8%	21.6%	16 y (7-19.9 y)
Low	580 (28%)	81.6%	8.1%	10.3%	16 y (14-21.7 y)
No*	4 (<1%)	75%	0%	25%	13.6 y (9-40.8 y)
Unknown	278 (14%)	41.1%	20.4%	38.5%	18.9 y (14-24 y)

*Not further analyzed due to only 4 patients

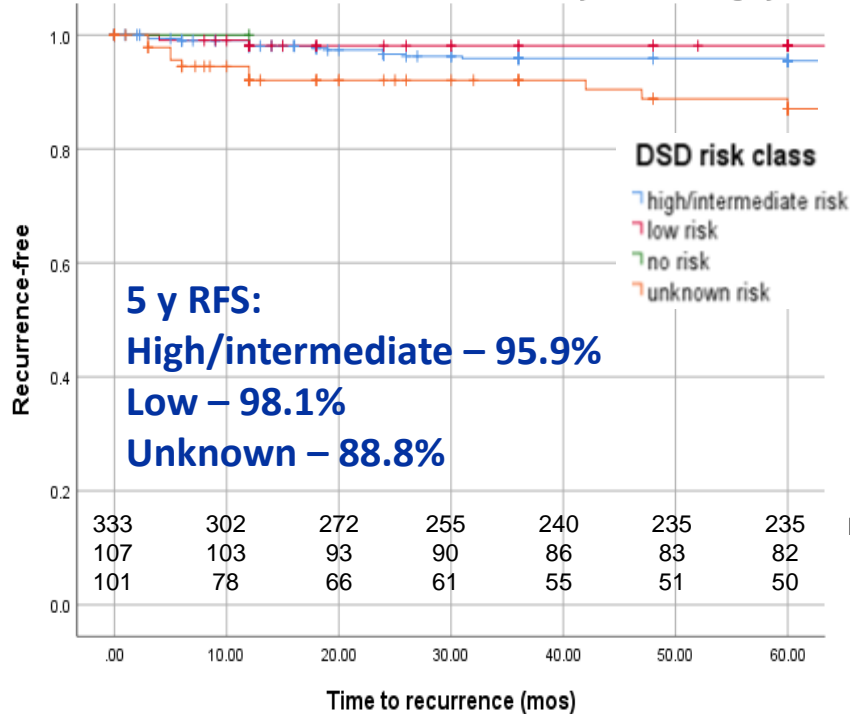
Gb/GCT-free and GCT-free Survival by Age at Gonadal Surgery



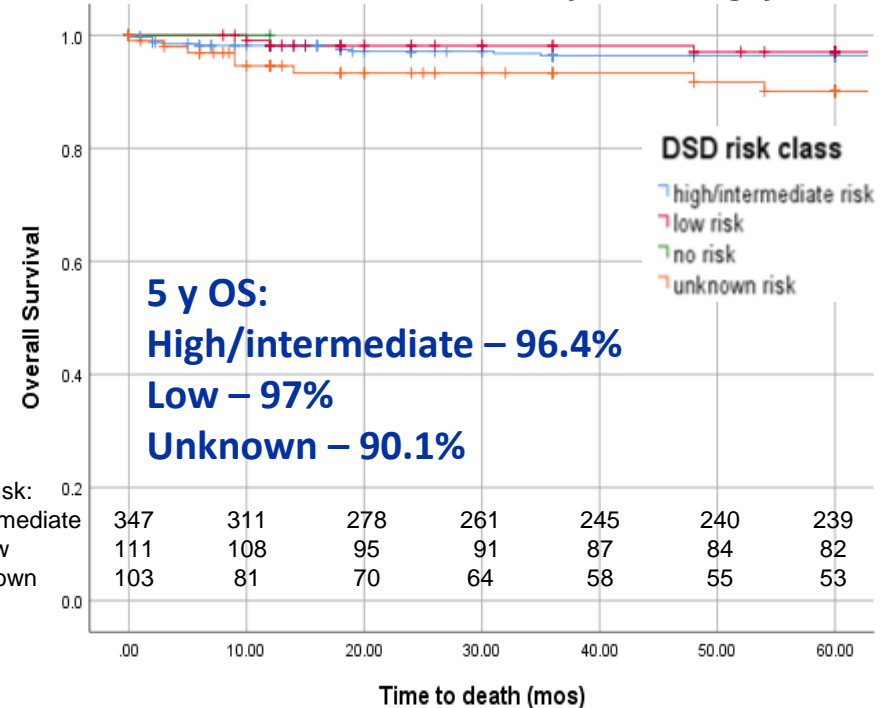
* $p < 0.001$

RFS and OS by Risk Category

Recurrence-free survival by DSD risk category

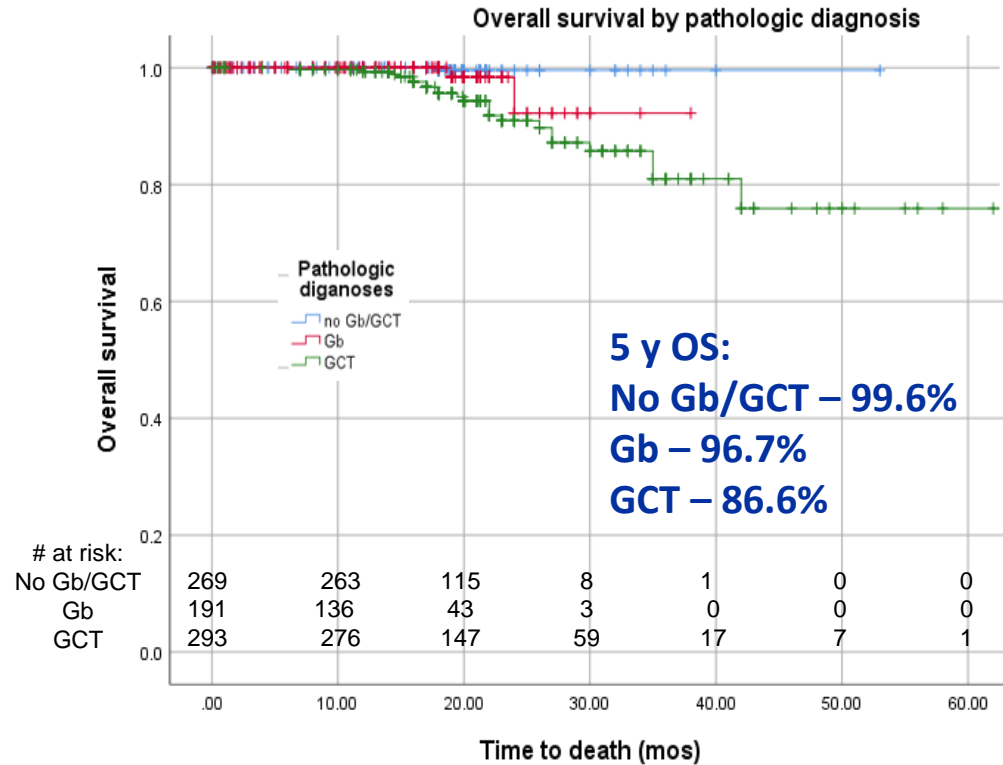
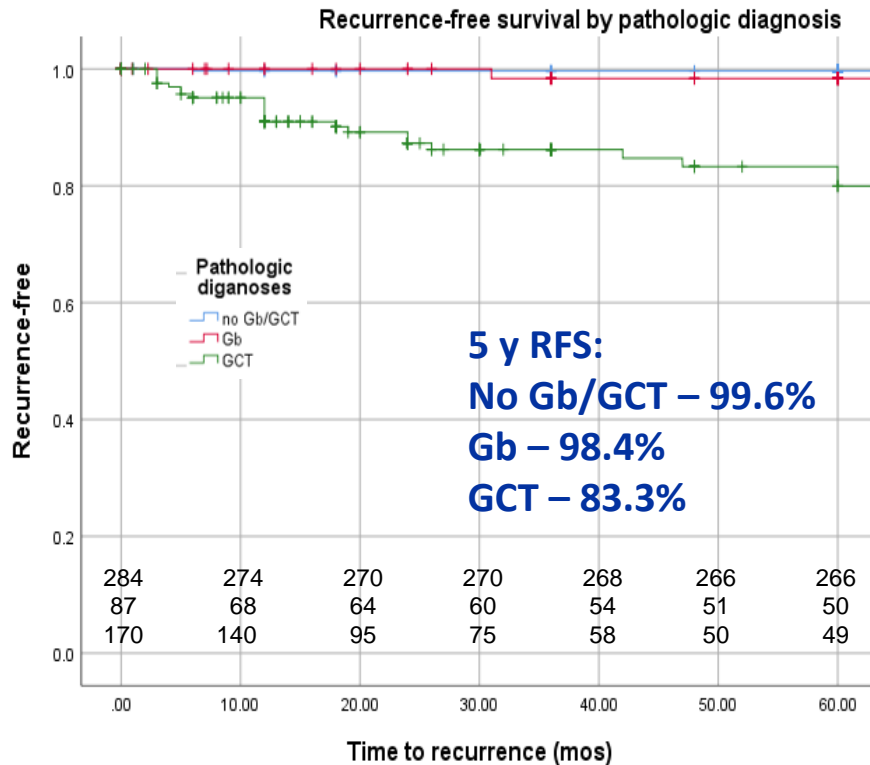


Overall survival by DSD risk category



*p<0.001

RFS and OS by Pathology



*p<0.001

Limitations

- Classification and accuracy of DSD diagnoses has changed significantly over time
- Reporting/publication bias
- Large studies had mean/medians used for individual patients
- Risk classification was limited based on data reported

Conclusions

- Previously reported malignancy risk classification system appears to work well
 - Some DSD diagnoses are missing
- Risk of finding Gb or GCT at surgery increases with age, regardless of risk
- 5 y RFS/OS equivalent for Gb and no Gb/GCT, worse for GCT
- This information can be useful when counseling families:
 - If/when to perform gonadectomy
 - Outcomes if any gonadal pathology is found

amanda.saltzman@uky.edu

