A potential acceptor with history of malignancy: a no go?

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September 13th, 2023

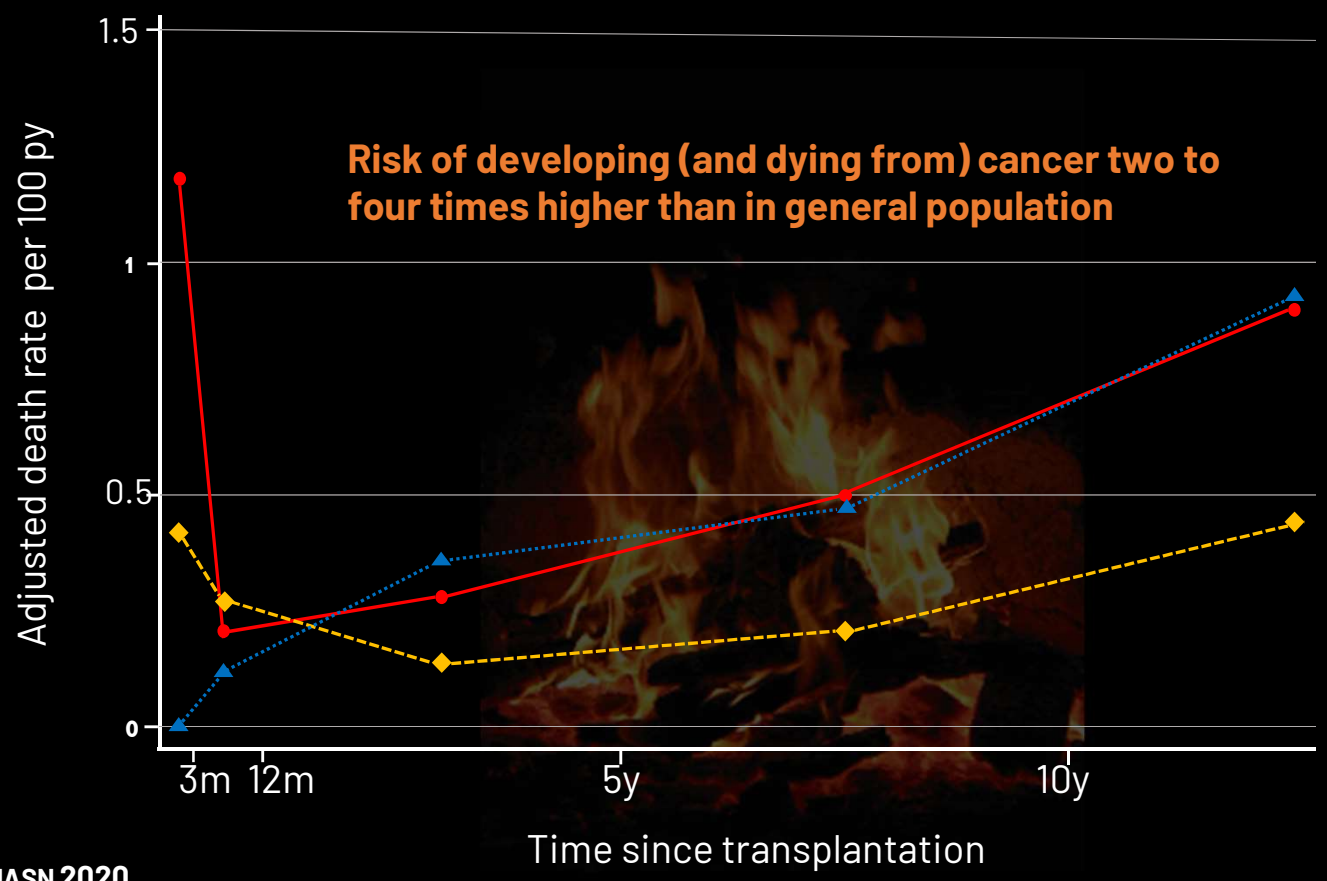
UZ GENT

OUTLINE

- The impact of cancer in ESKD
- Determinants of cancer after transplantation
- Outcome of cancer pretransplantation
- Time to waitlisting: approach/recommendations
- The ‘untransplantable’ cancer patient
- The case of prostate cancer
- Some words on checkpoint inhibitors
- CONCLUSION

NO DISCLOSURES

Cancer as cause of death after kidney transplantation



N=23,210

Death by infection

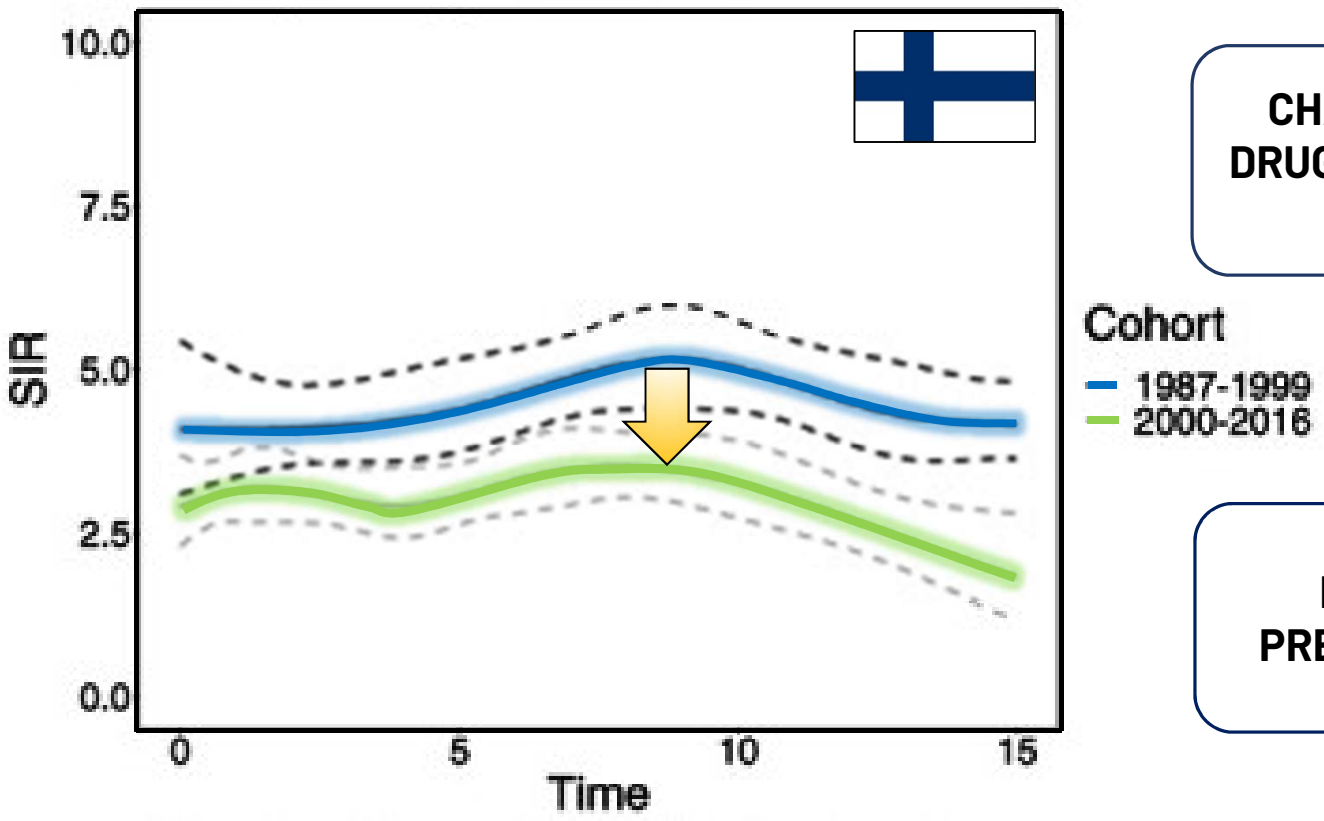
Death by malignancy

Cardiovascular death

Ying T et al. JASN 2020

The risk of cancer in KTR

BETTER SELECTION PRE-TRANSPLANT?

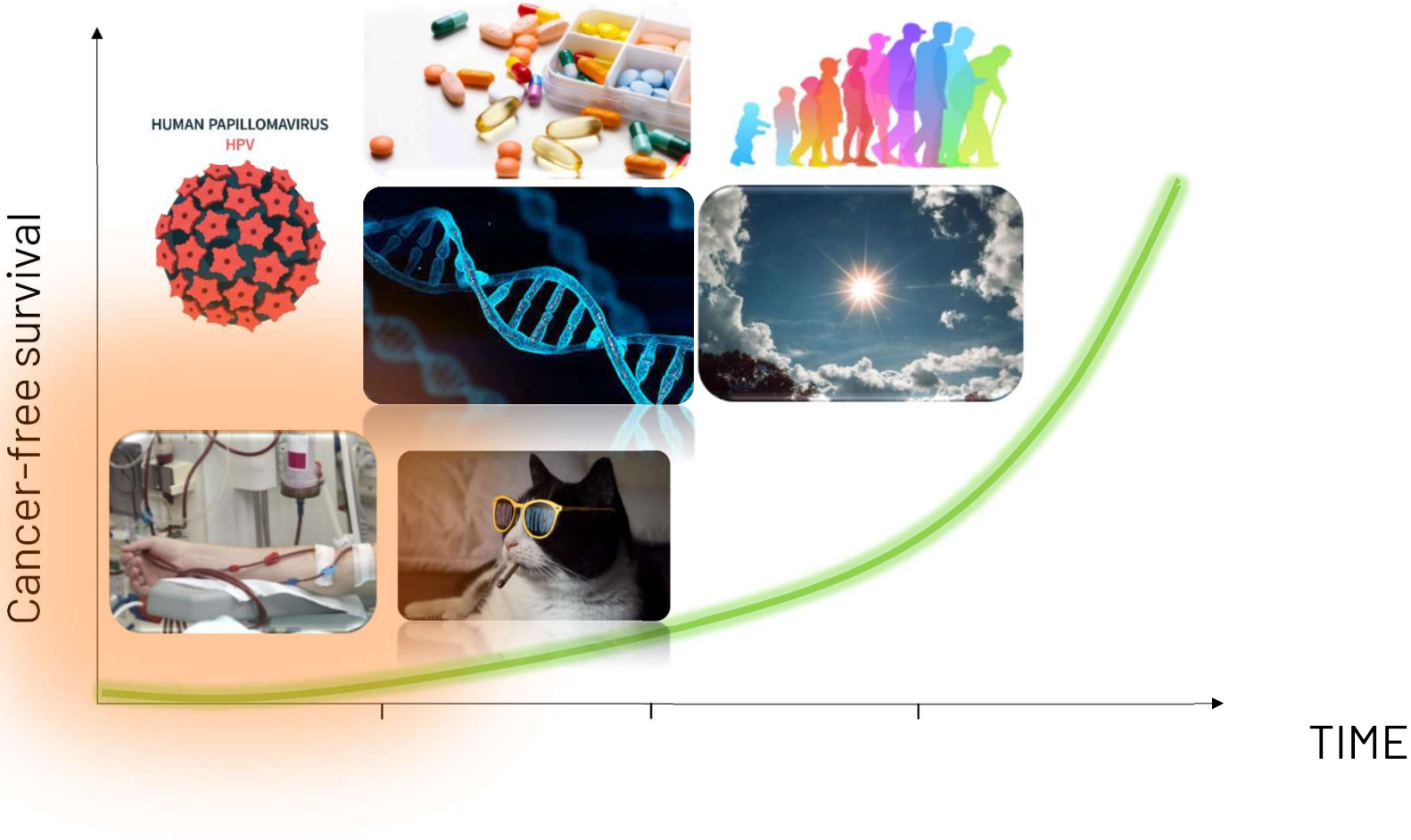


CHANGES IN DRUG REGIMEN?

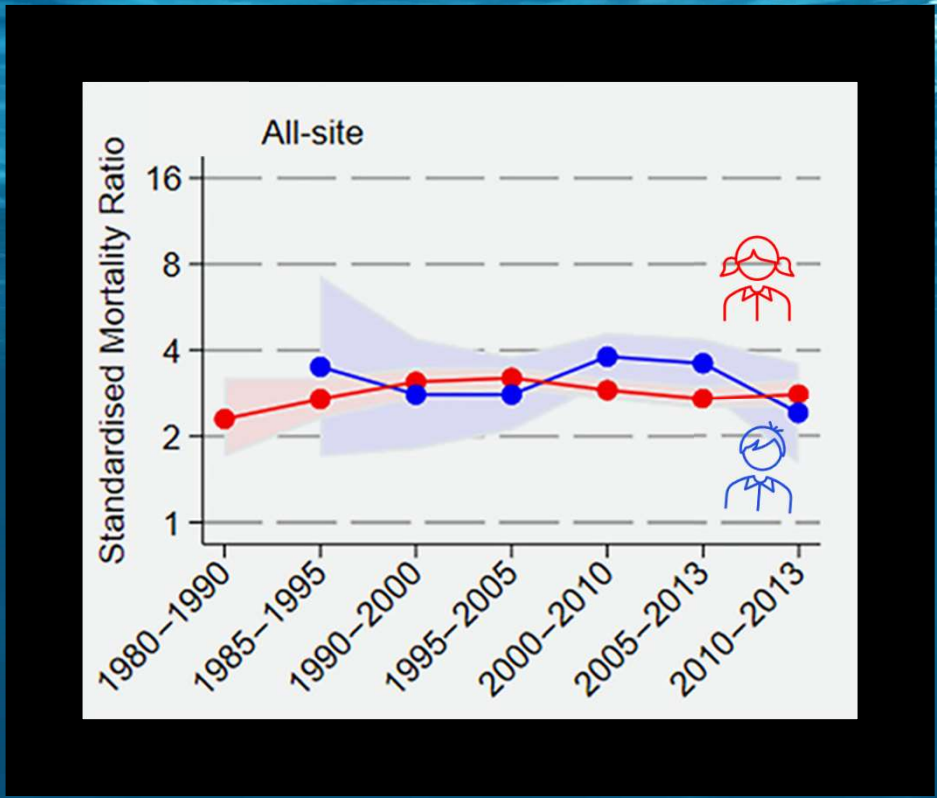
BETTER PREVENTION?

Friman TH et al. Int j Cancer 2020

Cancer after kidney transplantation



The cancer mortality risk in KTR

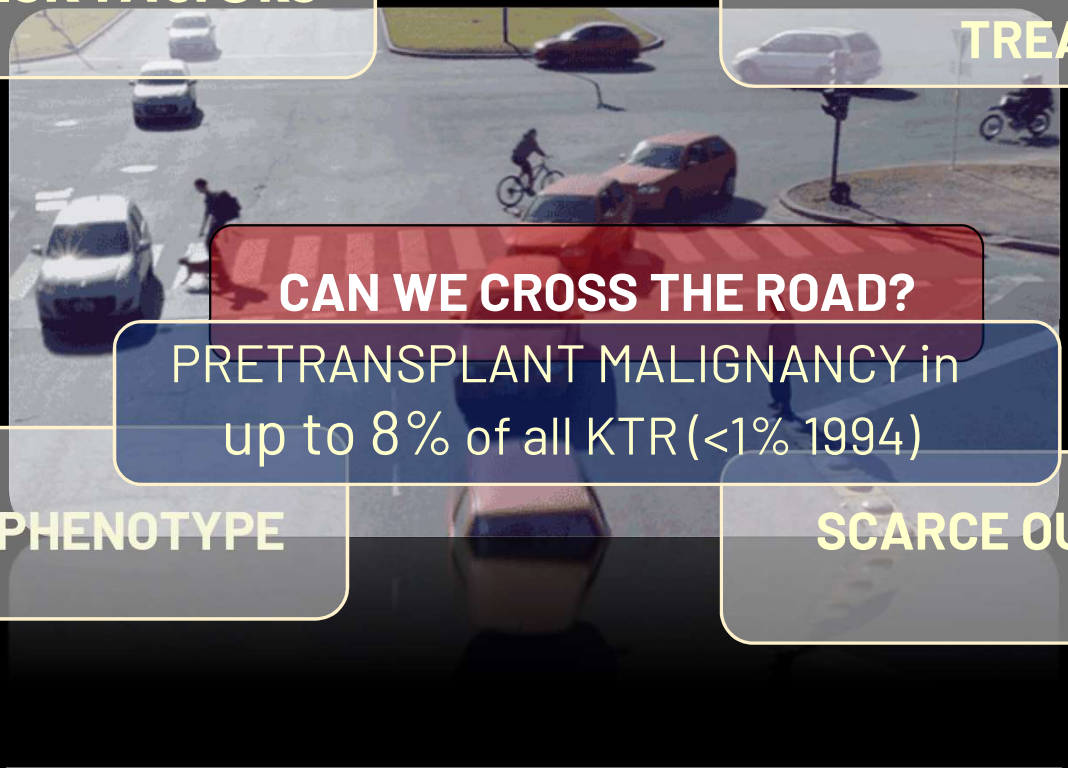


Rosales BM In J Cancer 2020

How to approach pretransplant cancer?

CUMULATIVE RISK FACTORS

INTOLERANCE 'CLASSICAL' TREATMENT



CAN WE CROSS THE ROAD?

PRETRANSPLANT MALIGNANCY in up to 8% of all KTR (<1% 1994)

MORE AGRESSIVE PHENOTYPE

SCARCE OUTCOME DATA

Pretransplant assessment cancer risk

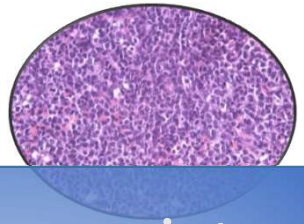
MIND PREVIOUS EXPOSURE TO IMMUNOSUPPRESSIVE DRUGS!

Outcomes	Malignancy	NMSC	PTLD
Control (N=579)	Ref	Ref	Ref
Cyclophosphamide	HR 2.59 (1.48-4.55)		
Rituximab	HR 3.82 (1.69-8.65)		
MMF, CNI	NS		

Should this be integrated into the waiting time before listing?

Massicotte-Azarniouch D et al. NDT 2023

Early de novo cancer: poor outcome



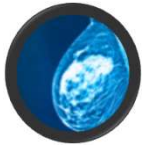
- Risk population: elderly, pre-existant diabetes and/or coronary artery disease, older donor.
- Accelerating effect immunosuppressive drugs?
- Escape of pretransplant screening?

- 8.8% de novo cancer: early
- 1/3 died after median of 4.7 months

Metastatic at presentation

Lung cancer: 50%

Colonic cancer: 42%



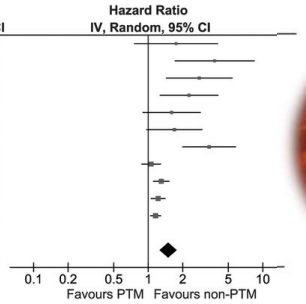
Breast cancer: 17%

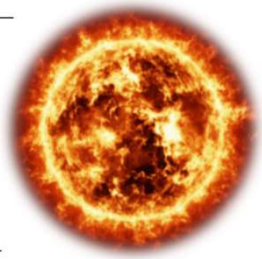
Krishnan A et al. Transplant Int 2022

Outcome after tpx and previous cancer

Study or Subgroup	log[Hazard Ratio]	SE	PTM Total	Non-PTM Total	Weight	Hazard Ratio IV, Random, 95% CI
Ladowski 2006	0.5596	0.4255	13	201	3.4%	1.75 [0.76, 4.03]
Cortazar 2012	1.335	0.4057	35	958	3.7%	3.80 [1.72, 8.42]
Koerner 1997	1.026	0.3375	20	682	4.9%	2.79 [1.44, 5.41]
Farrugia 2014	0.8198	0.2963	74	19029	5.9%	2.27 [1.27, 4.06]
Tovikkai 2015	0.47	0.2936	64	3773	5.9%	1.60 [0.90, 2.84]
Fernandez 2010	0.5247	0.2833	12	583	6.2%	1.69 [0.97, 2.94]
Chung 2014	1.2238	0.2707	31	1925	6.6%	3.40 [2.00, 5.78]
Beaty 2013	0.0583	0.095	1857	31573	14.8%	1.06 [0.88, 1.28]
Brattstrom 2014	0.2624	0.0797	416	10032	15.6%	1.30 [1.11, 1.52]
Santos 2014(a)	0.1989	0.0717	1128	5635	16.0%	1.22 [1.06, 1.40]
Santos 2014(b)	0.1484	0.0508	N/A	N/A	16.9%	1.16 [1.05, 1.28]
Total (95% CI)			**3650**	**74391**	**100.0%**	**1.51 [1.28, 1.80]**

Heterogeneity: Tau² = 0.04; Chi² = 38.88, df = 10 (P < 0.0001); I² = 74%
Test for overall effect: Z = 4.74 (P < 0.00001)

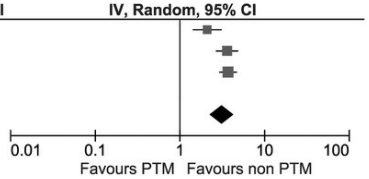




Overall mortality

Study or Subgroup	log[Hazard Ratio]	SE	PTM Total	Non-PTM Total	Weight	Hazard Ratio IV, Random, 95% CI
Farrugia 2014	0.7419	0.1925	74	19029	28.1%	2.10 [1.44, 3.06]
Brattstrom 2014	1.2809	0.1468	416	10032	33.9%	3.60 [2.70, 4.80]
Kiberd 2009	1.3083	0.1156	1641	162437	38.1%	3.70 [2.95, 4.64]
Total (95% CI)			**2131**	**191498**	**100.0%**	**3.13 [2.29, 4.27]**

Heterogeneity: Tau² = 0.05; Chi² = 6.84, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 7.16 (P < 0.00001)



Cancer-related mortality

Study or Subgroup	log[Hazard Ratio]	SE	PTM Total	Non-PTM Total	Weight	Hazard Ratio IV, Random, 95% CI
Ladowski 2006	0.5596	0.4255	13	201	3.4%	1.75 [0.76, 4.03]
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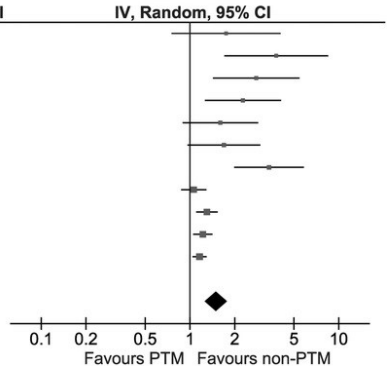
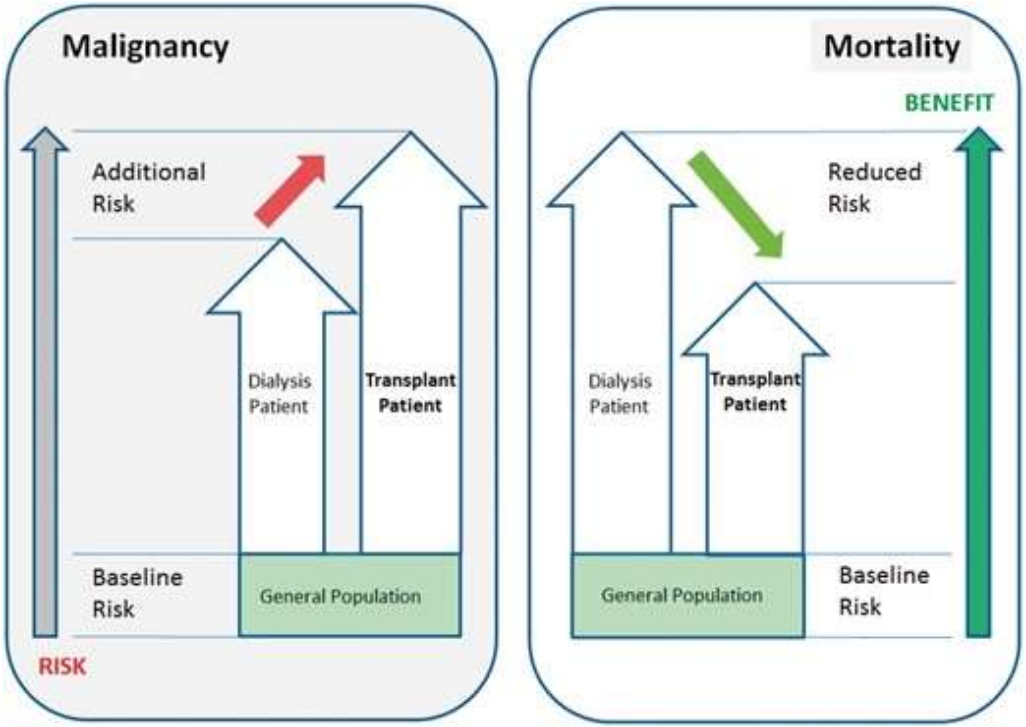


De-novo cancer

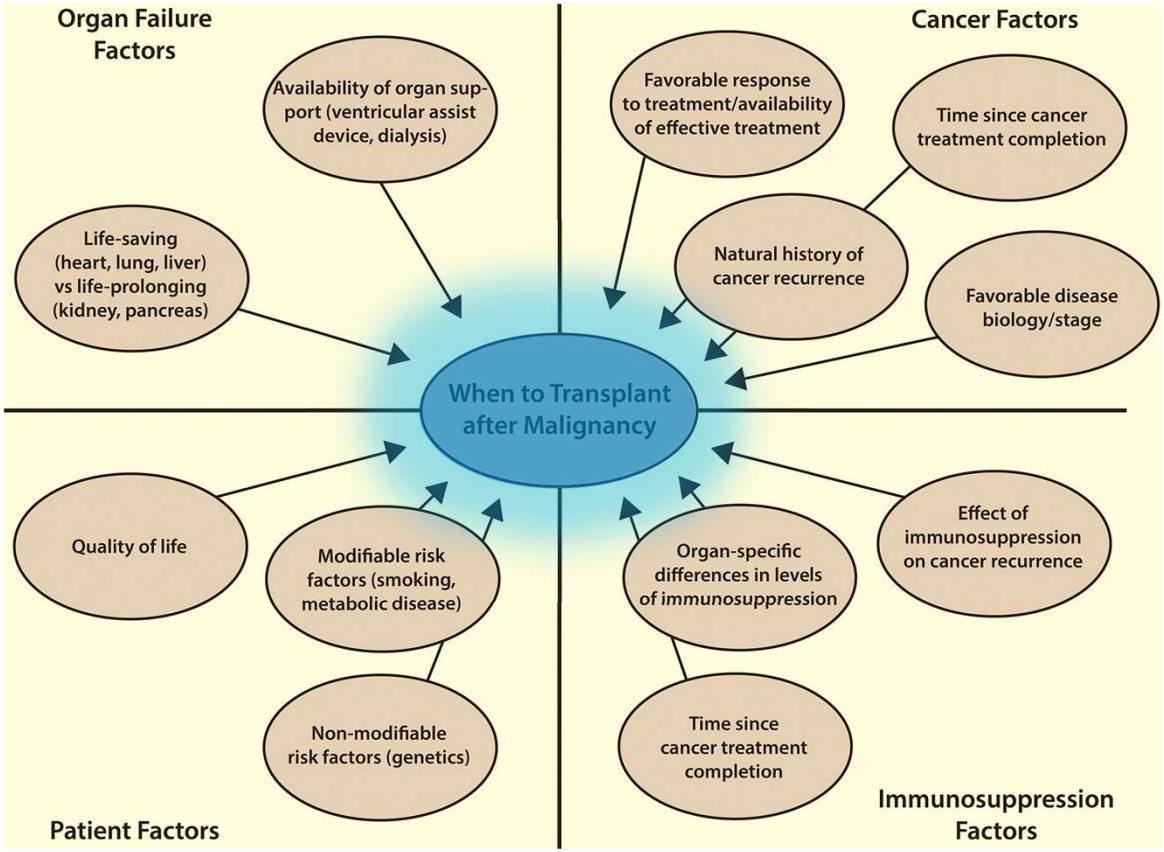
Acuna et al Transplantation 2017

Cancer in transplant patients: risk/benefit



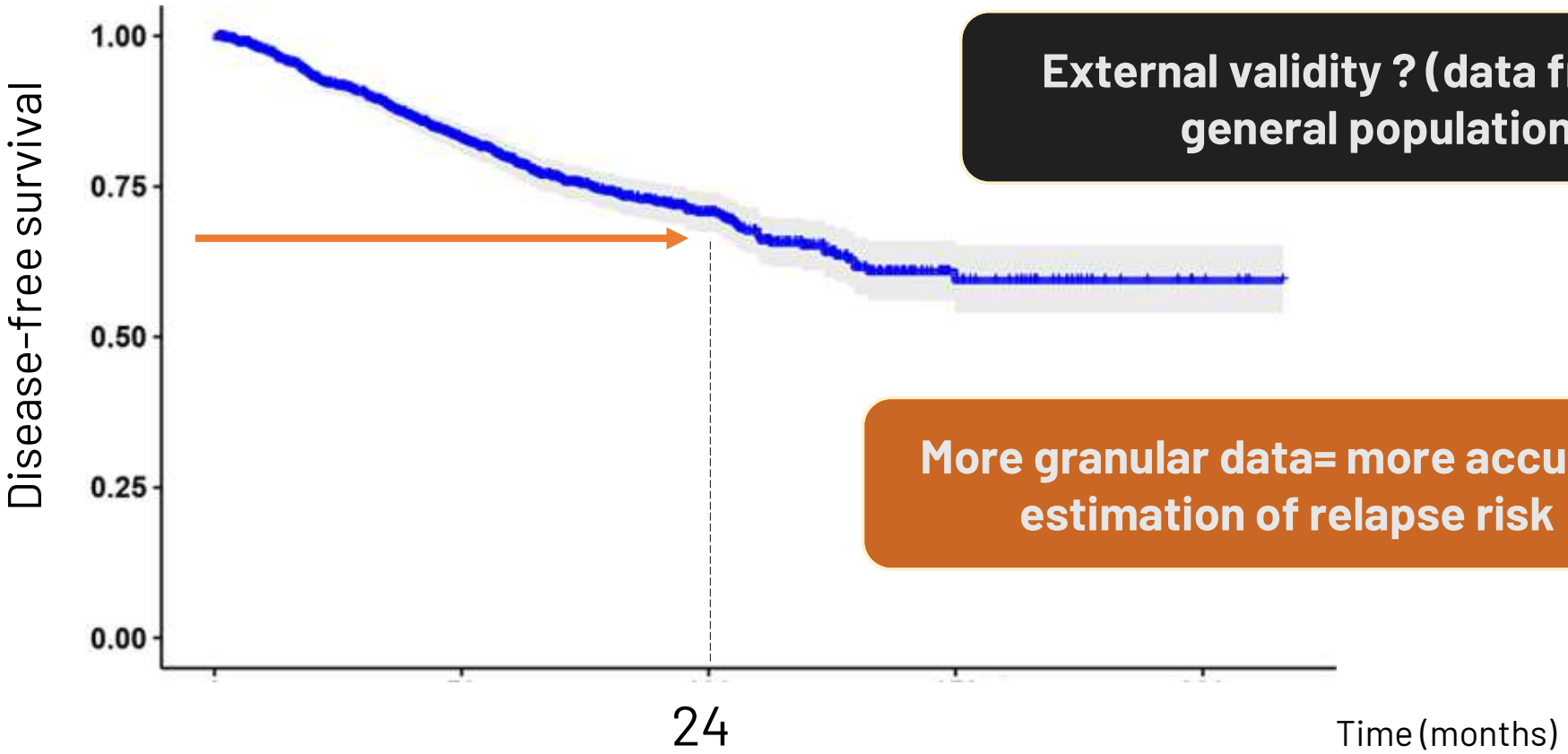
Watchinger B et al-ERA-EDTA DESCARTES GROUP NDT 2019

When to transplant after malignancy?



Al-Adra DP et al Am J Transplant 2021

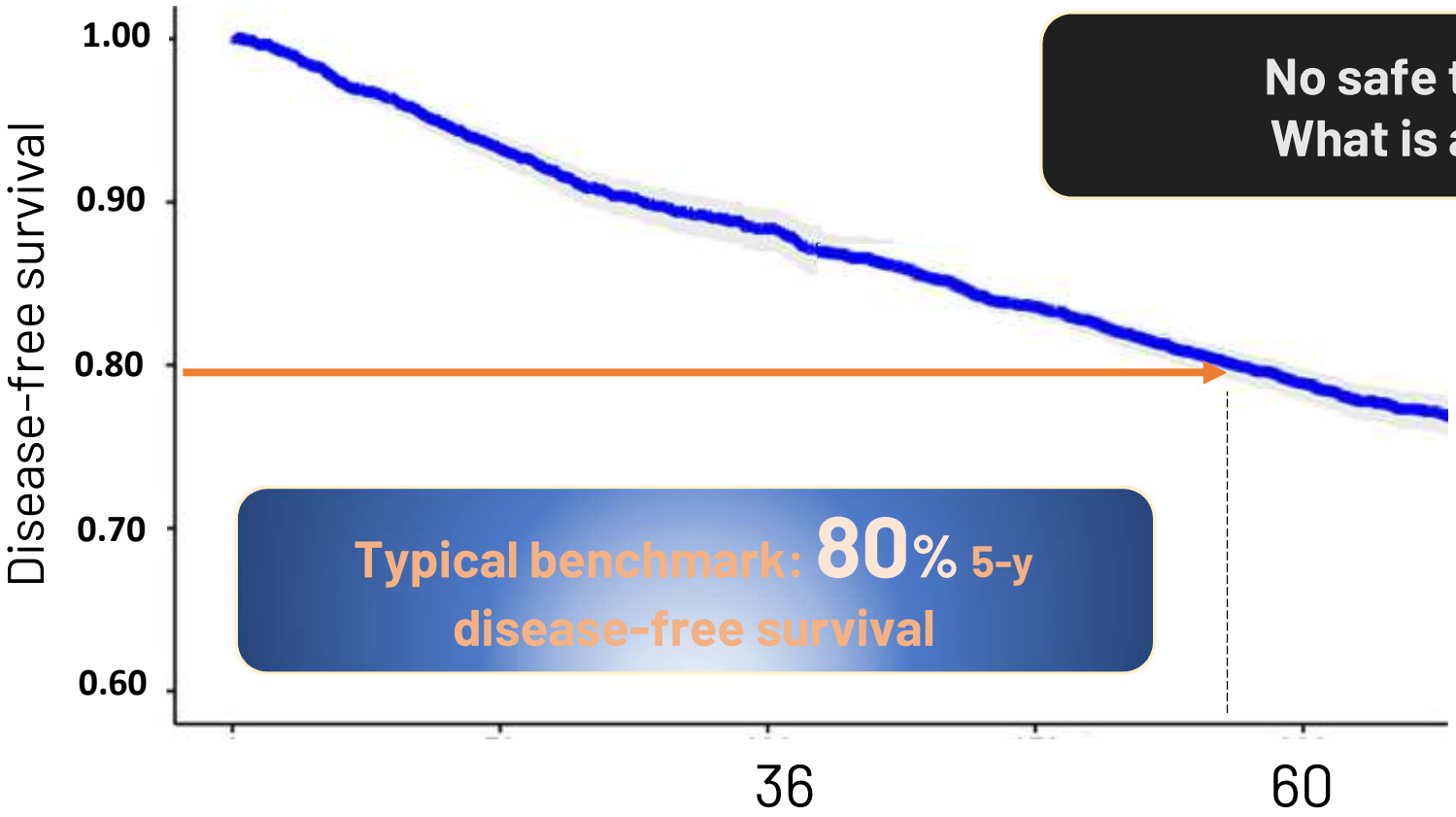
When do we feel safe?



External validity ? (data from the general population)

More granular data= more accurate estimation of relapse risk

When do we feel safe?



No safe tipping point
What is acceptable?

Recurrence-free period should exceed the highest risk of cancer recurrence

Typical benchmark: 80% 5-y disease-free survival

Pretransplant cancer and time to waitlist

Israel Penn International Transplant Tumor Registry
21% cancer recurrence

Waiting time 2-5+ years

Contemporary registries
Better outcome
5% cancer recurrence

Variable waiting time (1,2,3,4,5+y) +oncologist discussion

No waiting time or even no treatment for selected cancers

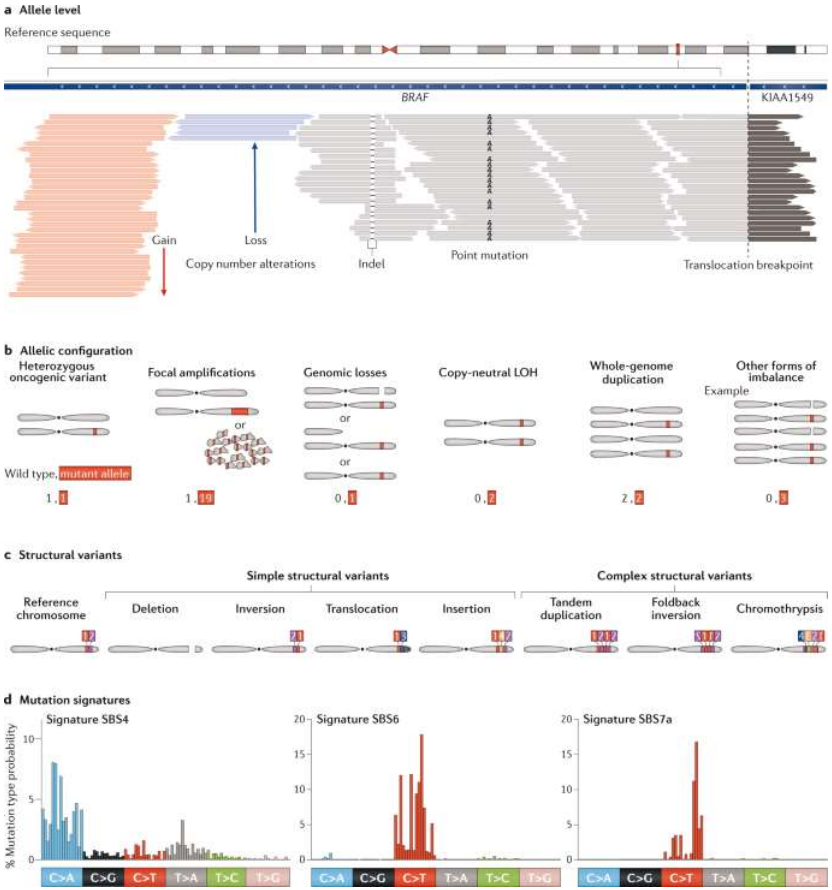
KDIGO

ERBP
European Renal Best Practice

PAUCITY OF DATA IN TRANSPLANT POPULATION

Schreiber B et al. Seminars in Nephrology 2022

Genomic profiling in oncology



Chakravarty D et al. Nature Rev Genetics 2021

Multiple myeloma:
NO deletion (17p), t (4;14), t (14;16)

Colorectal cancer:
Mismatch repair defect tumors: better prognosis
BRAF mutations: poor survival

FUTURE BIOMARKERS:
circulating tumor DNA?

Time to waitlisting after cancer remission

Waiting time[a]	Cancer: Type	Cancer: Stage/stadium (subtype)
No waiting time[b]	Kidney	Incidentaloma (<3 cm)
	Prostate	Gleason ≤6
	Thyroid[c]	Stage I
At least 2 years	Breast	Early[d]
	Colorectal	Dukes A, B
	Bladder	Invasive
	Kidney	Early
	Uterine, cervical	Localized
	Testicular	Localized
	Prostate	Gleason 7
	Thyroid[c]	Stage II
	HL, NHL	Localized
	PTLD	Nodal
2–5 years	Colorectal	Dukes C
	Lung	Localized
	Testicular	Invasive
3–5 years	HL, NHL	Regional
At least 5 years	Breast	Advanced
	Colorectal	Dukes D
	Kidney	Large and invasive
	Melanoma	Localized
	Prostate	Gleason 8–10
	Thyroid[c]	Stage III
	HL, NHL	Distant
	PTLD	Extranodal and cerebral

Malignancy	Recommended time interval to transplant	Risk group for recurrence/Stage[f]
Breast cancer[a]	No[a]	LR—DCIS, Stage I
	1–2 y NED	IR—Stage II
	3–5 y NED	HR—Stage III
Colon cancer	1 y	LR—Stage I (T1 or T2, N0, M0)
	2 y (longer if HR features)	LIR—Stage II (T3, N0, M0)
	3 y, 5 y if HR features	HIR—Stage II (T4, N0, M0), Stage III (any T, N+)
	5 y NED	HR—Stage IV (any T and N, M+)
Rectal cancer	1 y (consider 2 y if HR features)	LR—Stage I (T1 or T2, N0, M0), full oncologic resection
	2 y	LIR—Stage I (T1, N0, M0) local excision
	3 y, 5 y if HR features	HIR—Stage II (T3 or T4, N0, M0), Stage III (any T, N+)
	5 y NED	HR—Stage IV (any T, any N, M+)
Anal cancer	5 y DFI	Invasive
Prostate cancer	No	Very LR and LR (PSA <10 ng/ml, Gleason ≤6, T1c–2a)
	No, if surveillance, or predictive cancer-specific death over the next 15 y <10% when treated[e]	Low-volume IR (PSA >10 ng/ml or Gleason 7 or T2b)
	No, if predictive cancer-specific death over the next 15 y <10%[g]	High-volume IR, HR (PSA >20 ng/ml or high-volume Gleason 7 or 8–10, T3)
	Consider transplant, if stable disease for 2 y with prolonged estimated life expectancy	Metastatic castration-sensitive
RCC	No	T1a (≤4 cm) N0, T1b (>4 to ≤4 cm) N0, FG 1,2
	1–2 y	T1b (>4 to ≤4 cm) N0, FG 3,4
	2 y	T2 (7–10 cm) N0
	Minimum 2 y	T3, N0; T4, N0
Bladder cancer	6 months	NMIBC LR[g], IR[h]
	2 y	HR, MIBC, postradical cystectomy
Gynecological cancer	No	LR—Stage IA/IB, grade 1, 2 EEC without LVI, Stage IA, B, C grade 1, 2 epithelial ovarian cancer, Stage IA1, 2 squamous/adenocarcinoma of the cervix
	2–3 y	IR—Stage I, II EEC with risk feature, Stage IB squamous/adenocarcinoma of the cervix
	5 y	HR—NEEC, Stage III grade 1–3 EEC, Stage II, III epithelial ovarian cancer, Stage II, III squamous/adenocarcinoma of the cervix
NSCLC[b]	≥3 y	Stage I T1a, N0; T1b, N0
	3–5 y	Stage I T1c, N0
	5 y	Stage IB T2a, Stage IIA T2b, N0 Stage IIB T3, N0, Stage IIIA
Melanoma[c]	No	*In situ*
	1 y	Stage IA (T1a), Stage IB (T1b or T2a), Stage IIA (T2b or T3a)
	1–2 y	Stage IIIA (T1–2a, N1a or 2a)
	2–4 y	Stage IIB (T3b or T4a), Stage IIC (T4b), Stage IIIB (T0–3a and N1a/b/c, N2a/b)
	At least 5 y	Stage IIIC (T3b–4b and N2b/c–N3b/c), Stage IIID (T4b and N3a–3c), Stage IV

Serkies K et al NDT 2022-KDIGO guidelines 2020 (left)-2021 consensus AST expert opinion statement (right)

The 'untransplantable' with other perspective?

Multiple myeloma
Absolute contra-indication in the past (high recurrence, poor outcome)

ADVANCES in TREATMENT over past 2 decades: better outcome

NECESSITY
-received curative treatment
-stable hematological remission for more than 6 months
-good performance status
-no high-risk genetic profile

RELAPSE RISK
25-35%*

SEQUENTIAL ALLOGENEIC HSCT: better outcome

KDIGO 2020 guidelines update-* Chitty DW NDT 2020-Jolt F et al Blood 2019- Al Adra et al Am J Transplant 2021

Metastatic cancer and future tpx (yes/no)?

- 11.2.5: We recommend not excluding candidates with a history of metastatic cancer provided that potentially curative therapy has been administered and complete remission achieved; however, the risk of recurrence should be a major consideration and discussed with the candidate and their oncologist *(1D)*.

Table 2: Malignancies considered a contraindication for transplantation by recent recommendations (apart from the basic principle of not transplanting patients with active malignancy).

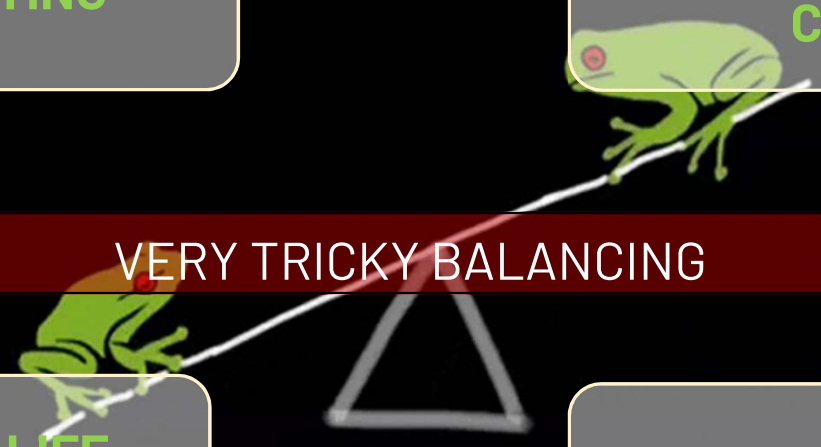
Recommendation by	Expert statement
KDIGO, 2020 for KT [19]	Not a SOT candidate are patients with: • anaplastic and Stage IV thyroid cancer • invasive melanoma Avoid transplanting patients with acute leukemia or high-grade lymphoma including PTLD until they achieved remission after curative therapy, and remained cancer free for a period to be determined in consultation with the patient, a hematologist/oncologist and the transplant program
AST, 2021 [21]	Not a SOT candidate are patients with: • Stage IV cancers, with the exception of metastatic castration-sensitive prostate cancer • node positive or with sarcomatoid and/or rhabdoid histologic feature or collecting duct or medullary RCC • MIBC postchemoradiation • recurrent gynecological cancers • Stage IIIB,C NSCLC Selected colorectal patients with liver metastases and without extrahepatic disease after hepatectomy for liver transplantation, and patients with resected solitary RCC metastasis may be discussed by board on candidacy Inflammatory breast cancer patients generally should not be considered as transplant candidates

Serkies K et al NDT 2022

A NOVEL DILEMMA: CURE AFTER CHECKPOINT-i

POTENTIAL OF RELISTING

LOSS OF IMMUNE CONTAINMENT

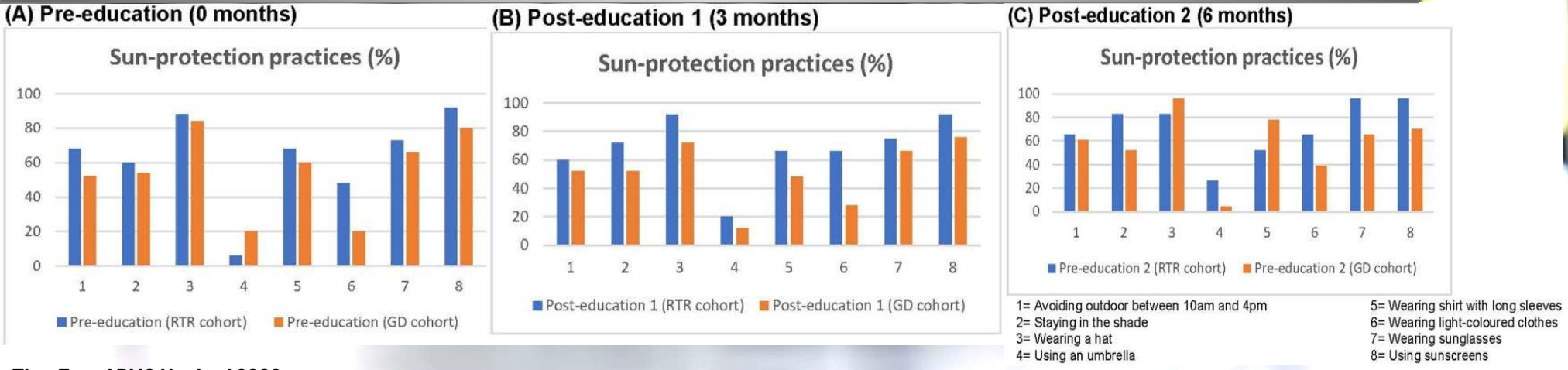


VERY TRICKY BALANCING

IMPROVED QUALITY OF LIFE
IMPROVED SURVIVAL (?)

REJECTION
GRAFT LOSS

Prevention and shared decision making



Thet Z et al BMC Nephrol 2022

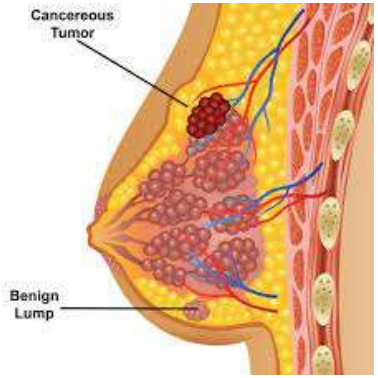
Colorectal cancer and future waitlisting

Risk/stage	Recurrence-free survival 5 years[41,46]	Time interval to transplant	Additional considerations
LOW RISK Stage I (T1 or T2, N0, M0)	91%	1 year	*Low-risk features:* - MSI without BRAF mutation *High-risk features:* - LVI or PNI - Mucinous or Signet Histology - Poorly differentiated histology - Bowel obstruction - Tumor perforation - <12 lymph nodes examined *Tumor deposits considered as N+ disease *Consider chemotherapy prior to transplantation for high-risk stage II disease *Patients with stage III disease should complete chemotherapy
LOW INTERMEDIATE RISK Stage II (T3, N0, M0)	72%	2 years, consider longer if high-risk features present	
HIGH INTERMEDIATE RISK Stage II (T4, N0, M0) Stage III (Any T, N+, M0)		3 years, 5 years if high-risk features present	
HIGH RISK Stage IV (Any T, Any N, M+)	13%	5 years NED	SOT not recommended prior to 5 years; see special consideration regarding resectable CRC metastasis

High risk features define waiting time (granularity of data- need for oncologist advice)

Al-Adra et al. Am J Transplant 2021

Breast cancer and future waitlisting



More Stage I (grading, genomic biomarkers ER/PR/HER-2)

Stage I low risk breast carcinoma/DCIS:
5-year risk of recurrence <2%
NO additional waiting time after treatment
Stage II 1-2y of waiting time after treatment

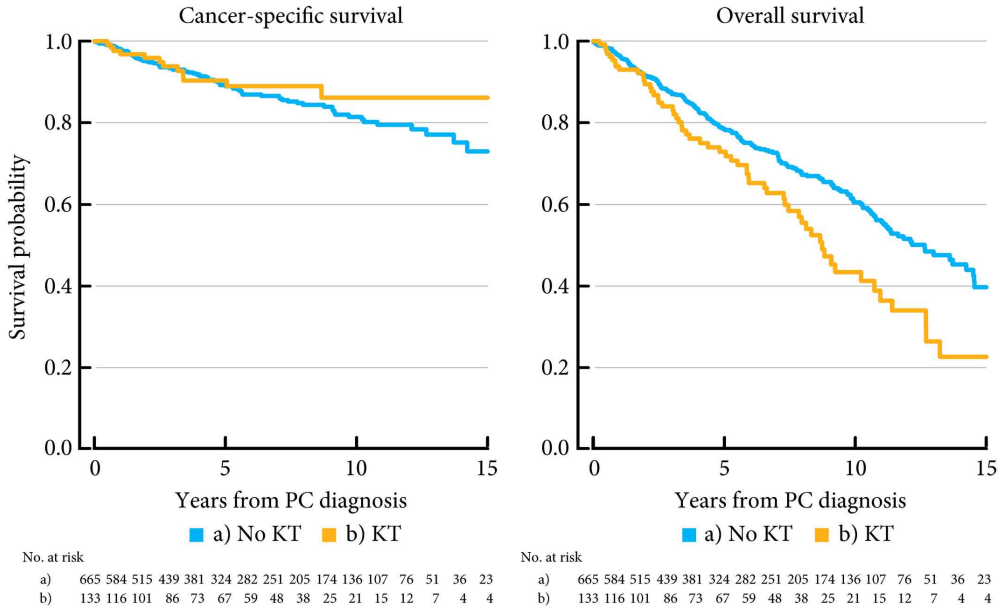
Stage III
Most recurrence within the first 3 year: 3-5 y waiting time after treatment

Assumption: no effect immunosuppression on breast cancer post-tpx (?)

NO-GO
Inflammatory breast cancer
Metastatic disease

Al-Adra et al. Am J Transplant 2021

Prostate cancer and future waitlisting



Editorial

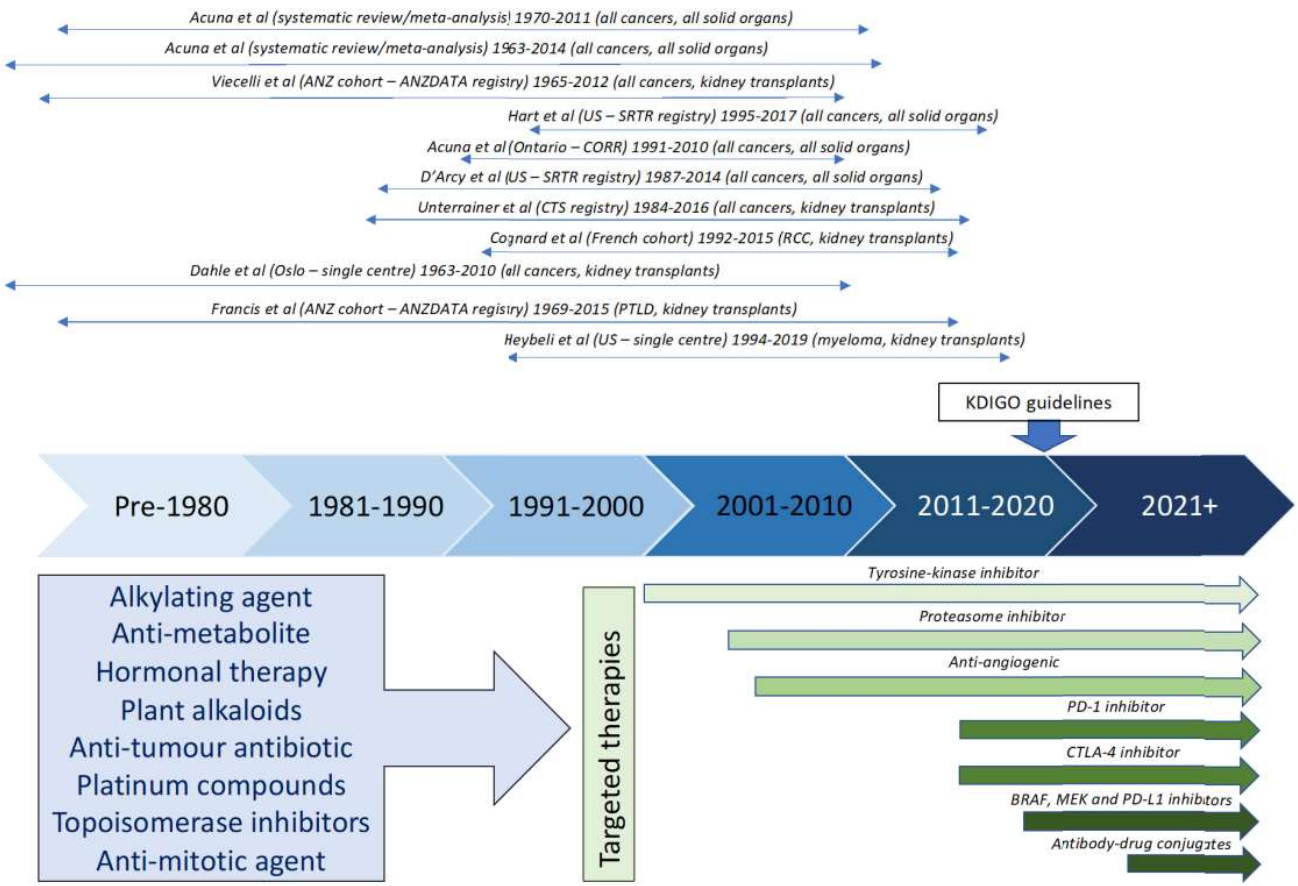
BJUI
BJU International

Prostate cancer and kidney transplantation – exclusion or coexistence?

To summarize, this study, and others before that, suggests that immunosuppression after kidney transplantation is unlikely to adversely affect prostate cancer initiation or progression. Men with low-risk prostate cancer should be considered for transplantation without first undergoing definitive therapy. There is evidence around the world – and at our institution – that transplant specialists are finally starting to accept this pathway. This study will further reinforce this concept.

Bratt O et al. BJU Int 2020

Current recommendations: outdated



DFS novel drugs remains an open question

Wong G et al. CKJ 2023

TAKE HOME MESSAGES

- Pretransplant cancer: on the rise
- Evolution towards shorter waiting time for listing (competing risk model)
- Caution with ungraded recommendations based on general population epidemiology and with ethical disparities
- More refined prediction: genomics?
- Case-by case discussion with oncologist (no one size fits all)
- Outcome data checkpoint inhibitors scarce
- Shared-decision making
- Prevention post-transplant (RCC!)
- Mind the immunized retransplant patient!