Heart transplantation in adult cancer survivors with end stage heart failure

Dr. KL Wong

Associate consultant

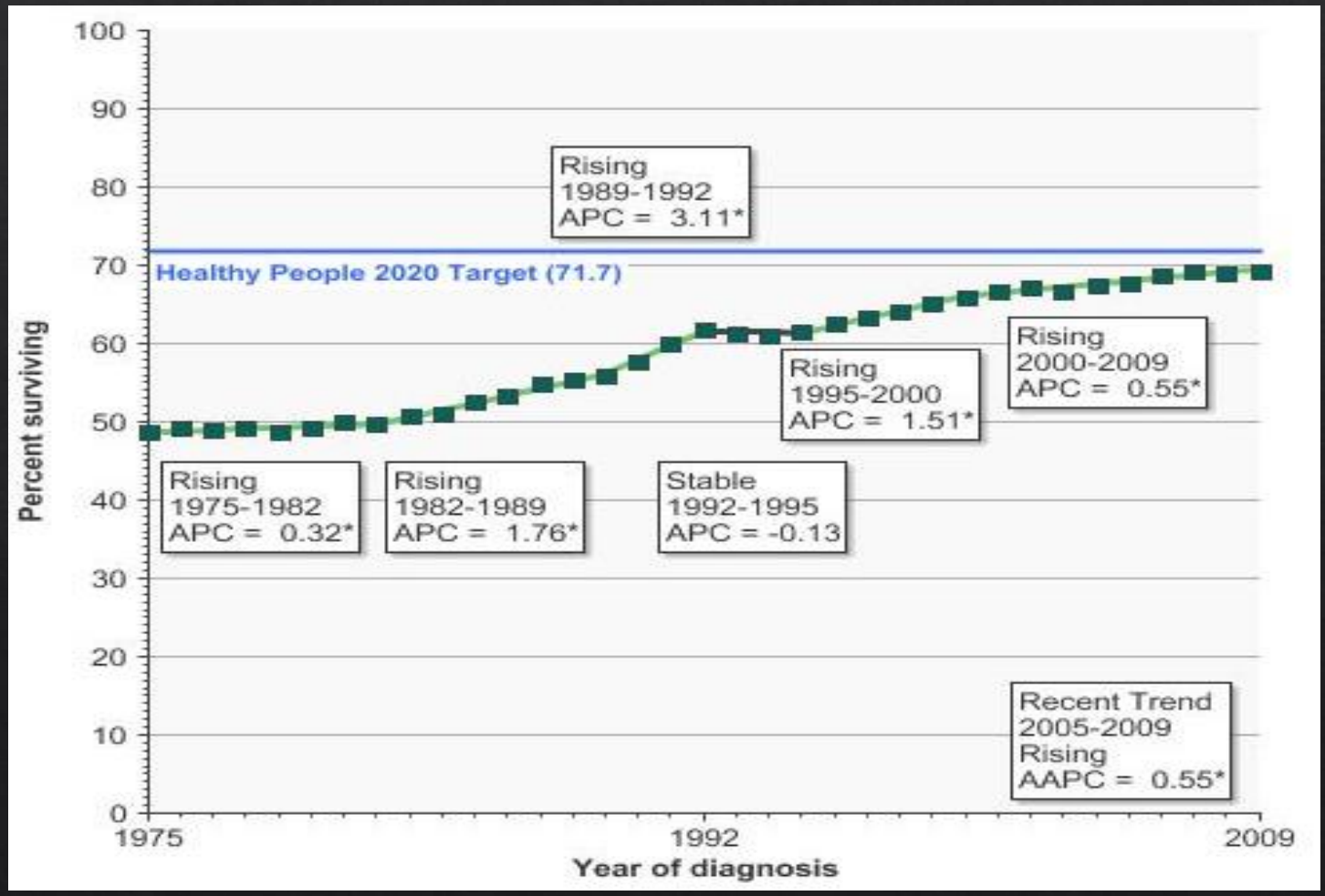
Grantham Hospital

Outline

- Malignancy and heart failure
- Is any pretransplant malignancy a contraindication for transplant?
- Review of guideline on this matter
- Review the challenges of transplant candidacy evaluation in patients with prior malignancy
- Pretransplant malignancy vs post transplant outcome
- Local data

Malignancy and Heart Failure

5-year relative survival
All cancer sites 1975-2009



SEER Program. National Cancer Institute.

Morbidity of cancer survivor

Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

Condition	Survivors (N = 10,397)	Siblings (N = 3034)	Relative Risk (95% CI)
	percent		
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
Congestive heart failure	1.24	0.10	15.1 (4.8–47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2–30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6–43.0)
Coronary artery disease	1.11	0.20	10.4 (4.1–25.9)
Cerebrovascular accident	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2–36.6)
Hearing loss not corrected by aid	1.96	0.36	6.3 (3.3–11.8)
Legally blind or loss of an eye	2.92	0.69	5.8 (3.5–9.5)
Ovarian failure‡	2.79	0.99	3.5 (2.7–5.2)

Cancer therapies of greatest risk:
- Anthracyclines
- Chest radiation

N Engl J Med. 2006 Oct 12;355(15):1572-82

Survival of different CHF

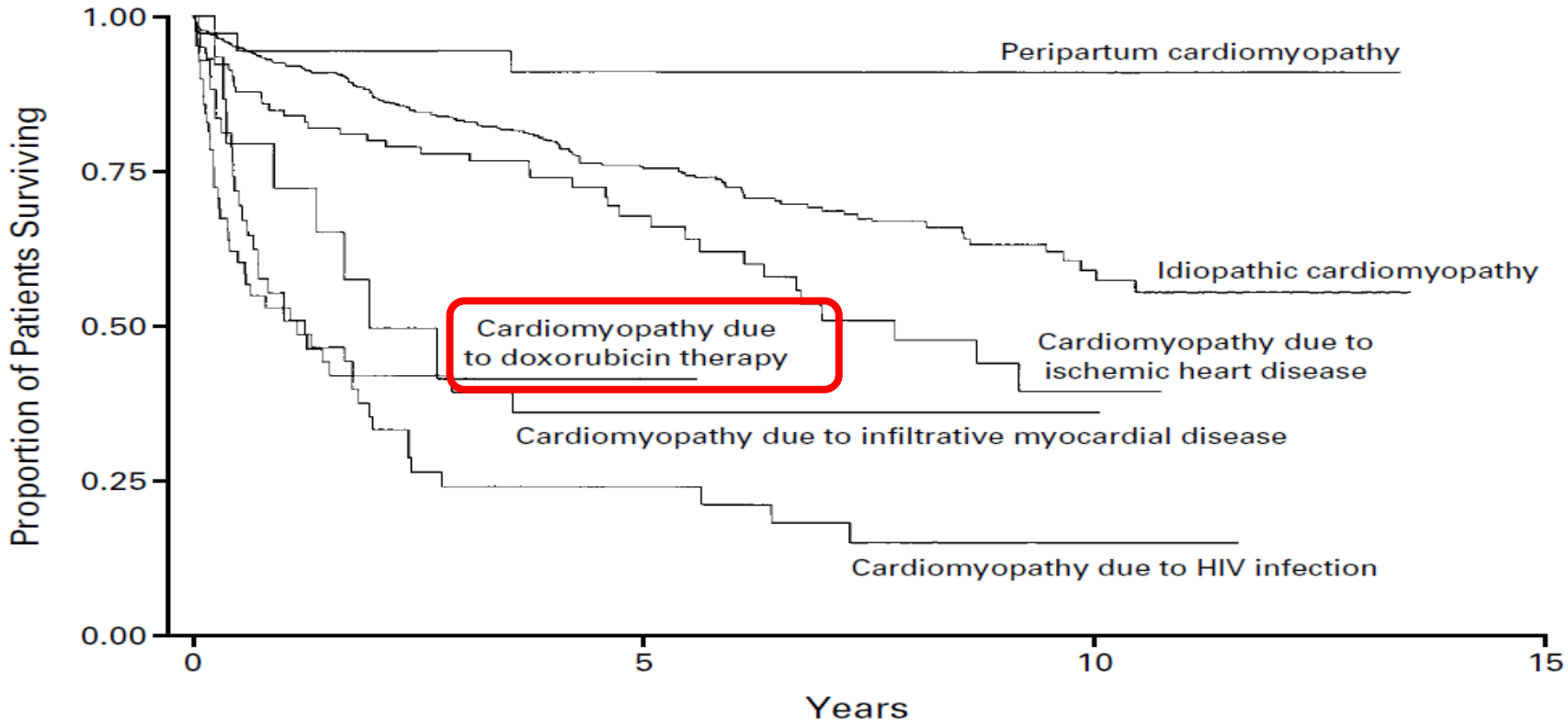
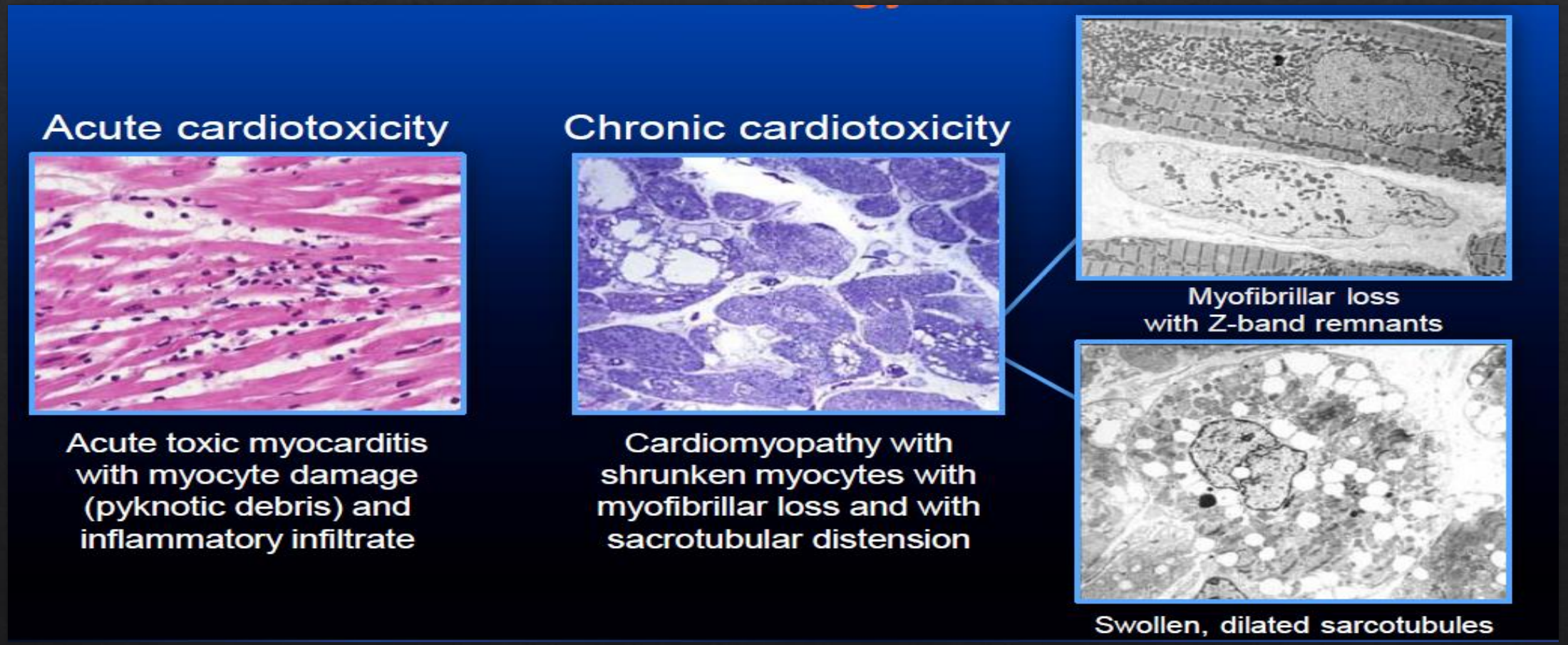


Figure 1. Adjusted Kaplan–Meier Estimates of Survival According to the Underlying Cause of Cardiomyopathy. Only idiopathic cardiomyopathy and cardiomyopathy due to causes for which survival was significantly different from that in patients with idiopathic cardiomyopathy are shown.

N Engl J Med. 2000 Apr 13;342(15):1077-8

Anthracycline cardiotoxicity



Pediatr Blood Cancer. 2005 Jun 15;44(7):630-

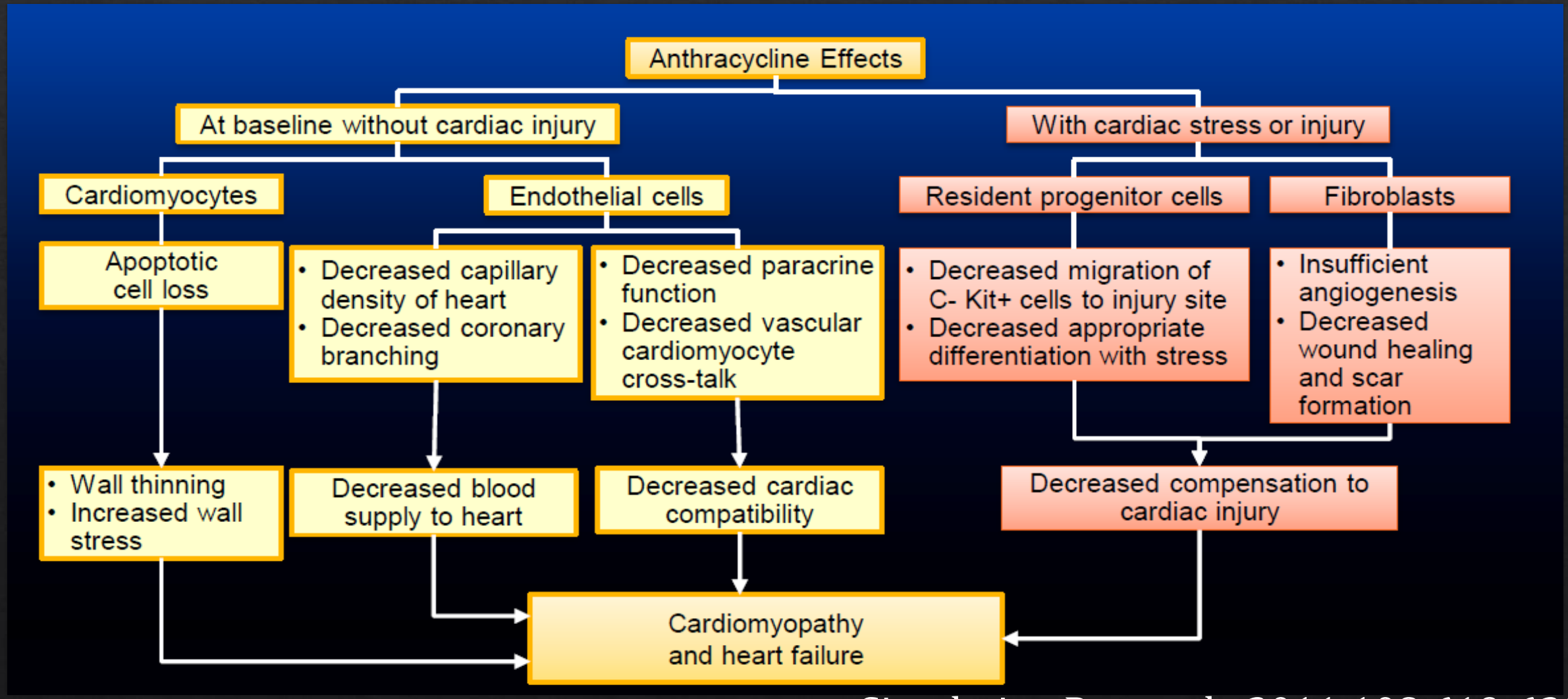
Anthracycline therapy

Table 1 Cancers responsive to anthracycline chemotherapy

Carcinoma	Leukaemia	Lymphoma	Sarcoma
Breast, small cell lung, bladder, oesophagus, stomach, liver and thyroid	Acute lymphoblastic Acute myeloblastic	Hodgkin's disease Non-Hodgkin's lymphoma Cutaneous T-cell lymphoma	Osteogenic bone Soft tissue Ewing

Heart. 2018 Jun;104(12):971-97

Anthracycline cardiotoxicity



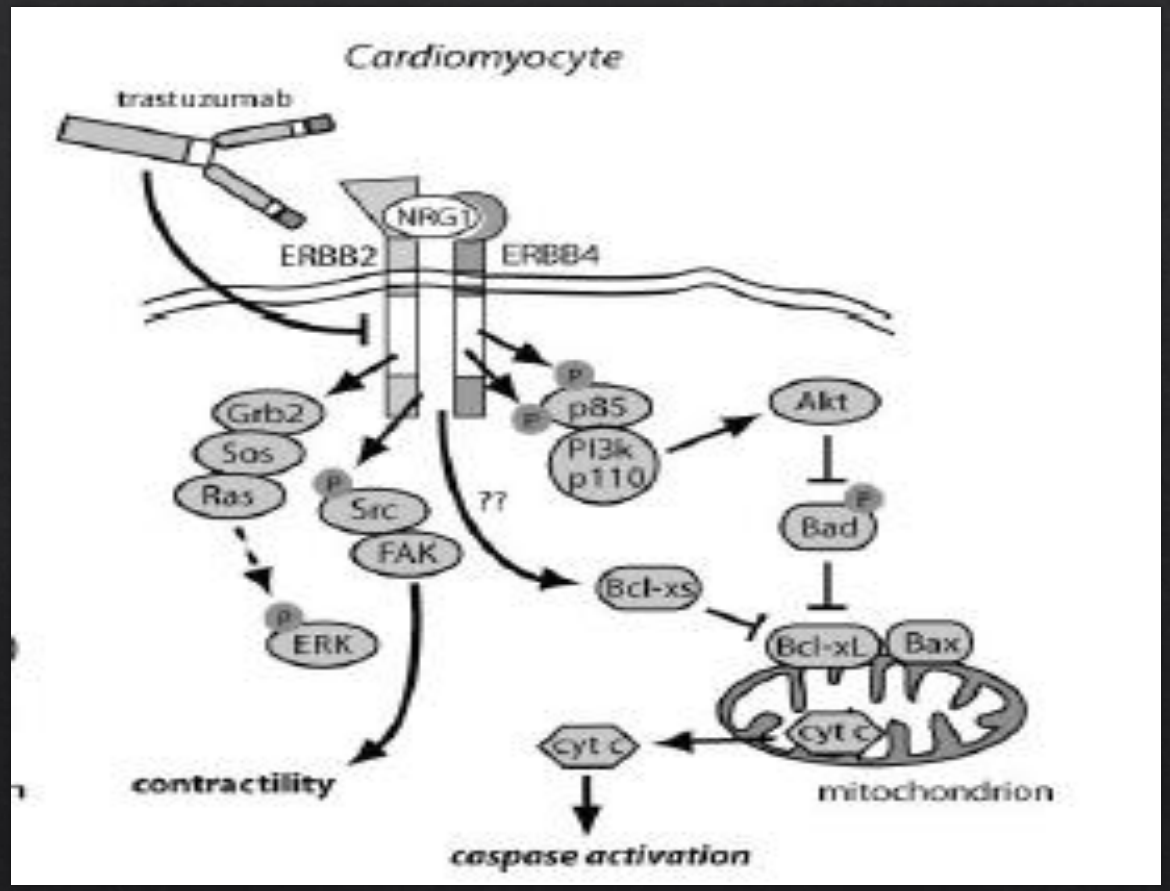
Circulation Research. 2011;108:619-628

Conceptual classication

	Type I (damage)	Type II (dysfunction)
Prototype	Doxorubicin	Trastuzumab
Ultrastructure	vacuoles, necrosis microfibrillar disarray	no abnormalities
Mechanism	Oxidative injury mitochondrial function ↓ altered calcium homeostasis altered cardiac gene expression apoptosis of cardiomyocytes	ErbB2 signaling inhibition
Clinical course	likely irreversible	likely reversible
Rechallenge	likely progressive	likely safe
Late sequential stress	likely not tolerated	likely tolerated

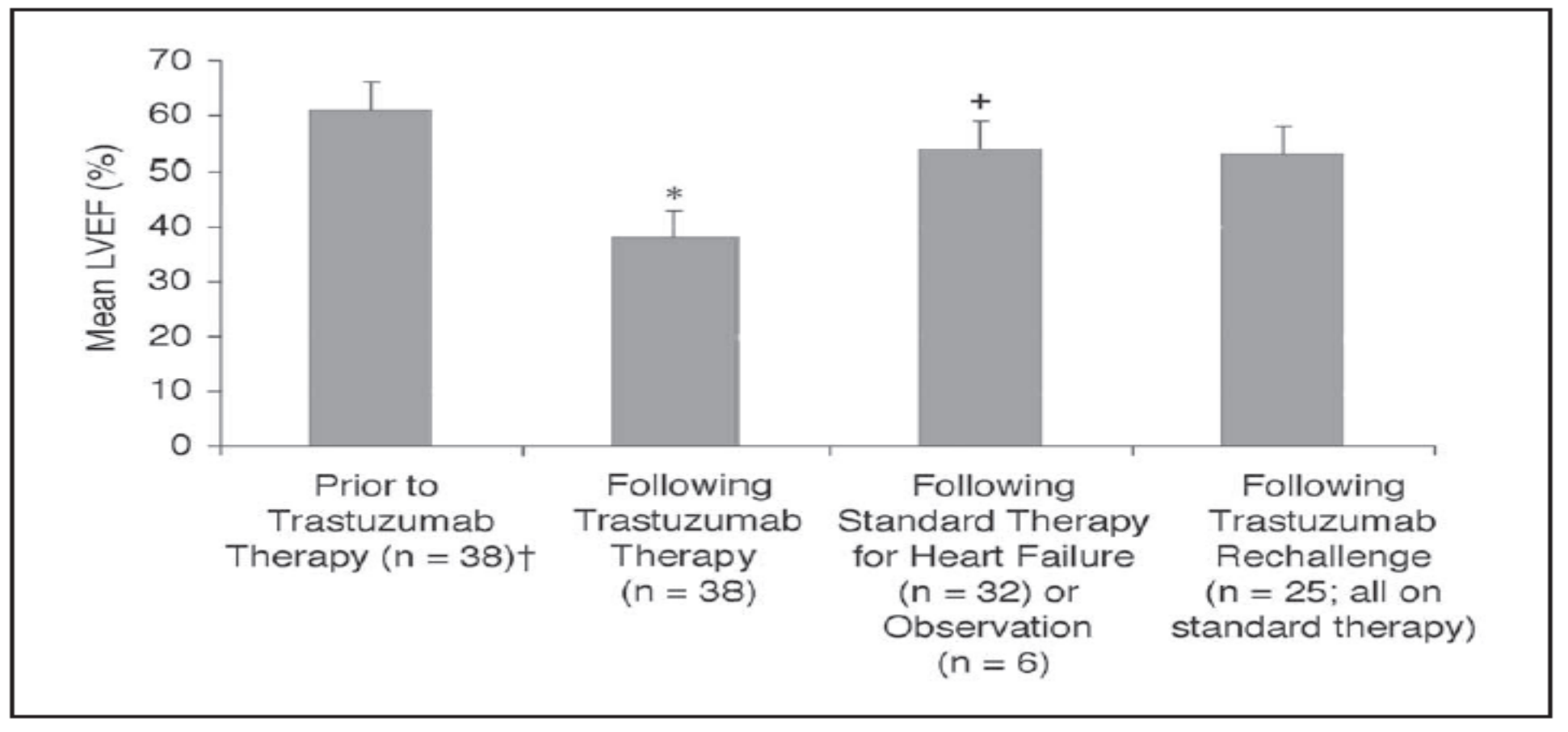
J Clin Oncol. 2005 Nov 1;23(31):7820-

Trastuzumab Cardiotoxicity



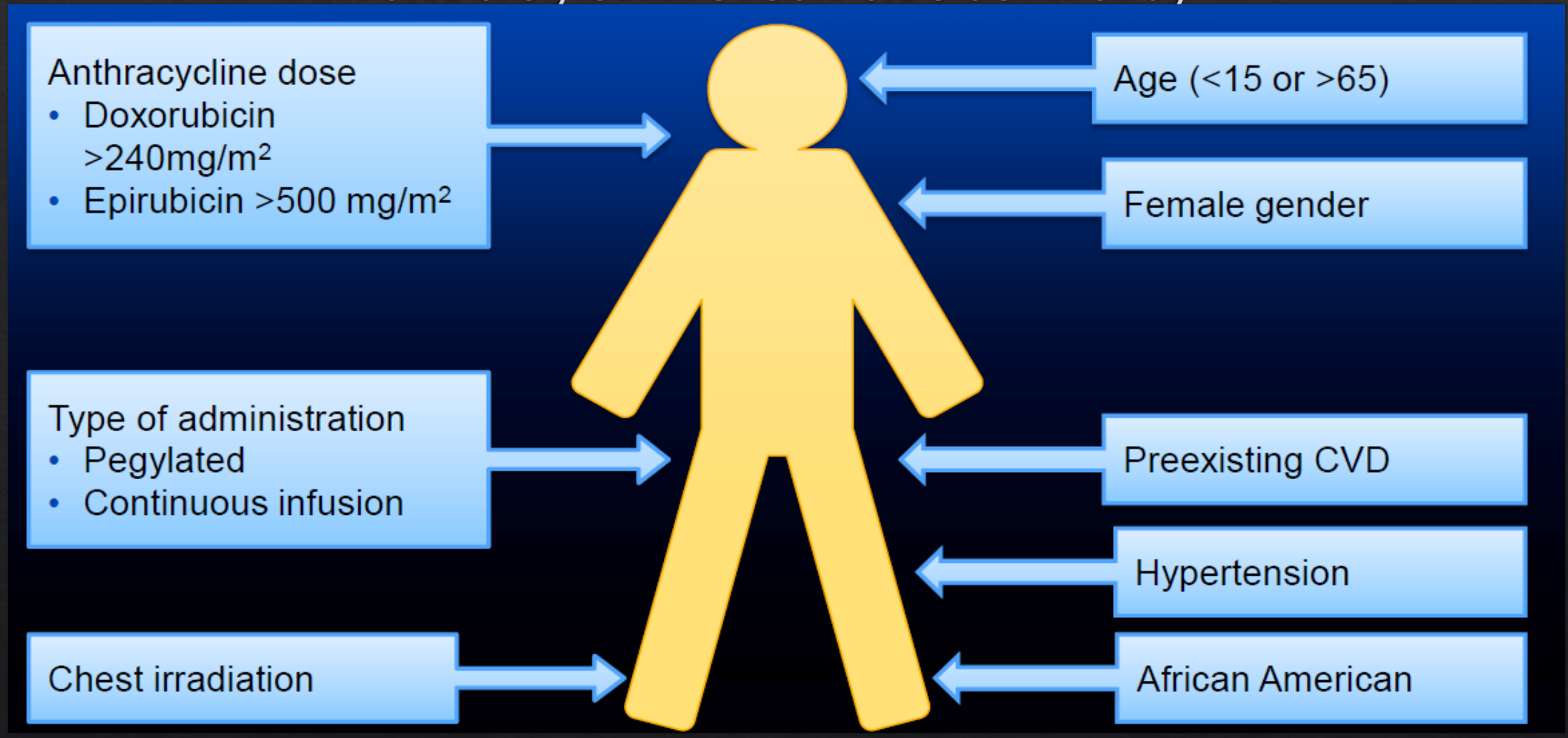
Circulation. 2008;118:84-95

Trastuzumab Cardiotoxicity



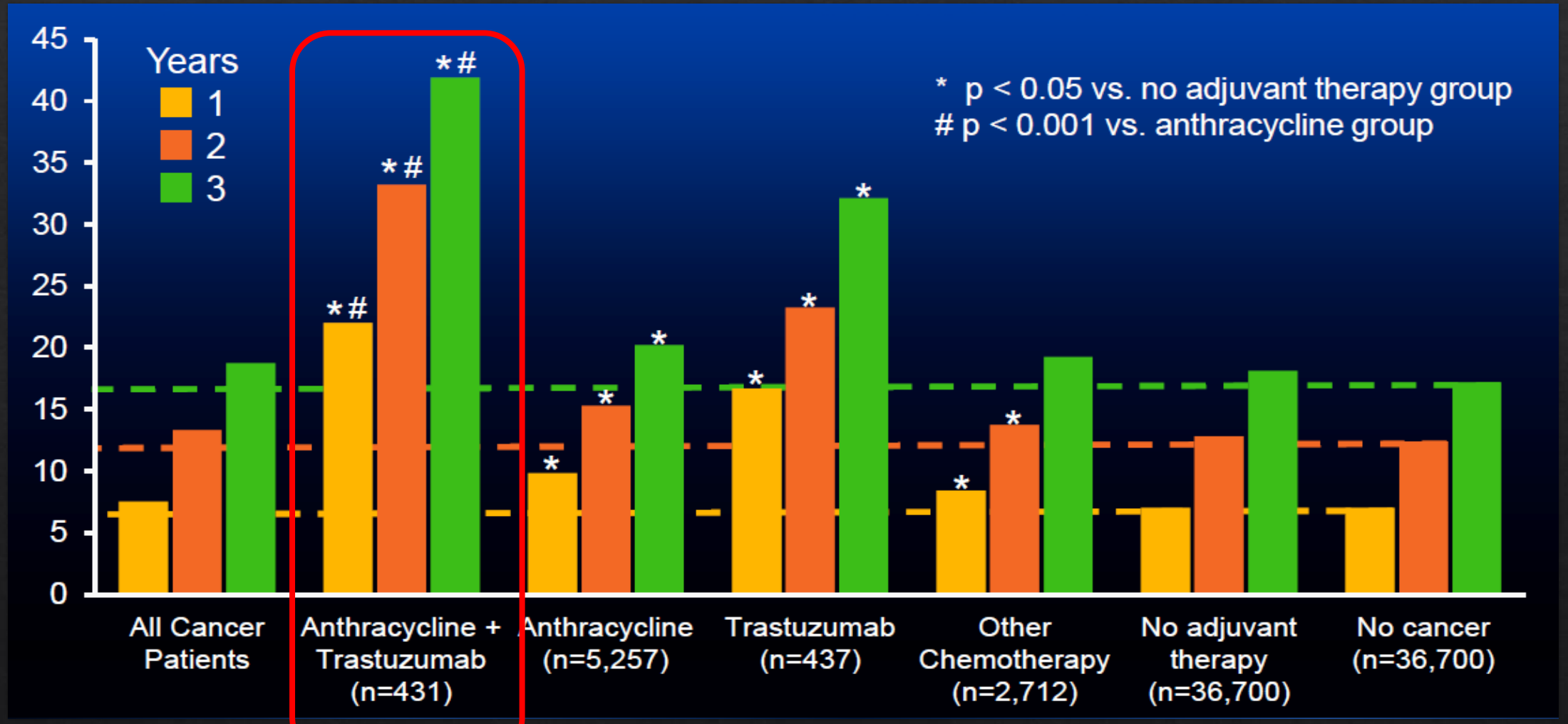
J Clin Oncol. 2005 Nov 1;23(31):7820-6

Anthracycline cardiotoxicity



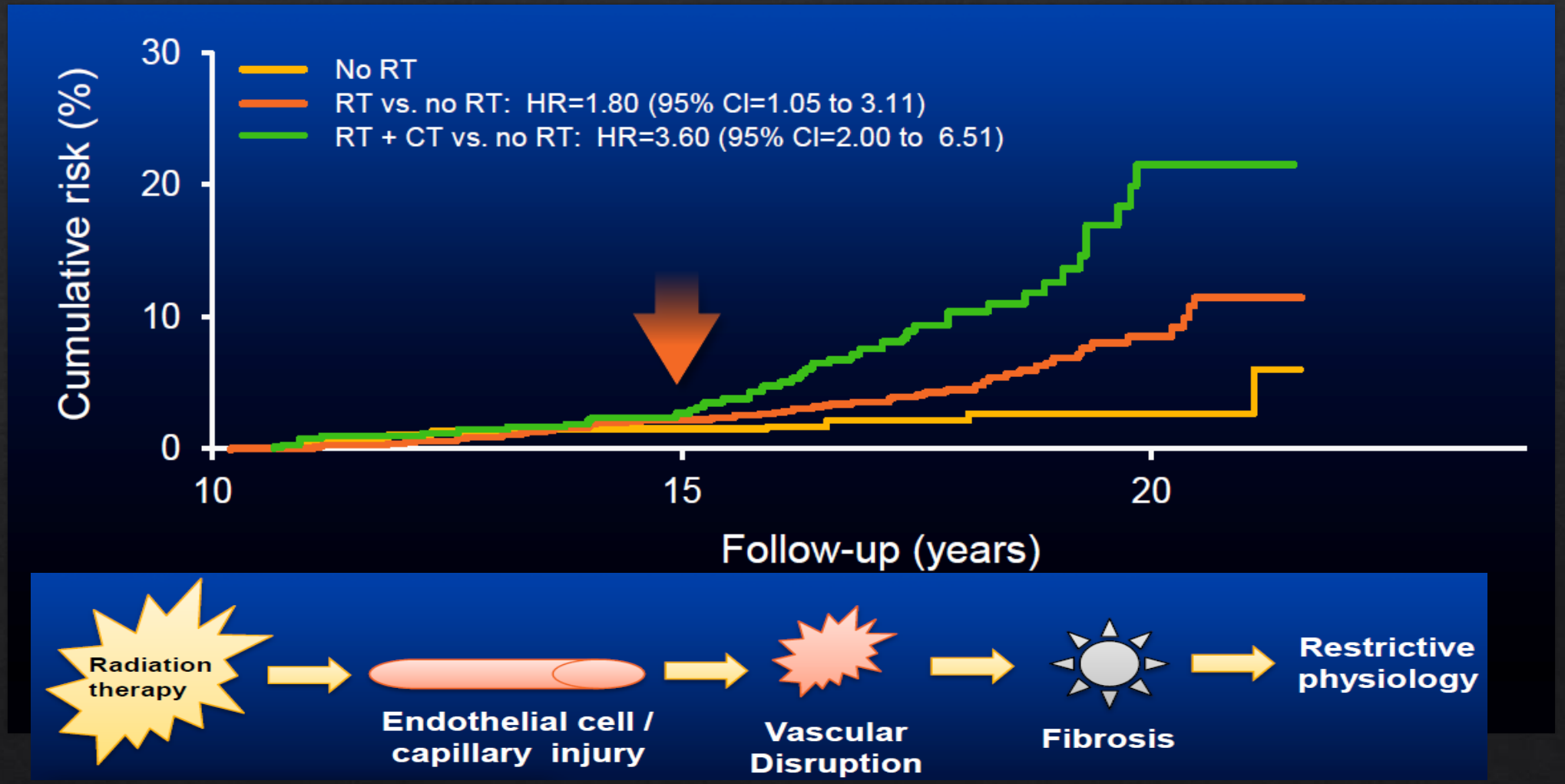
Nature Reviews Cardiology **volume7**, pages564–575 (2010)

HF/CMP in breast cancer



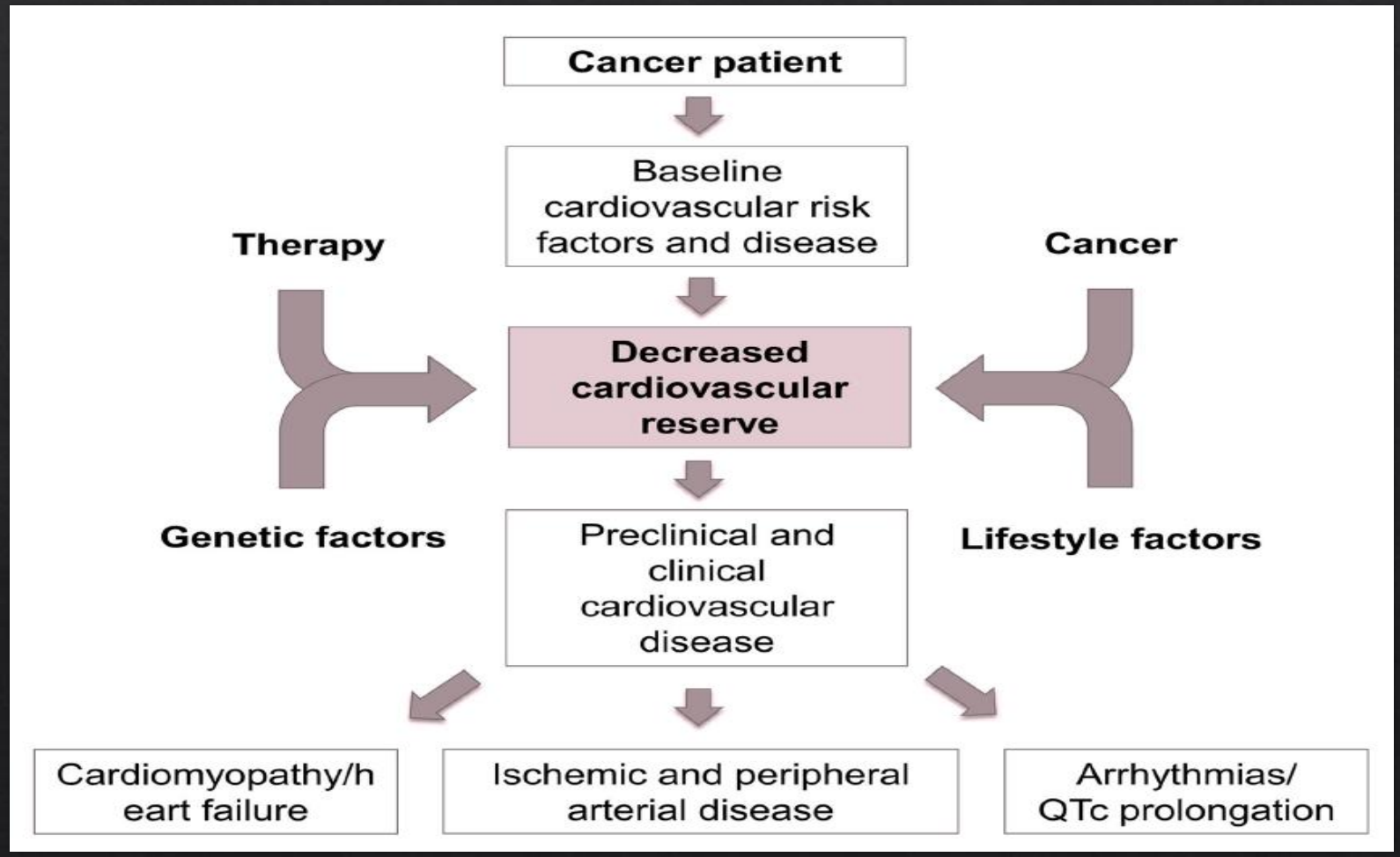
J Am Coll Cardiol. 2012 Dec 18;60(24):2504-1

Breast Cancer



J Natl Cancer Inst. 2007 Mar 7;99(5):365-75.
Pediatr Blood Cancer. 2005 Jun 15;44(7):630-7.

Multifactorial



Estimated and projected cancer survivors

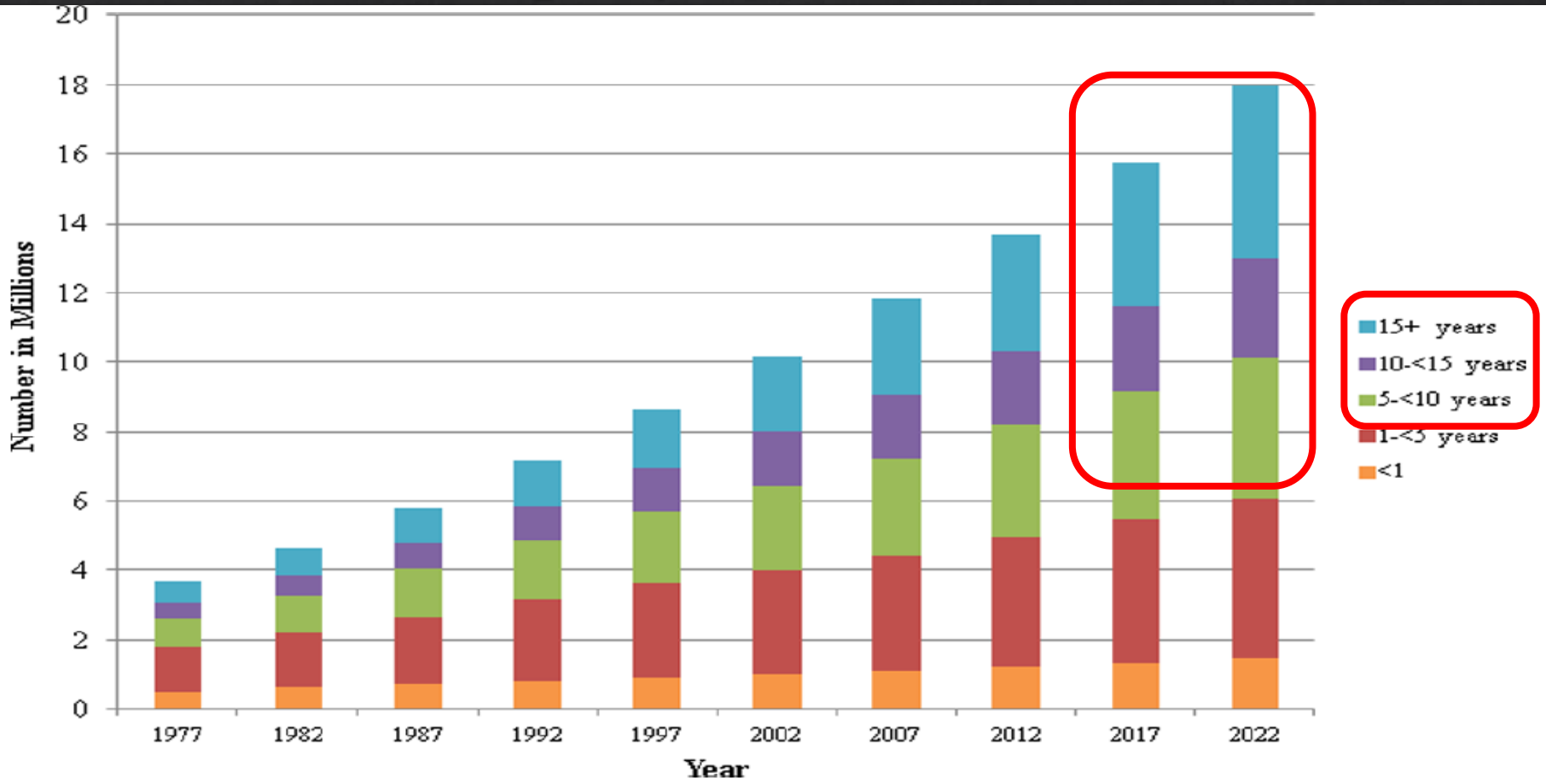


Figure 1.
Estimated and projected number of cancer survivors in the United States from 1977–2022 by years since diagnosis.

Cancer Epidemiol Biomarkers Prev. 2013 Apr; 22(4): 561–570.

Is any pretransplant malignancy a contraindication for transplant?

What did the guidelines say?

ISHLT 2006 HTx guideline

- Pre-existing neoplasms are diverse and many are treatable with excision, radiotherapy or chemotherapy to induce cure or remission.
- In these patients needing cardiac transplantation, collaboration with oncology specialists should occur to stratify each patient as to their risk of tumor recurrence. Cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up. The specific amount of time to wait to transplant after neoplasm remission will depend on the aforementioned factors and no arbitrary time period for observation should be used (Class I, *Level of Evidence: C*).

1. Active neoplasm other than skin origin → contraindication
2. History of neoplasm in general not a contraindication as some are curable
3. Collaboration with oncologist regarding prognosis
4. No arbitrary time period for observation should be used – cancer in remission for 5 years (arbitrary) or low grade may be acceptable for transplant evaluation

- *1.4.1.3. Pre-transplant cancer history requires individualization of treatment.*
- Active neoplasm from origins other than skin has been an absolute contraindication to cardiac transplantation due to limited survival rates.
- Currently, heart failure patients with cancers that have been in remission for 5 years and cancers that are low grade, such as prostate, may be acceptable for transplant evaluation. The 5-year remission threshold to safely proceed with transplant appears somewhat arbitrary and depends on the type of pre-existing neoplasm.
- There is also concern that immunosuppression after transplant might reactivate the pre-existing neoplasm that went into remission. Nevertheless, there have been many reports of patients with pre-existing neoplasm (0 to 240 months before transplant) undergoing successful cardiac transplantation without recurrence of the primary tumor.77– 81

There are reports of patients being successfully transplanted with co-existing tumors, such as primary cardiac tumors and low-grade prostate cancer.79 Pre-existing neoplasms are diverse and many are treatable with chemotherapy to induce remission. In these patients needing cardiac transplantation, collaboration with oncology must occur to assess each patient as to their risk of tumor recurrence. When tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up, then cardiac transplantation may be considered. The specific amount of time to wait to transplant after neoplasm remission depends on the factors already discussed.

ISHLT 2016 Guideline

- Pre-existing neoplasms are diverse, and many are treatable with excision, radiotherapy, or chemotherapy to induce cure or remission. In these patients needing cardiac transplantation, collaboration with oncology specialists should occur to stratify each patient as to their risk of tumor recurrence. Cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic work-up. The specific amount of time to wait to transplant after neoplasm remission will depend on the aforementioned factors and no arbitrary time period for observation should be used (Class I, Level of Evidence: C).

No change from 2006 guideline!

Netherland HTx guideline 2006

- Active malignancy or history of malignancy with probability of recurrence.
- Active neoplasm from origins other than the skin is an absolute contraindication to heart transplantation due to the limited survival rates.
- Patients with a history of malignancy can be considered for heart transplantation when the risk of tumour recurrence is low, preferably after a reasonable time of complete remission, depending on the tumour type, response to therapy and negative metastatic work-up

Guideline wordings are ***vague*** regarding type of cancer and observation time of complete remission

Canadian Guideline

Canadian Guideline 2001

- Contraindication: Recent non basal cell malignancies within 5 years

Simple
Easy to follow
5 year ? arbitary

Canadian Transplant Network 2012

- Malignancy, specifically active neoplasm from origins other than the skin, is an absolute contraindication to transplantation.
- Although the general recommendation is that the patient be in remission for 5 years prior to being considered for transplantation, a pre-transplant cancer history should be assessed individually, with input from the treating oncologist regarding the risk of tumour recurrence, particularly in the setting of post-transplant immunosuppression.
- In the paediatric population, there is precedence for cardiac transplantation within 2 years post-malignancy in the setting of low risk malignancies with high response rates to treatment.

Other Guidelines

Australia 2016

- “Active malignancy”

ESC HF Guideline 2016

- Contraindication - Cancer (a collaboration with oncology specialists should occur to stratify each patient as to their risk of tumour recurrence).

Once again, no clear instruction

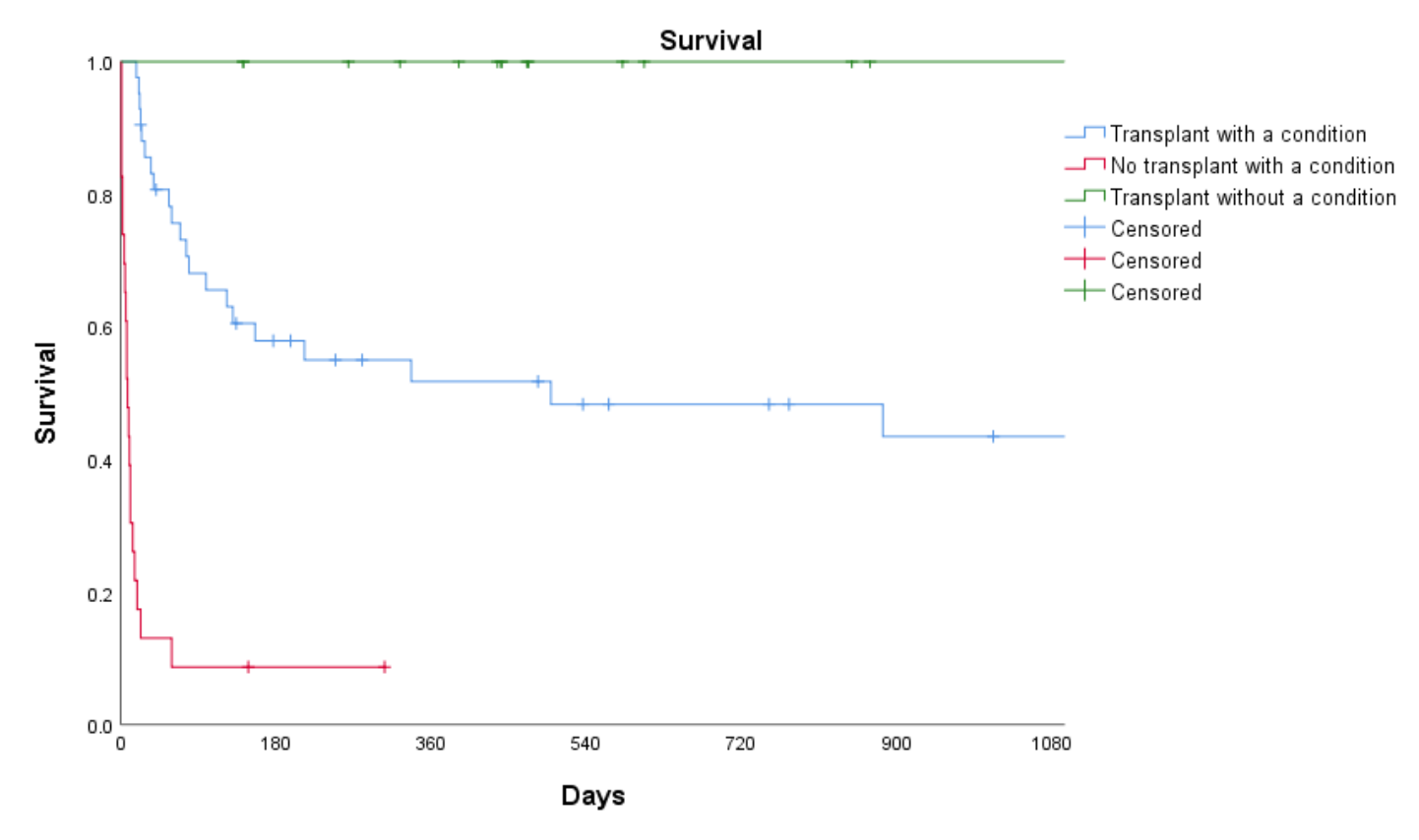
Why is eligibility important?

- Practical application
- Ethical principles
- Medical legal

Practical Application

- Basics of indication and contraindication
- Indication
  - Heart transplant is a high-risk procedure, 1-year mortality ~ 10%
  - If heart disease is severe with estimated 1-year mortality > 10% (higher than HTx mortality) → HTx is justified and thus indicated
- Contraindication
  - Conditions that known to worsen post-transplant outcome especially in terms of survival → contraindicated

Illustrative Example



- Transplant with a condition is indicated as compared to no transplant
- Transplant with a condition is considered contraindicated due to significant worsen survival compared to transplant without a condition

How to decide?

Highly variable reported outcomes

Table 2 Post-transplant outcomes: hospital mortality, survival rates and cancer recurrence

Reference		Hosp. mort.	1-year	2-year	5-year	10-year	CA
(1)		9%	100%		82%		9%
(7)	PTM		84% (est)	80% (est)	73% (est)		
(7)	no PTM		84% (est)	80% (est)	76% (est)		
(8)		11%	7/8			6/8	12.5%
(9)		10%	75%*		50%*		15%
(10)			90%	85%*	75%*	65%	
(12)	I				55%*		63%
(12)	II				75%*		26%
(12)	III				80%*		6%
(13)						63%	0%
(15)	AL	3%	77%	64%**	64%	50%	
(15)	HO		69%		54%	31%	
(16)			86%	79%**	71%		5%
(24)			100%	92%	60%		
(25)					74%	67%	
(26)	PTM		90.6%		80.3%	65.0%	13.0%
(26)	no PTM		84.4%		73.8%	57.7%	5.4%#

AL: all lymphomas, CA: cancer recurrence, (est): estimated from survival curve, HO: Hodgkin only, hosp. mort: hospital mortality, * % estimated from survival curves ** at 3 years, # de novo cancer, I: interval < 1 year, II: interval between 1 and 5 years, III: interval > 5 years.

Acta Cardiol 2015; 70(2):123-130

Practical application - challenges

- Many case report/series quote “successful” for patients with prior malignancy
  - Beware of publication bias
  - Beware of issue of limited sample size in power – i.e. p-value not significant does not mean no effect on clinical outcome but just sample size too small
  - Beware of definition – a good short-term outcome (e.g. in-hospital/1-year survival) really means success?
  - Those apparently successful series still only represent “highly selected” cases with prior malignancy
- Prognosis/risk of recurrence of cancer
  - Is estimation reliable?
  - Where is the cut off for being considered “non-acceptable”

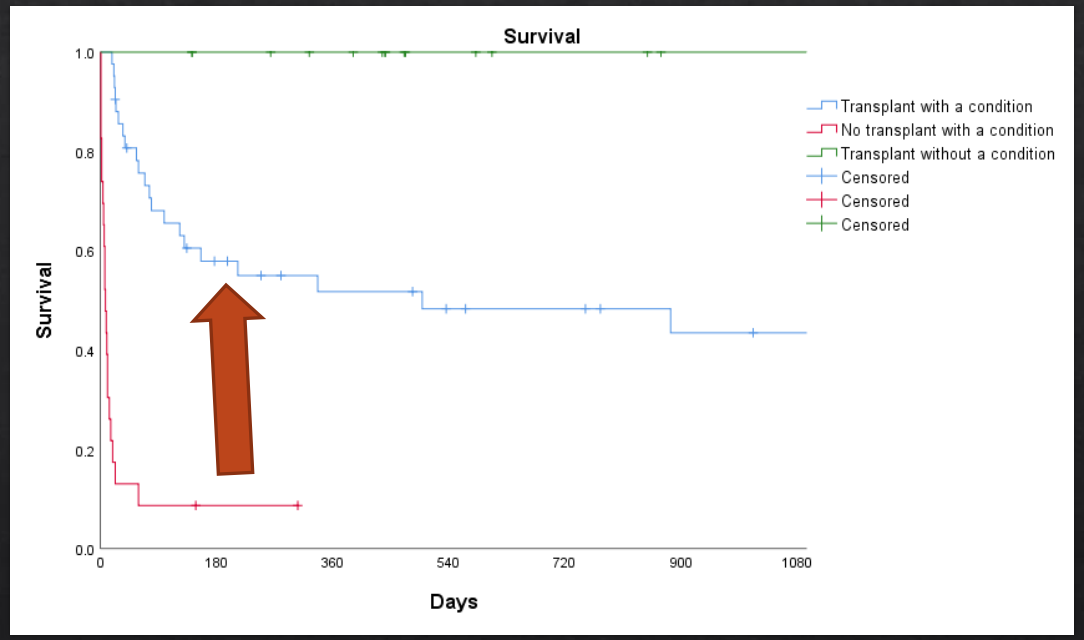
Ethical principles

- Beneficence
- Autonomy
- Non-maleficence
- Justice

Ethical Principles - beneficence

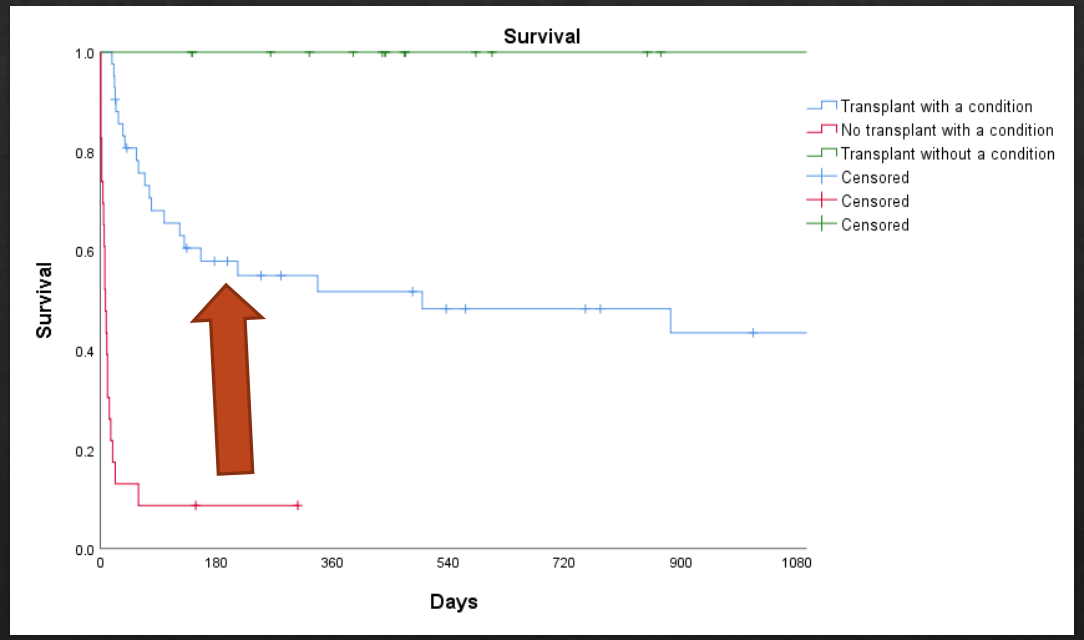
- To provide beneficial treatment to patient

  →We should do transplant for the patient



Autonomy

- Patient is willing to take the risk of transplant knowing her risk without transplant is much worse
  - → We should do transplant for the patient



Non-maleficence

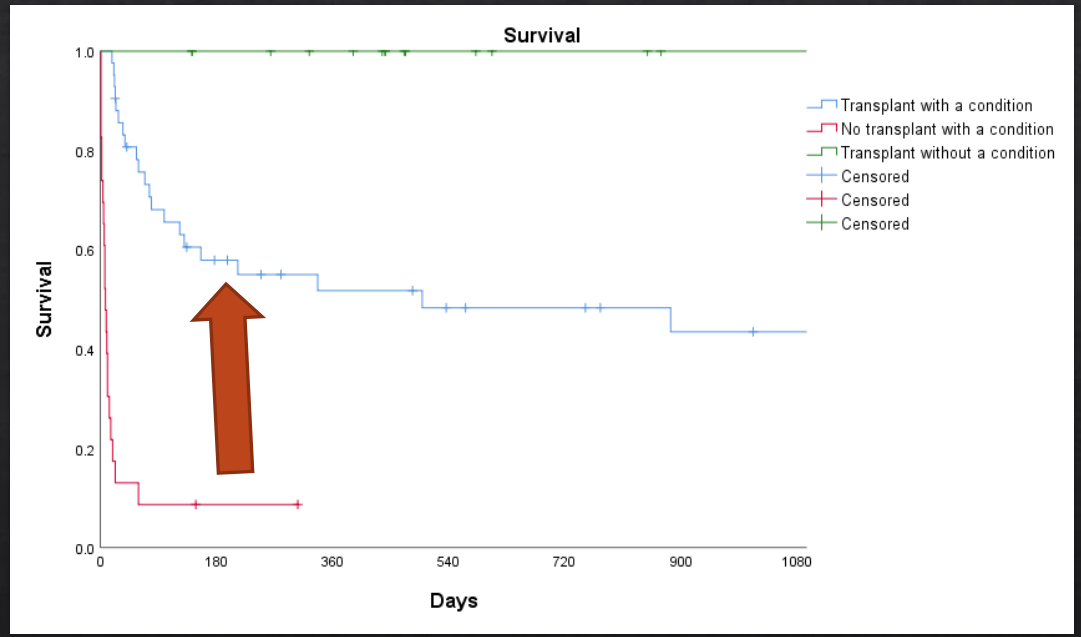
- Although transplant cannot attain usual post-transplant outcome without a condition → outcome is still surely better than no transplant, thus definitely do no harm to this patient

  → We should do transplant for the patient

Wait!

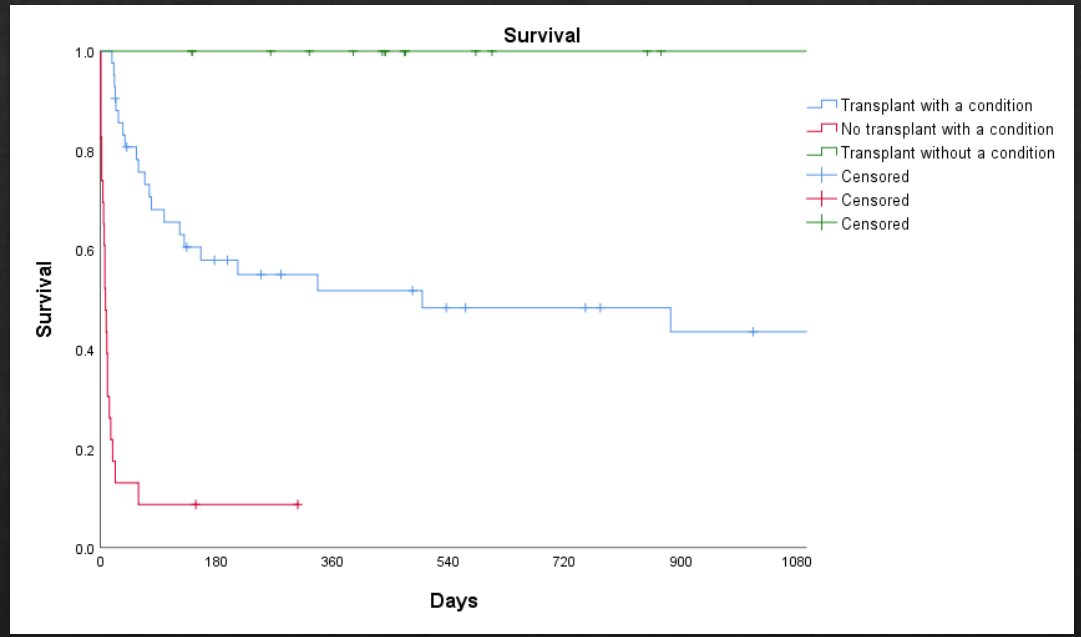
Heart Transplant donor availability is limited
Organ allocated to one person in reality means deprived other suitable recipients from transplant and thus prolong waiting time and increase risk of death

Violate non-maleficence principle to another patient on transplant waiting list!



Justice

- Heart donor – limited
- NOT everybody eligible can get a heart
- Transplant team need to determine eligibility criteria so as to maximize clinical benefit with a transplant
- Thus the importance of maximizing benefit (indication) and minimizing post-transplant risk (contraindication)



Medical legal - challenges

- Advanced heart failure is lethal disease
- Patient and family are in distress
- Very common to grasp every single chance for treatment available
- Very common to challenge the rationale for being “declined” for heart transplant consideration
- They provide recommendations from their own oncologist with the comments of “favorable” treatment response and “good” prognosis from oncological point of view
- No guideline on the clear cutoff on prognosis assessment and duration of observation to “decline” for heart transplant – which means the patient will die from this lethal disease
- What if patient/family initiate lawsuit for their “personal rights” to get a heart transplant
- From the ethical principle – we know that transplant team cannot accept all patients with prior malignancy without any criteria
- However no clear criteria to follow from international guideline even with the input from oncologists
- There are many case report/series reporting “successful” experience which favor patient’s claim

Importance of timing

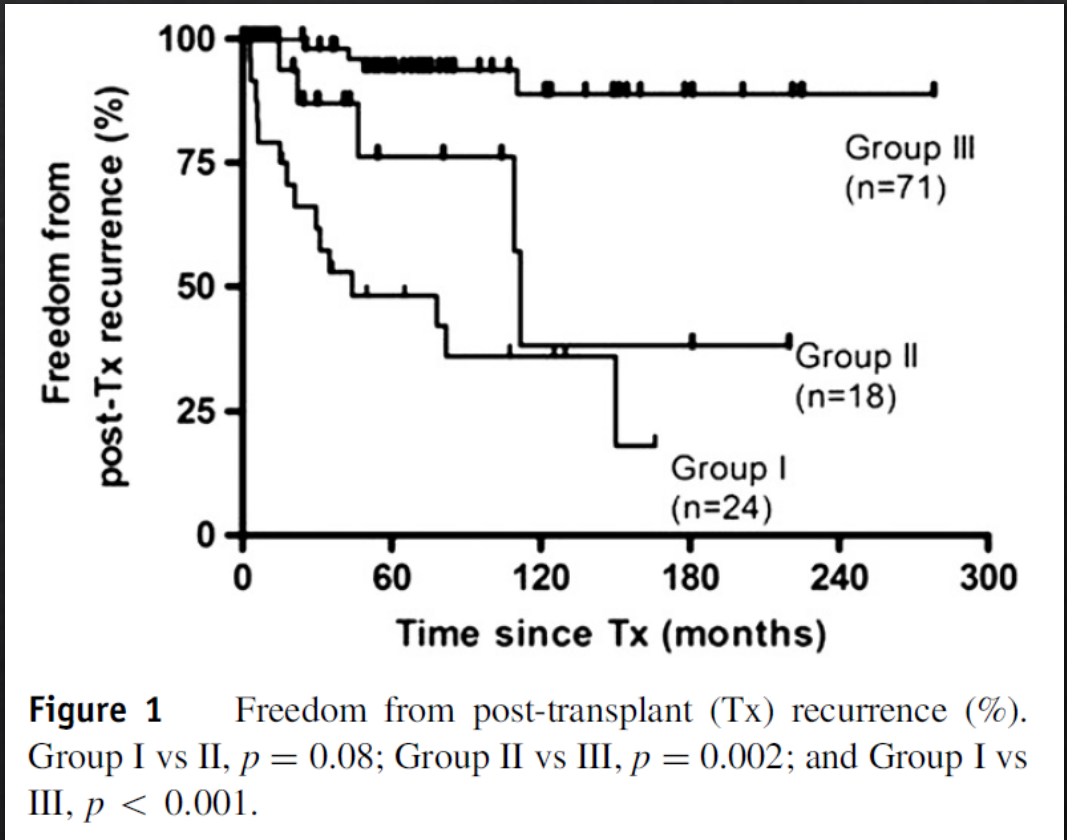


Figure 1 Freedom from post-transplant (Tx) recurrence (%). Group I vs II, $p = 0.08$; Group II vs III, $p = 0.002$; and Group I vs III, $p < 0.001$.

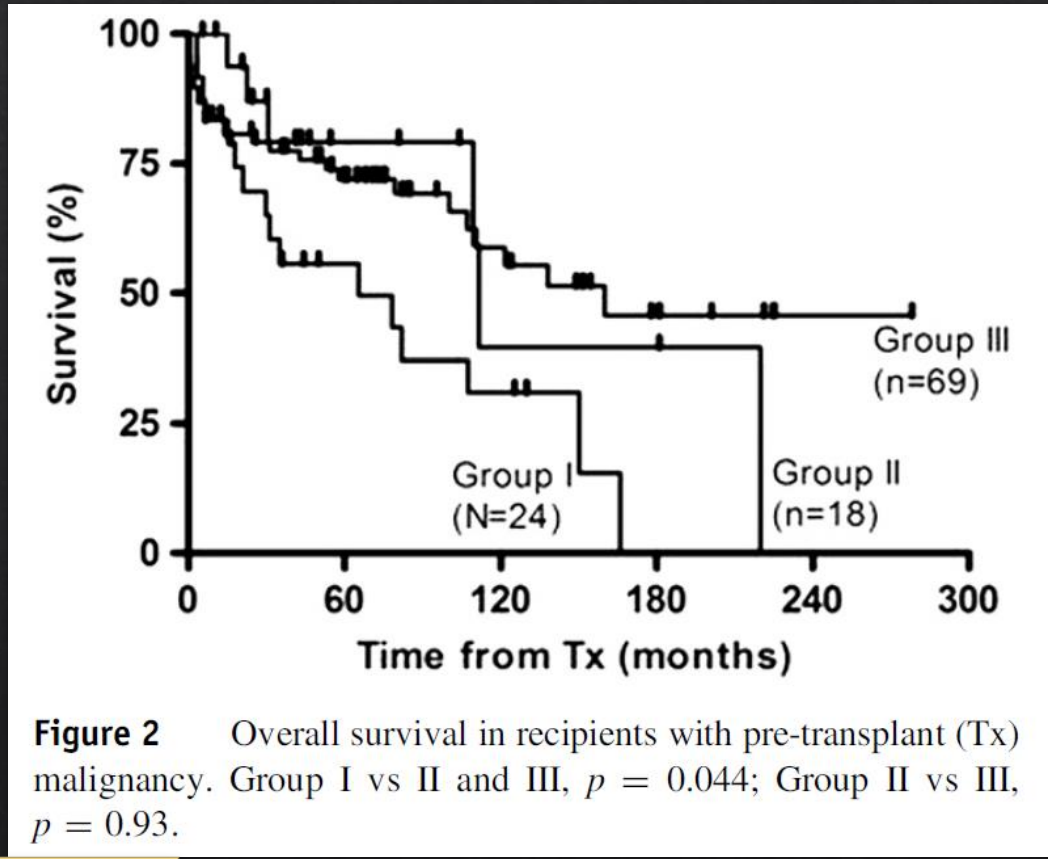


Figure 2 Overall survival in recipients with pre-transplant (Tx) malignancy. Group I vs II and III, $p = 0.044$; Group II vs III, $p = 0.93$.

Group I <12 months(n = 24)
Group II >=12 to <60 months (n = 18)
Group III >=60 months(n = 71).

J Heart Lung Transplant. 2012 Dec;31(12):1276-

Type of malignancy matter

Table 3 Type of Pre- and Post-transplant Malignancy Events

	Frequency			Recurrence	New malignancy	Death because of malignancy		
Type of malignancy	No. (%)	Heart No.	Lung No.	No.	No.	Group I ($n = 24$)	Group II ($n = 18$)	Group III ($n = 69$)
Lymphoma	31 (28)	27	4	4	1	1[a]		1
Leukemia	16 (14)	6	10	2			1	
Lung	15 (13)	2	13	10	2	8[b]	1	
Genital organ	22 (19)	14	18	2	4	1	1	
Urinary system	8 (7)	7	1		1			
Digestive system	7 (6)	5	2	2	1	1[a]		1
Sarcoma	7 (6)	7	0	4		3		1
Skin	3 (3)	3	0		3			
Various others	4 (4)	3	1		1			
Total	113 (100)			24	13	14	3	3

[a]Incidentally diagnosed at the time of transplantation.
[b]Incidentally diagnosed at the time of transplantation in 7 recipients where 5 received induction with polyclonal anti-thymocyte globulin.

J Heart Lung Transplant. 2012 Dec;31(12):1276-

Risk profile

Factor	No Increase Risk	Risk Likely	Definite Risk
Tumor type, interval	Localised Prostate	Interval < 1 year	No cure achieved or metastasis detected
	In situ bladder Ca	If expected 5-year survival > 70%	Multiple myeloma
	Skin Ca		Hodgkin's disease with splenectomy
	High interval (>10 years)		

Acta Cardiol 2015; 70(2):123-130

KDIGO Renal Transplant Guideline 2020

TABLE 14.
Recommended waiting times between cancer remissior and kidney transplantation[91]

Breast	Early	At least 2 years
	Advanced	At least 5 years
Colorectal	Dukes A/B	At least 2 years
	Duke C	2-5 years
	Duke D	At least 5 years
Bladder	Invasive	At least 2 years
Kidney	Incidentaloma (< 3 cm)	No waiting time
	Early	At least 2 years
	Large and invasive	At least 5 years
Uterine	Localized	At least 2 years
	Invasive	At least 5 years
Cervical	Localized	At least 2 years
	Invasive	At least 5 years
Lung	Localized	2-5 years
Testicular	Localized	At least 2 years
	Invasive	2-5 years
Melanoma	Localized	At least 5 years
	Invasive	Contraindicated
Prostate	Gleason ≤6	No waiting time
	Gleason 7	At least 2 years
	Gleason 8-10	At least 5 years
Thyroid	Papillary/Follicular/ Medullary	
	Stage 1	No waiting time
	Stage 2	At least 2 years
	Stage 3	At least 5 years
	Stage 4	Contraindicated
	Anaplastic	Contraindicated
Hodgkin Lymphoma	Localized	At least 2 years
	Regional	3-5 years
	Distant	At least 5 years
Non-Hodgkin Lymphoma	Localized	At least 2 years
	Regional	3-5 years
	Distant	At least 5 years
Post-transplant lymphoproliferative disease	Nodal	At least 2 years
	Extranodal and cerebral	At least 5 years

- Mortality
- Invasiveness
- Recurrence rate
- Response to treatment
- Prognosis in case of recurrence

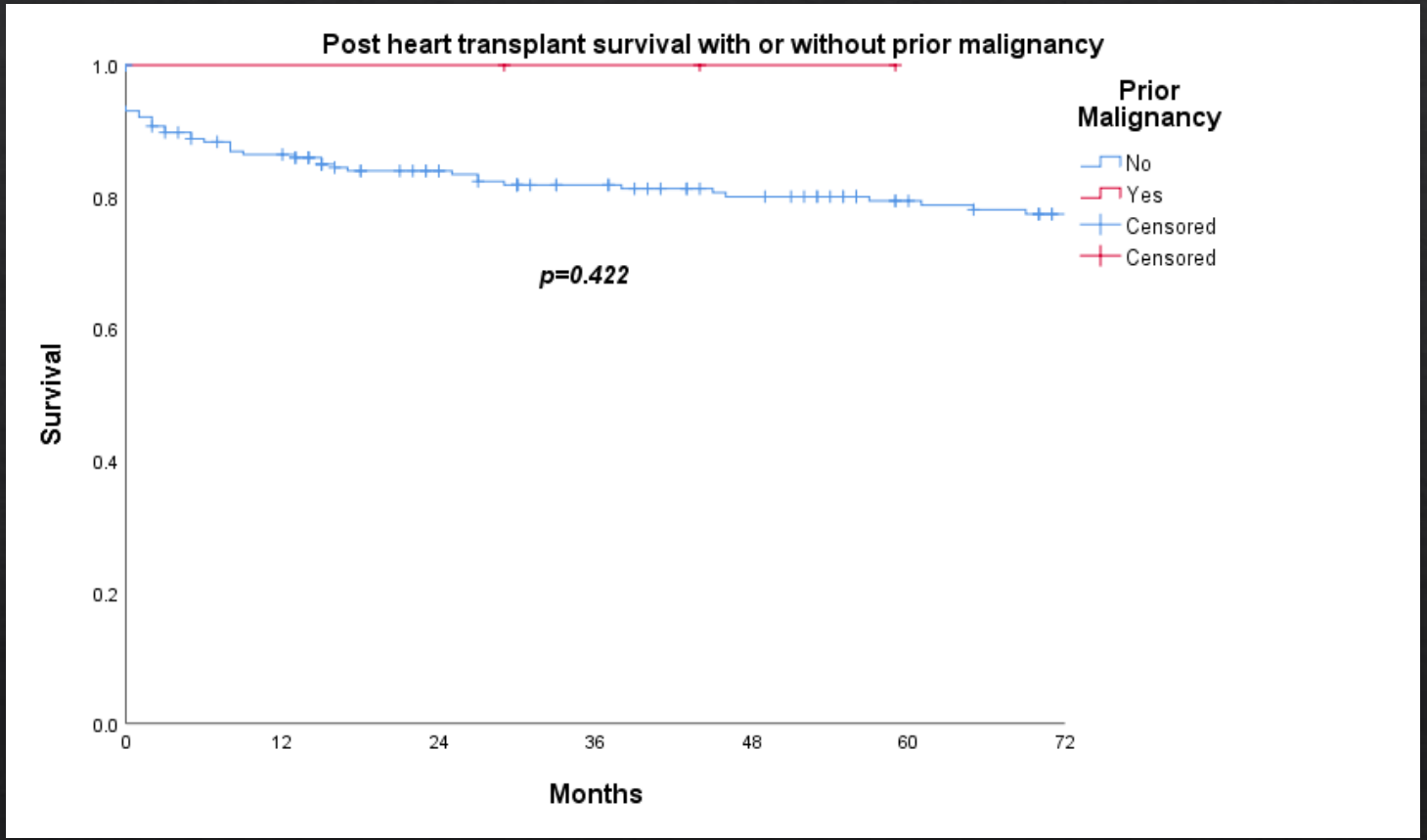
Based on previous studies which showed a reduction in cancer recurrence with time.
~50% of cancer recurrences occurred in patients treated for cancer within 2 years of transplantation
~13% in patients treated more than 5 years prior to transplantation

Transplant Proc. Feb-Mar 2001;33(1-2):1830-1
Transplantation. 2020 Apr;104(4S1 Suppl 1):S11-

Hong Kong Data

- 1992-2019
- 3/219 1.4%
- All female
- 2 breast cancer 1 burkitt's lymphoma
- All > 5 years from remission of malignancy
- Mean age at transplant 50 vs 44.7 with vs without prior malignancy p=0.489
- So far no evidence of recurrence post-transplant

Hong Kong Data

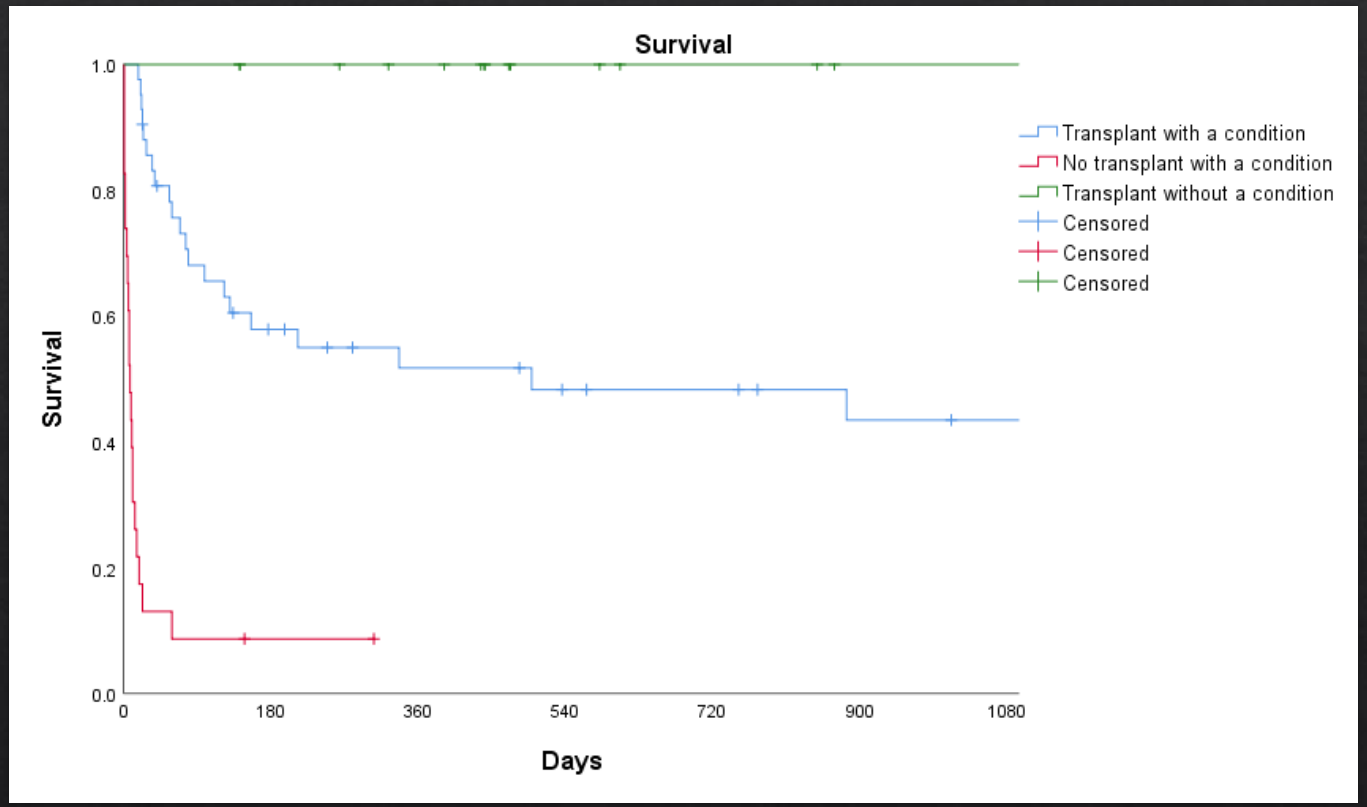


If time is needed to declare candidacy

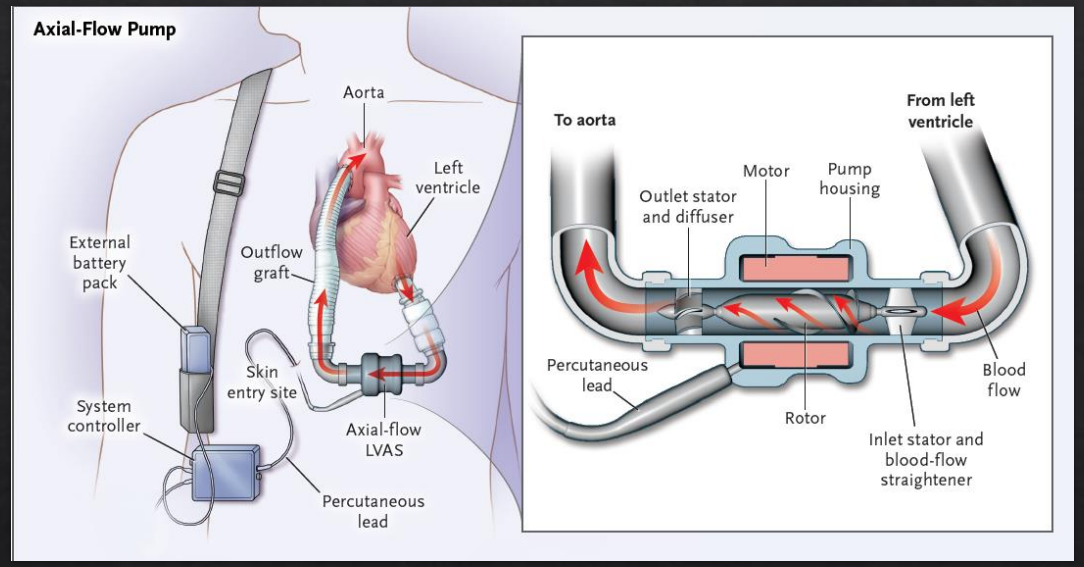
TABLE 14.

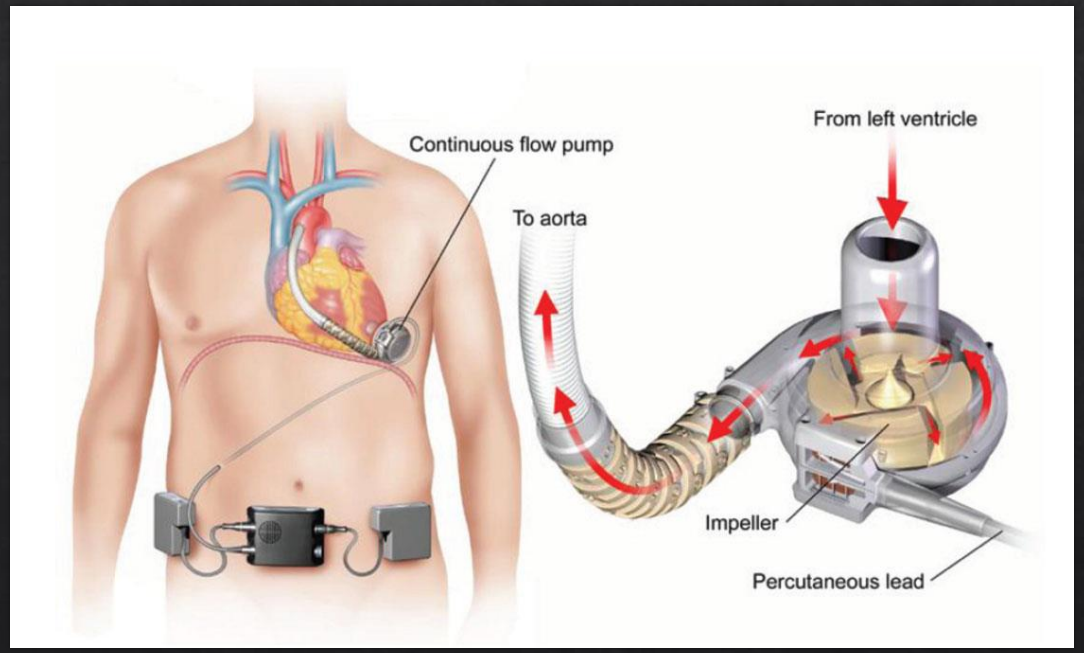
Recommended waiting times between cancer remissior and kidney transplantation[91]

Breast	Early	At least 2 years
	Advanced	At least 5 years
Colorectal	Dukes A/B	At least 2 years
	Duke C	2-5 years
	Duke D	At least 5 years
Bladder	Invasive	At least 2 years
Kidney	Incidentaloma (< 3 cm)	No waiting time
	Early	At least 2 years
	Large and invasive	At least 5 years
Uterine	Localized	At least 2 years
	Invasive	At least 5 years
Cervical	Localized	At least 2 years
	Invasive	At least 5 years
Lung	Localized	2-5 years
Testicular	Localized	At least 2 years
	Invasive	2-5 years
Melanoma	Localized	At least 5 years
	Invasive	Contraindicated



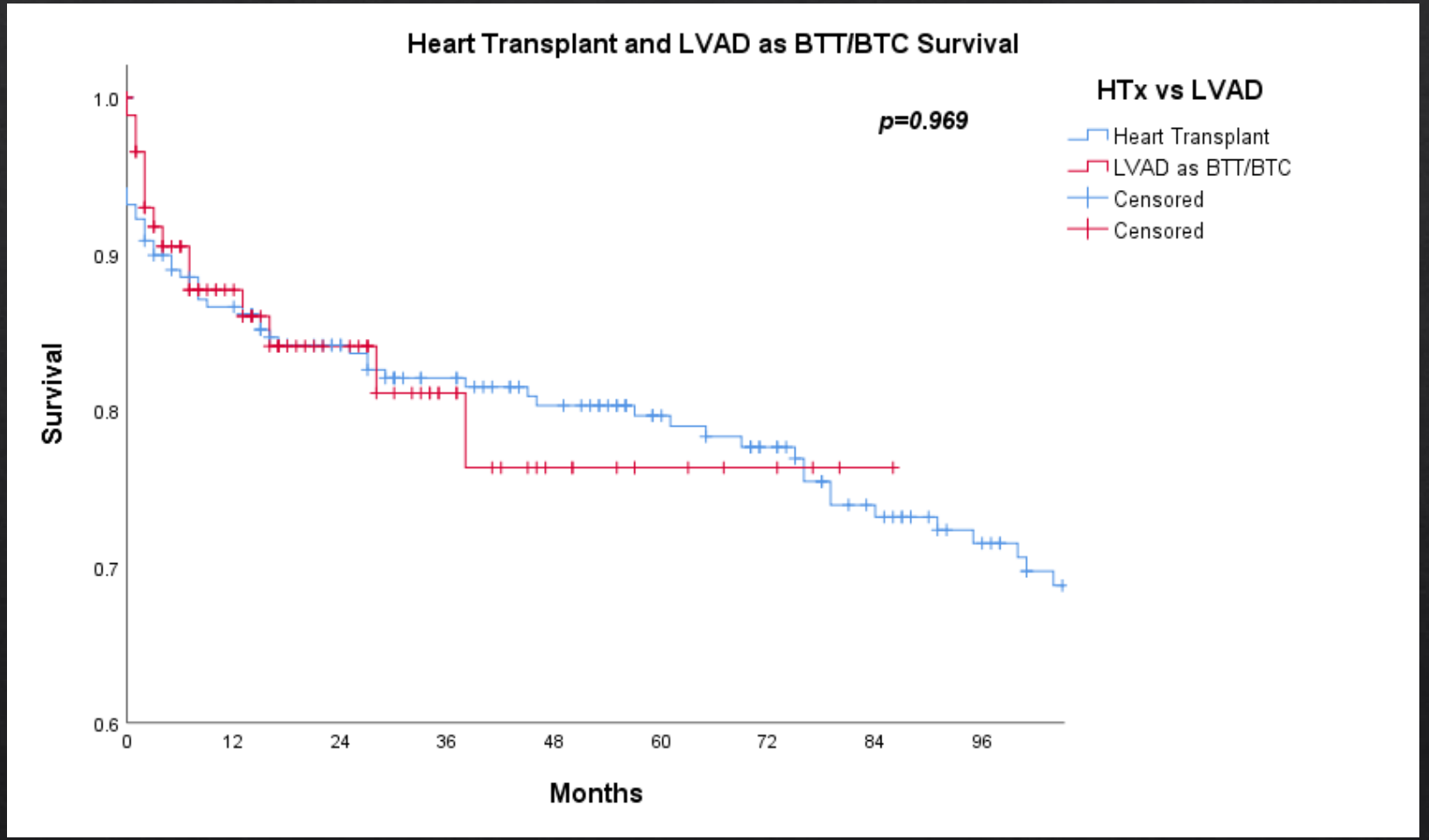
LVAD
Potential role as bridge to candidacy





Slaughter MS et al. *N Engl J Med. 2009;361:2241-51.*

Heart Transplant and BTT/BTC LVAD Survival



Conclusion

- Field of cardio-oncology is rapidly evolving
- Long term outcome of oncology patients is improving and expected more long term survivor will suffer from heart failure
- Consideration of eligibility of candidacy for heart transplant in patient's with prior malignancy is challenging and collaboration with oncologists is recommended
- Decision should be individualized both for patient and transplant center
- LVAD as BTC may be a potential alternative in arbitrary case that need time to declare candidacy

Thank you!