Cardio-Oncology

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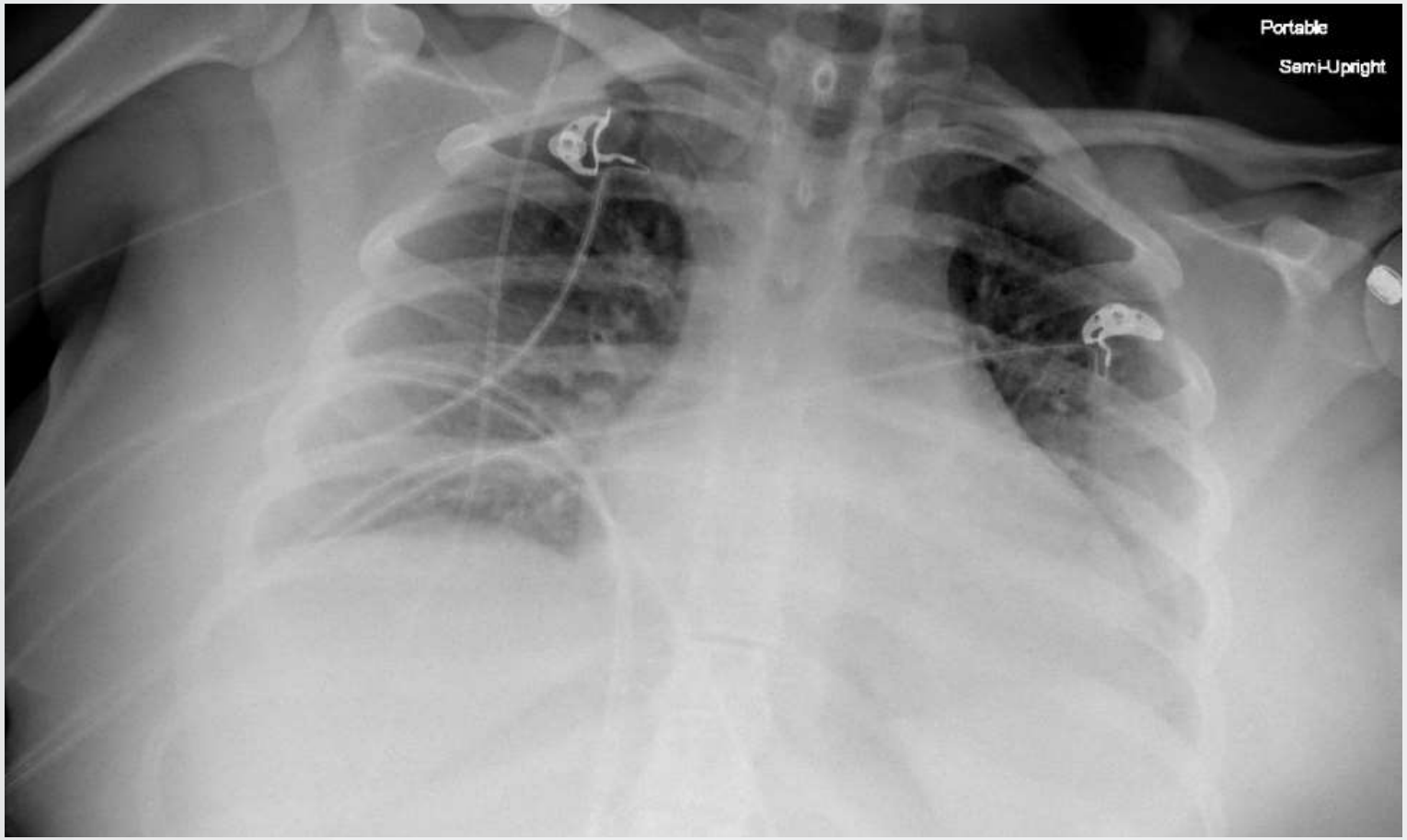
Disclosures

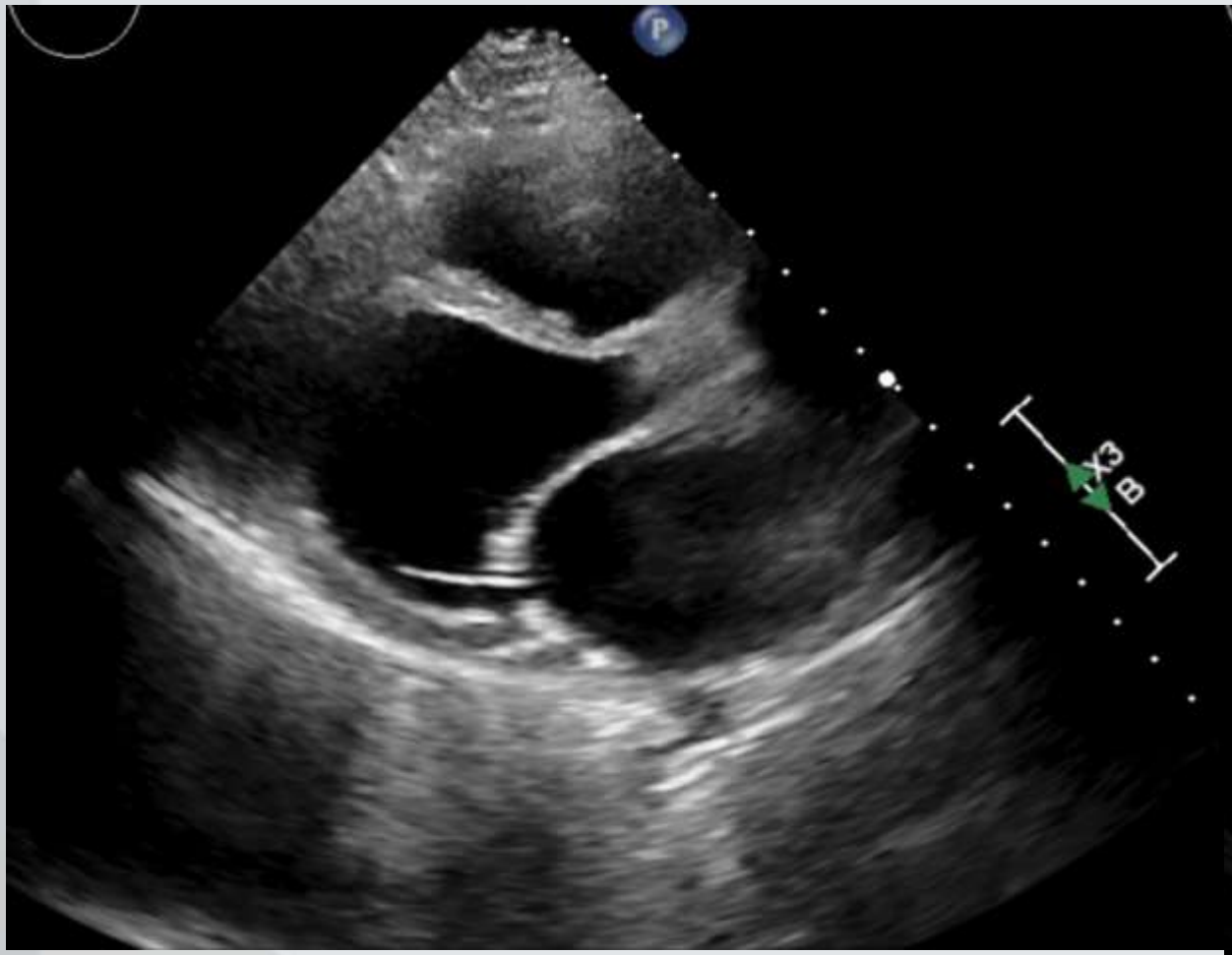
- None

Case

- 20 year old male presented to ED with malaise
- Vitals:
- **BP:** 95/70 **HR:** 104 bpm **RR:** 30 **O2:** 90%
- Prior history of AML treated as a child and had been in remission since he was 3
- Treatment included doxorubicin
- Followed with her pediatric oncologist annually. Previously had followed with his pediatric cardiologist until he was 16 then lost to follow up.



- Patient had been having a nocturnal cough with abdominal complaints for about a month
- **Labs**
  - CBC, mildly elevated WBC
  - BMP creatinine 1.5 (previously 0.7)
  - Lactic acid: 5 mmol/L
  - Probnp (< 124): 8,000 pg/mL
  - AST/ALT: 4400/3500
- he was transferred to UNMC for further management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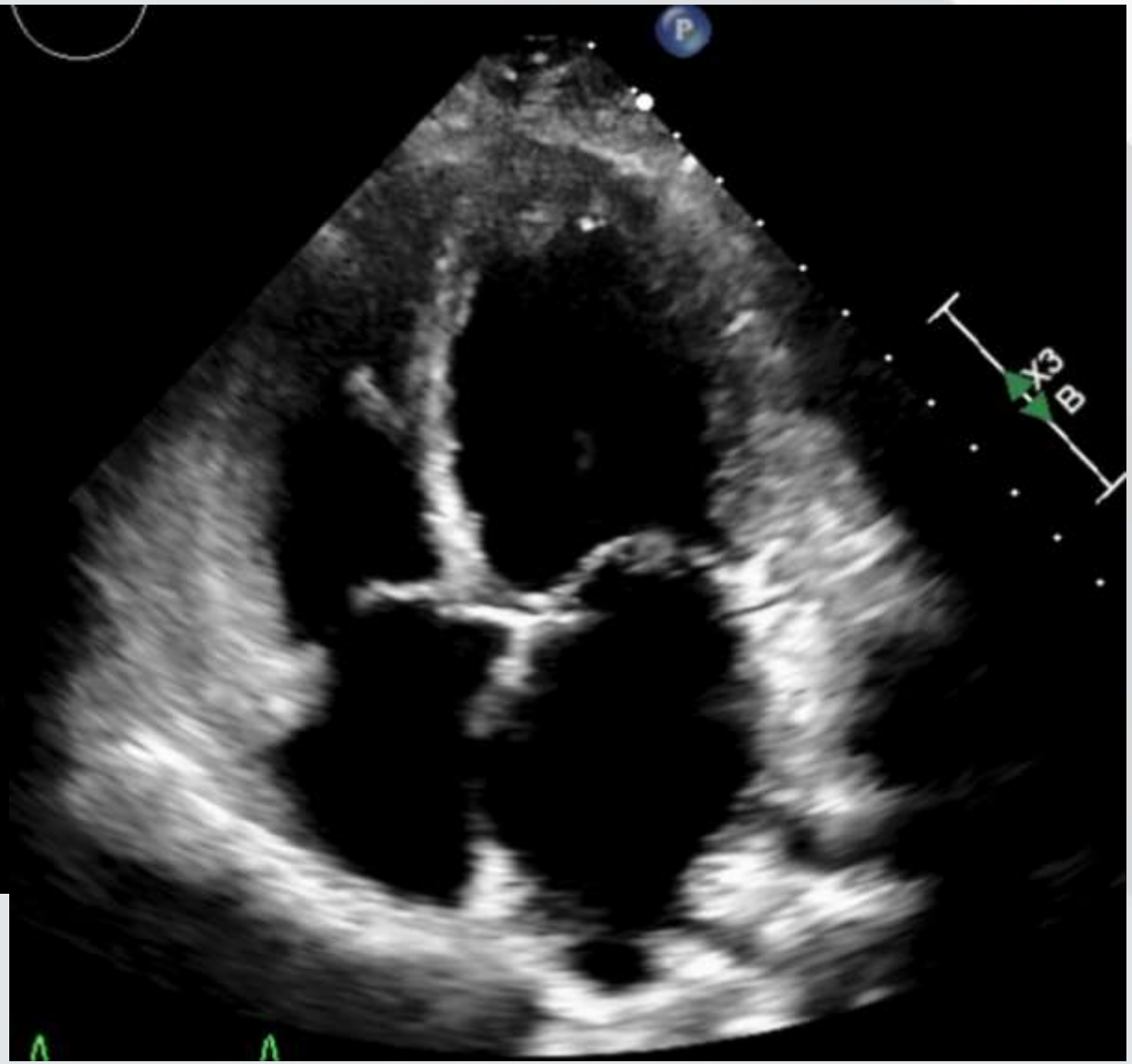
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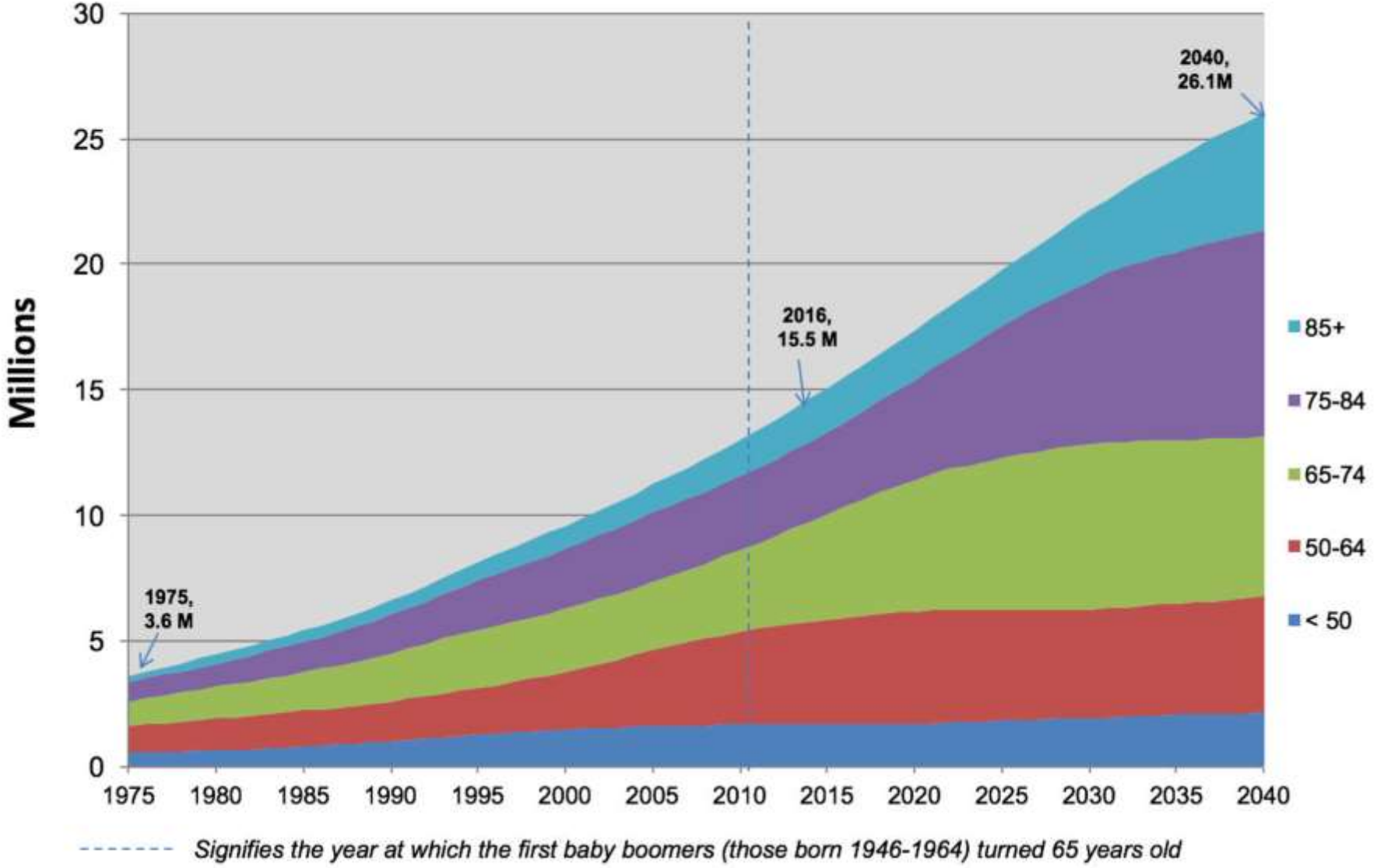
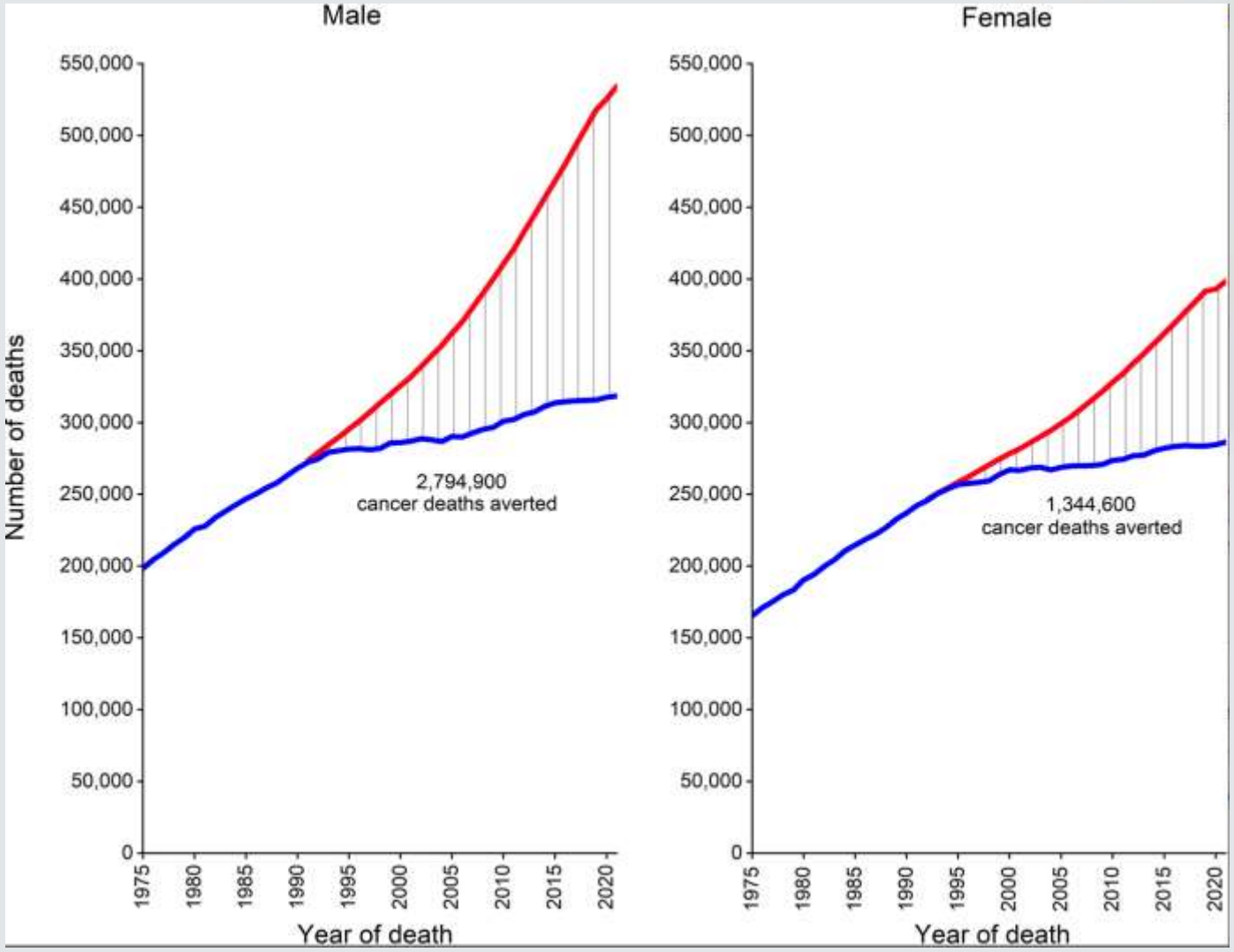
Figure 1: Estimated cancer prevalence by age in the US population from 1975 (216 M) to 2040 (380 M)



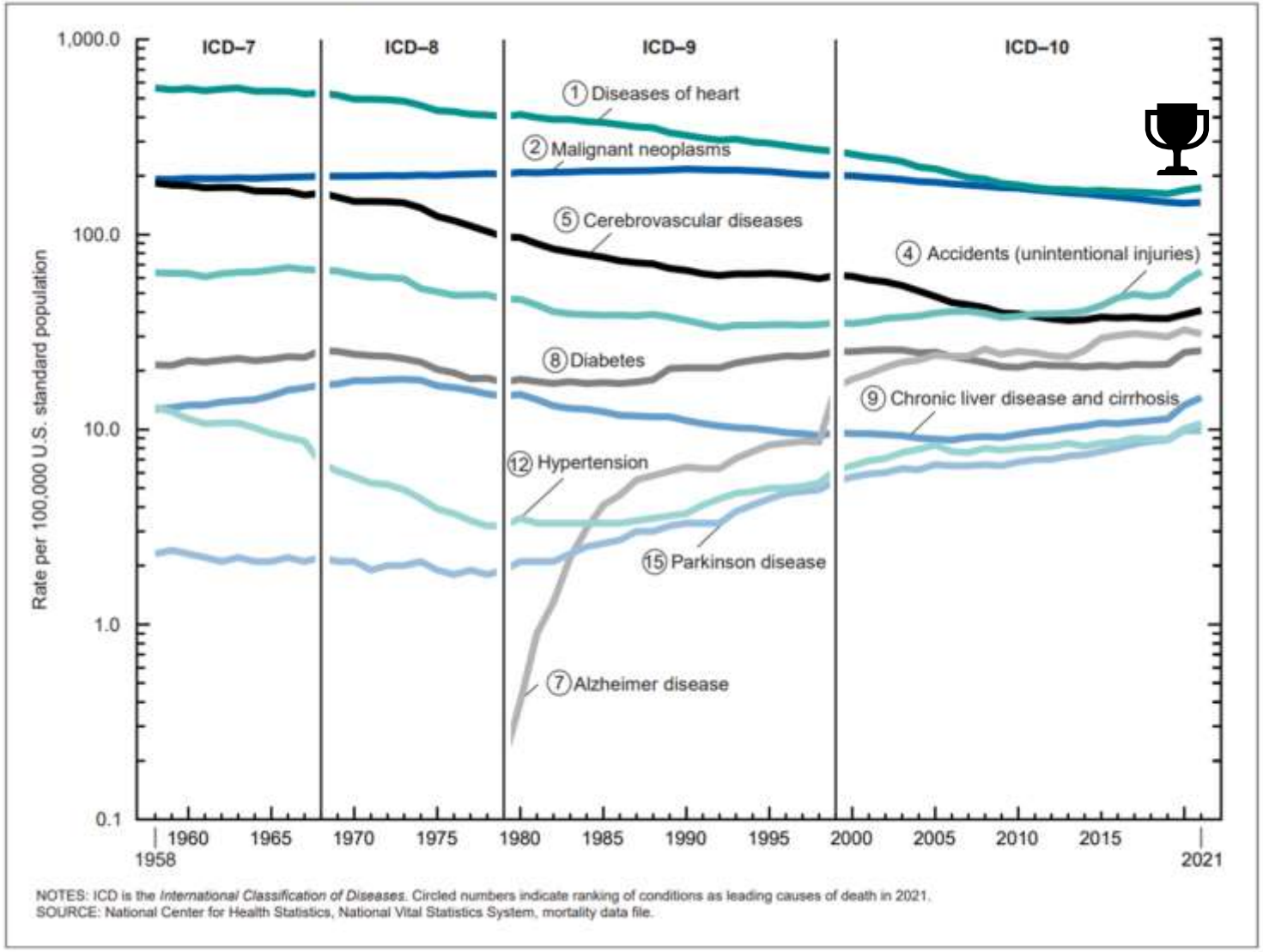


American Cancer Society®

Leading Causes of Death

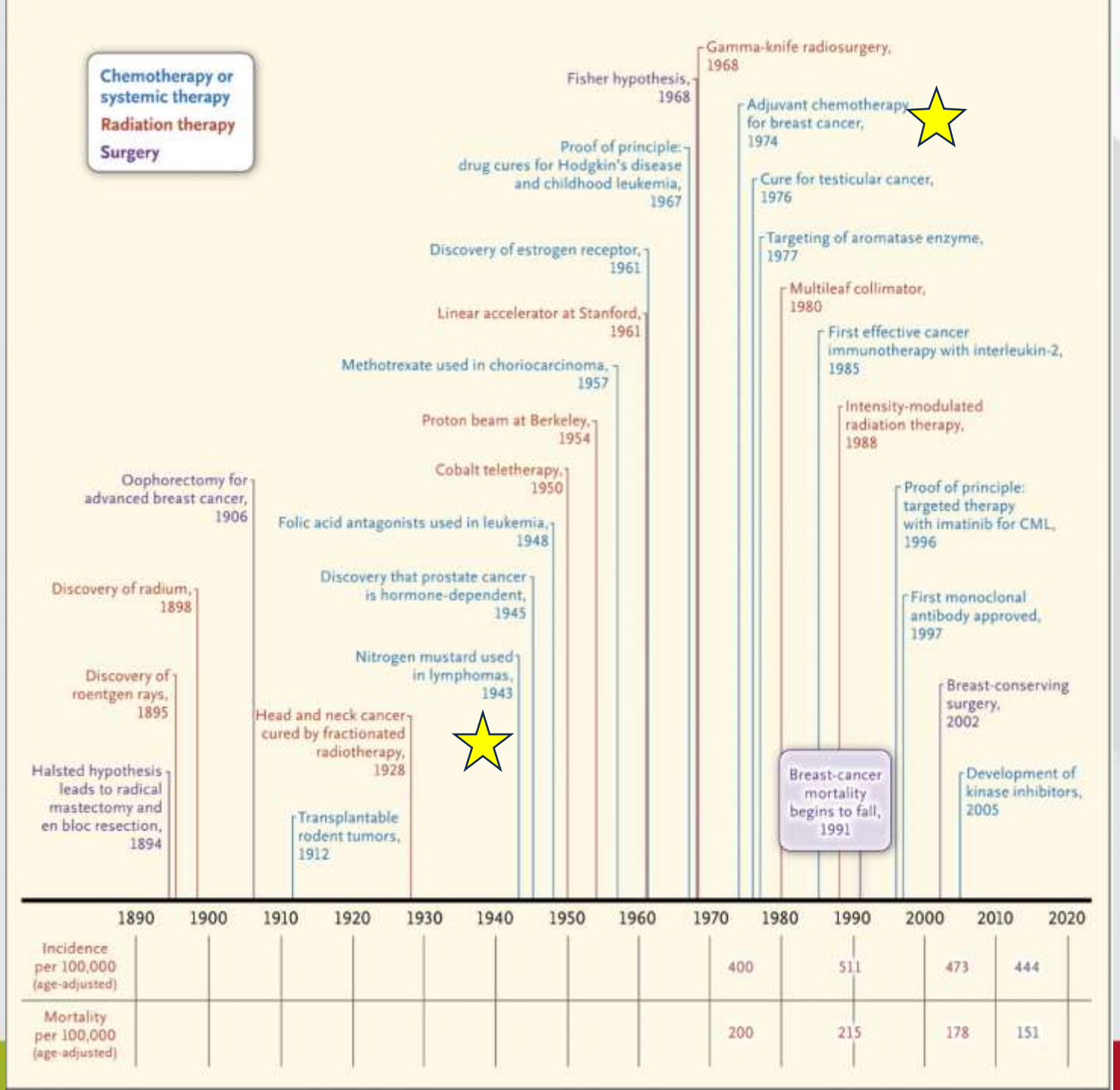
Rank[1]	Cause of death (based on ICD–10)	Number	Percent of total deaths, 2021[2]	Crude death rate, 2021	2021	Percent change from 2020 to 2021
…	All causes	3,464,231	100.0	1,043.8	879.7	5.3
1	Diseases of heart (I00–I09,I11,I13,I20–I51)	695,547	20.1	209.6	173.8	3.3
2	Malignant neoplasms (C00–C97)	605,213	17.5	182.4	146.6	1.7
3	COVID-19 (U07.1)	416,893	12.0	125.6	104.1	22.5
4	Accidents (unintentional injuries) (V01–X59,Y85–Y86)	224,935	6.5	67.8	64.7	12.3
5	Cerebrovascular diseases (I60–I69)	162,890	4.7	49.1	41.1	5.9

Figure 4. Age-adjusted death rate for selected leading causes of death: United States, 1958–2021



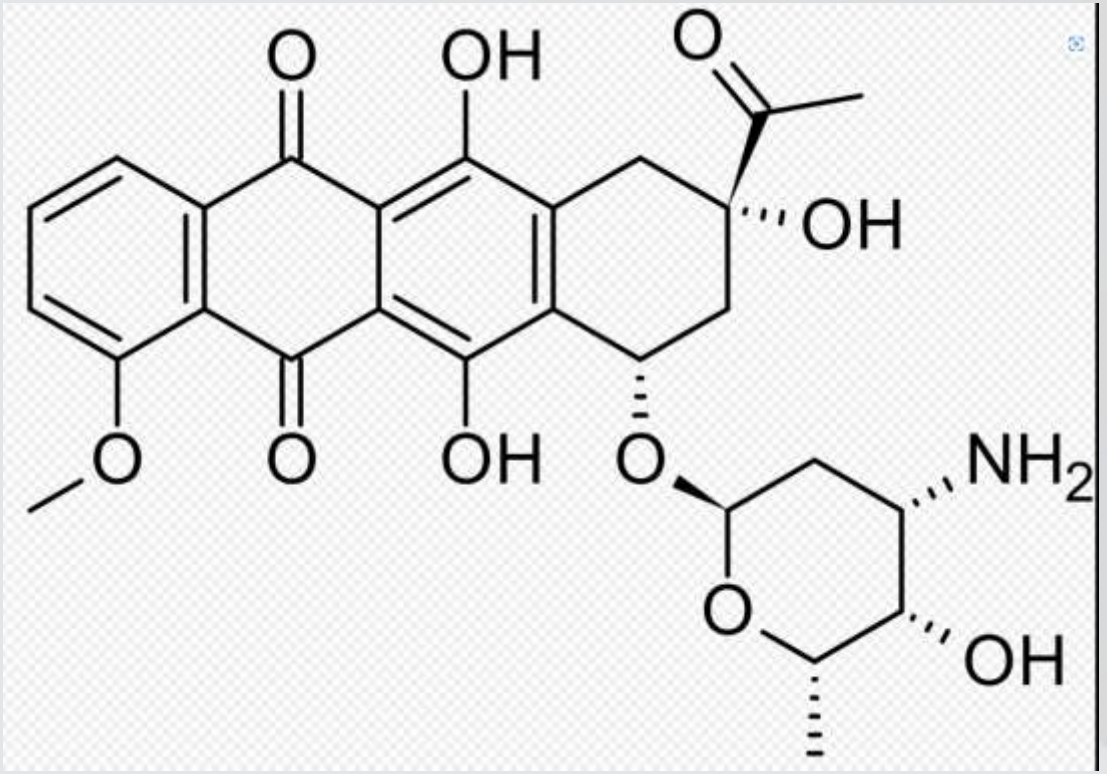
NOTES: ICD is the *International Classification of Diseases*. Circled numbers indicate ranking of conditions as leading causes of death in 2021.
SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data file.

Cancer Therapy



Anthracyclines

- Discovered from fungi, *Streptomyces peucetius*
- Mechanism is Topoisomerase I and II inhibition
  - Inhibition promotes growth arrest and eventually cell death



Anthracyclines

- Used since the 1960s
- Cornerstone for several different therapies still today
- 1976 Dr. Lefrak published a case series on cardiac toxicity and was recognized to be dose-dependent
- Their recommendation was to no more than 550 mg/m²
- This persisted until 2003…

A CLINICOPATHOLOGIC ANALYSIS OF ADRIAMYCIN CARDIOTOXICITY

EDWARD A. LEFRAK, MD,* JAN PIŤHA, MD, PHD,†
SIDNEY ROSENHEIM, MD‡ AND JEFFREY A. GOTTLIEB, MD§

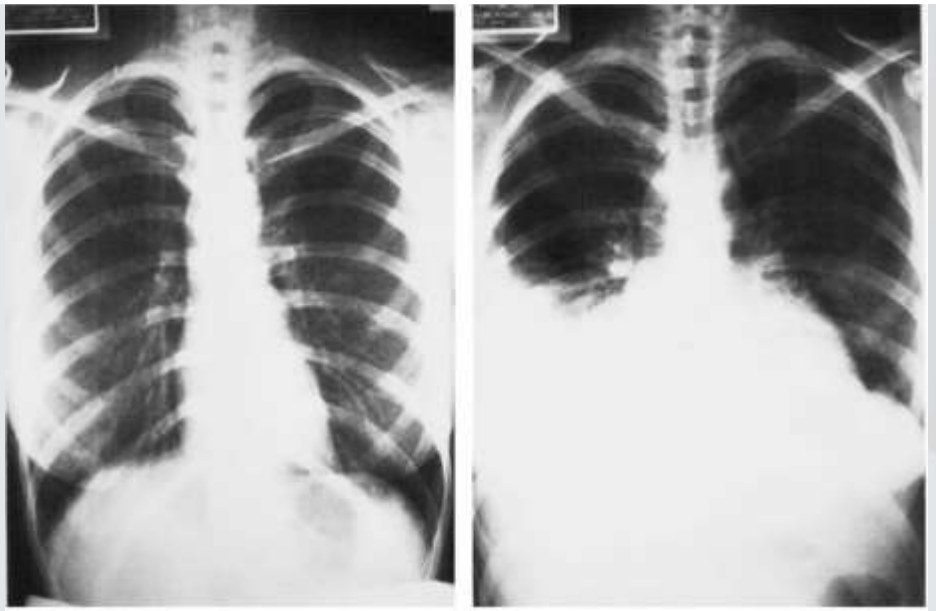


FIG. 1A *(left)*. Normal chest x-ray film during adriamycin therapy (case 1).
FIG. 1B *(right)*. Following 720 mg/m² of adriamycin, the chest roentgenogram revealed increase in the heart size, a large right pleural effusion, and blunting of the left costophrenic angle.

Anthracyclines

- 2003 retrospective study of 603 TTEs of patients who developed heart failure after treatment with doxorubicin for both breast and lung cancer
- Found that recommended dose of 550 mg/m² comprised of 25% of cohort while 400 mg/m² only comprised 5%.
- New recommendation that < 400 mg/m²

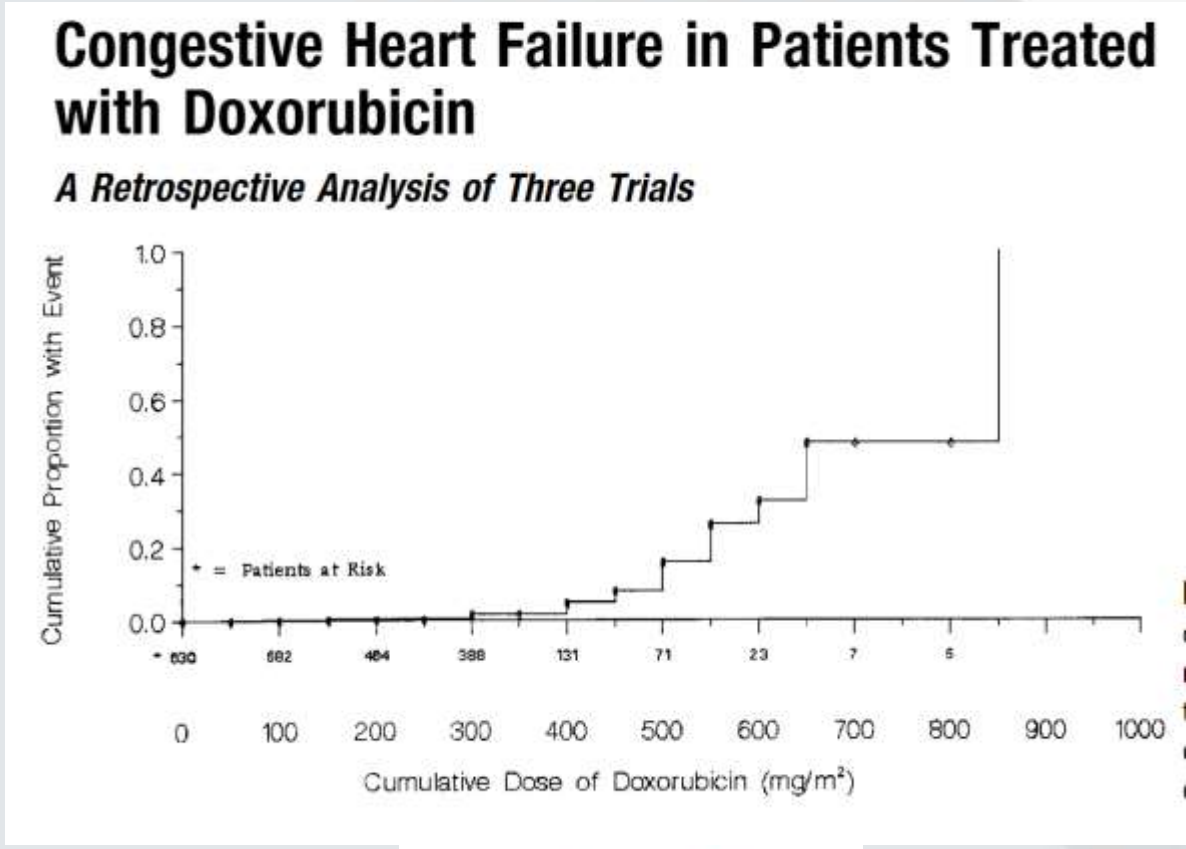
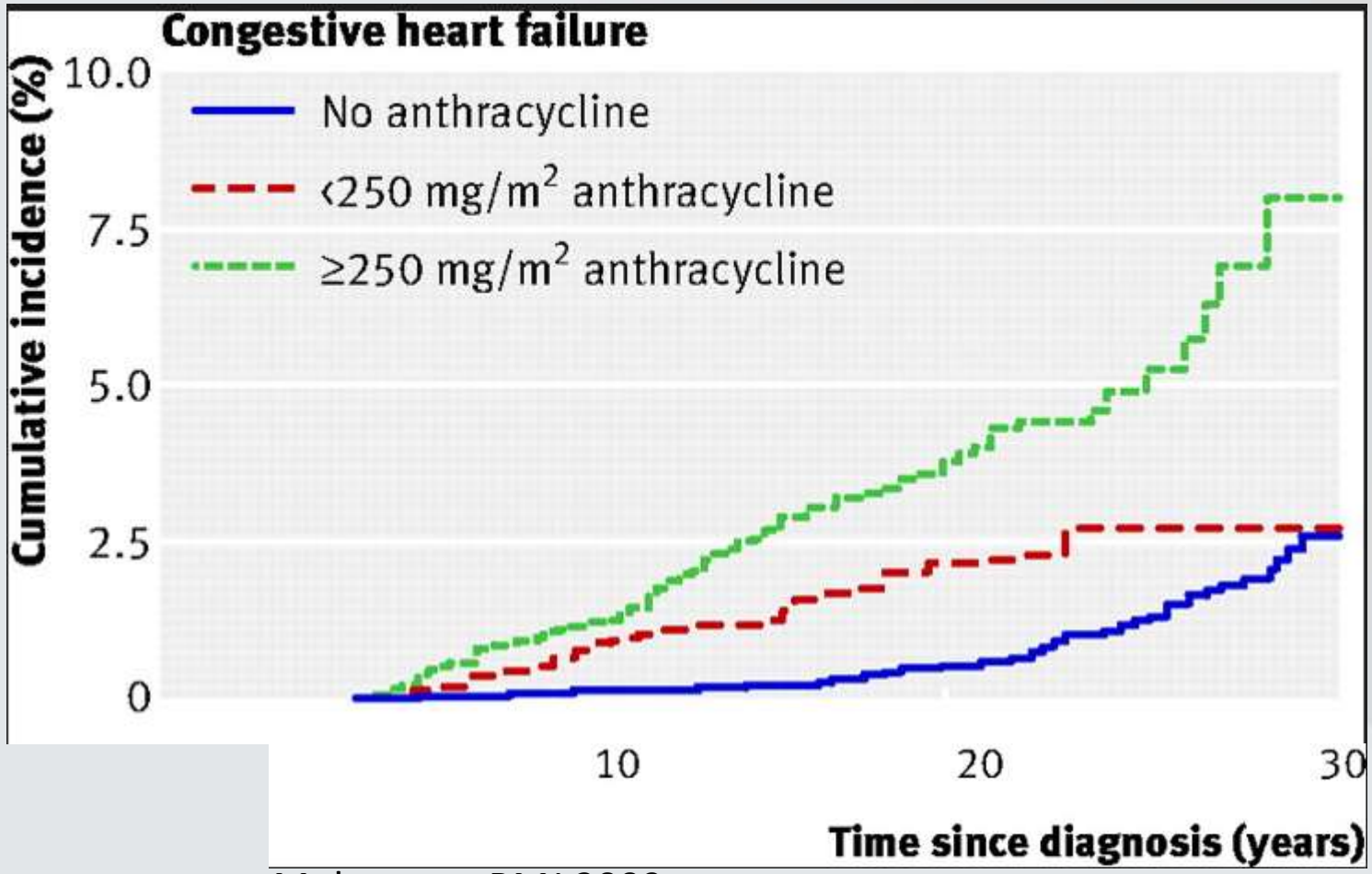


FIGURE 1. Cumulative doxorubicin dose at onset (on study or off study) of doxorubicin-related congestive heart failure in 630 patients who were randomized to receive a doxorubicin-containing regimen plus placebo.

Anthracyclines

- While TTE is more specific than clinical symptoms recognized that if patients continued to be monitored there could also be a time component



Mulrooney, BMJ 2009

Anthracycline damage

- Acute (days)
- Subacute (months)
- Chronic (years)

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

Daniela Cardinale, MD, PhD, FESC; Alessandro Colombo, MD; Giulia Bacchiani, MD; Ines Tedeschi, MSc; Carlo A. Meroni, MD; Fabrizio Veglia, PhD; Maurizio Civelli, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Giuseppe Curigliano, MD, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

- 98% of damage from anthracycline occurs within 1 year
  - Recommended to have TTE done after treatment and 6 months after tx

Cardioprotective Studies

- 2015 Italian study showed improved recovery in patients with anthracycline induced HF who were treated with beta blocker/ACEi or ARB
- PRADA trial (2018): primary prevention of cardiac dysfunction during adjuvant breast cancer therapy with candesartan and metoprolol; slight benefit of candesartan
- PRADA II: trial with ARNI – results pending
- STOP-CA trial: showed benefit of statin therapy with anthracyclines

Mitigating Cardiac toxicity

- Recognition of anthracycline induced cardiotoxicity initiated the need for cardiac care for these patients after recovered from cancer
- As cancer treatments continue to evolve with new therapies many of these also have cardiac side effects/toxicity
- Aging population, many with pre-existing cardiovascular disease are also being diagnosed with cancer
- Development of cardio-oncology

Role of Cardio-Oncologist

- Pre-Cancer
  - CVD Risk assessment, modifiable risk factors, consideration of cardioprotective strategies, monitoring strategies
- Treatment
  - Monitoring, Management of cardiotoxicity
- Post-Treatment
  - Serial monitoring, management of long-term side effects

Cardio-Oncology

- Maximize cancer treatments
- Minimize cardiovascular toxicity
- Improve overall outcomes

- Requires a multi-disciplinary team-based approach with coordination between the patient, oncologist, primary care provider, and cardiologist

Case

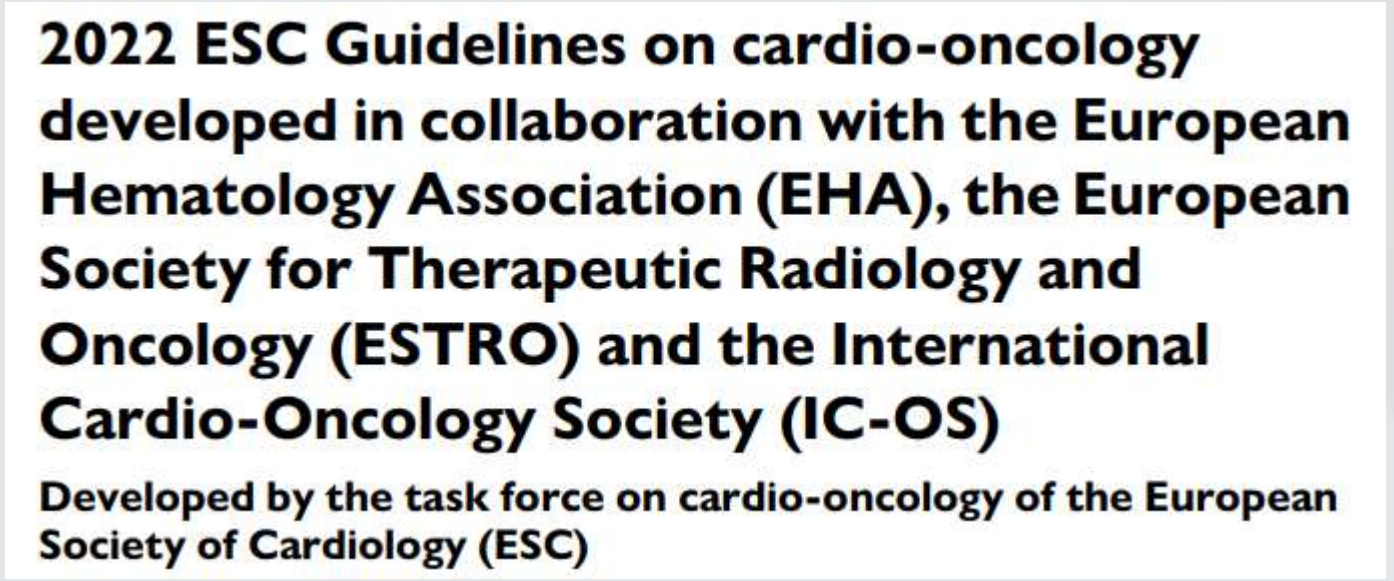
- Patient ultimately listed and underwent transplant.
- He is doing well > 2 years after transplant

Conclusion

- Cardio-oncology

- Thank you!

Get with the Guidelines



- ESC guidelines
  - 133 page document, 837 ref, 272 recommendations

Cardiac Toxicity in Cancer Patients

- Can interrupt or discontinue cancer therapy
- Physical morbidity/mortality with CVD in addition to psychological impact

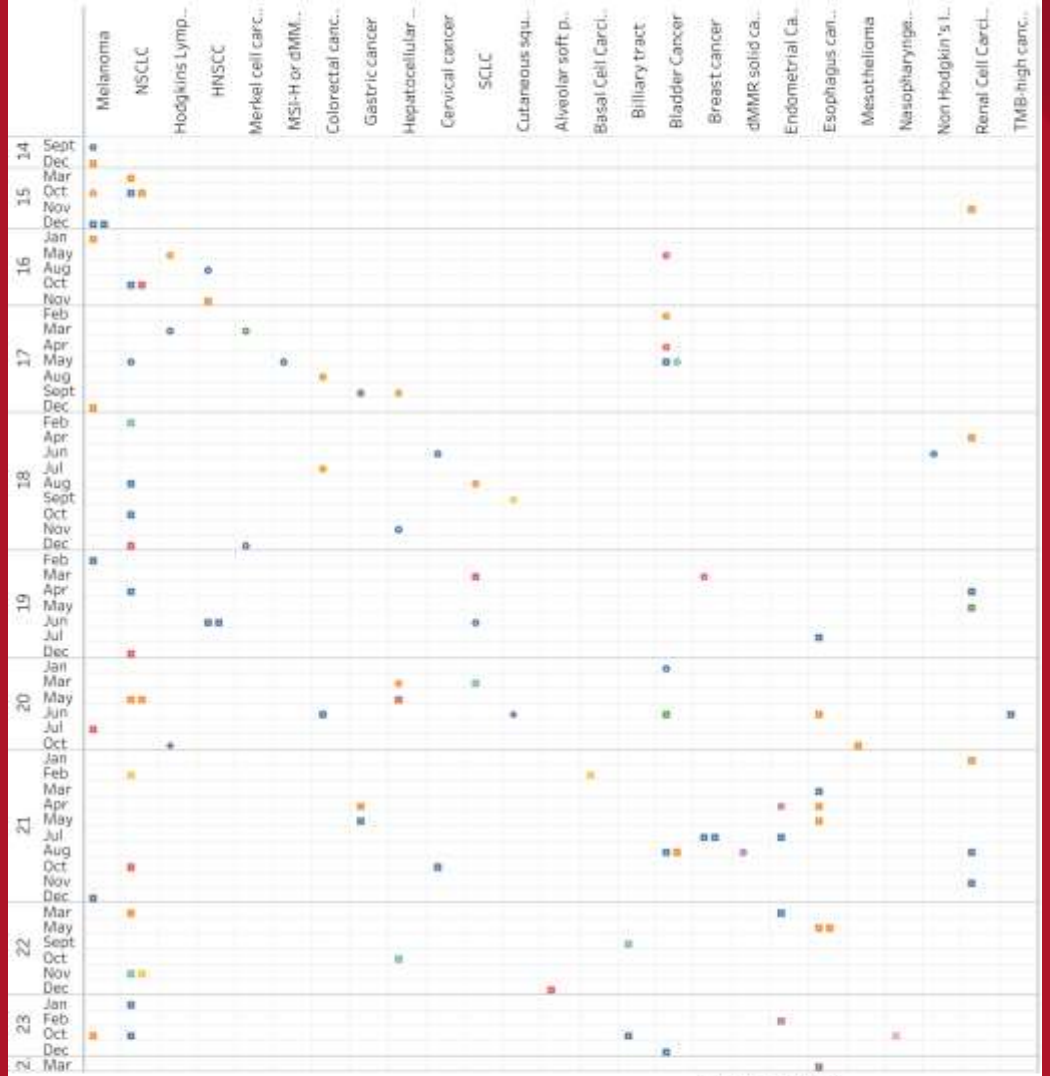
Immunotherapy

- Immune check point inhibitors act to

Timeline of Anti-PD-1/L1 Antibody Approvals by the FDA

Updated March 21, 2024

Sources: CRI, CRI Analytics, and FDA



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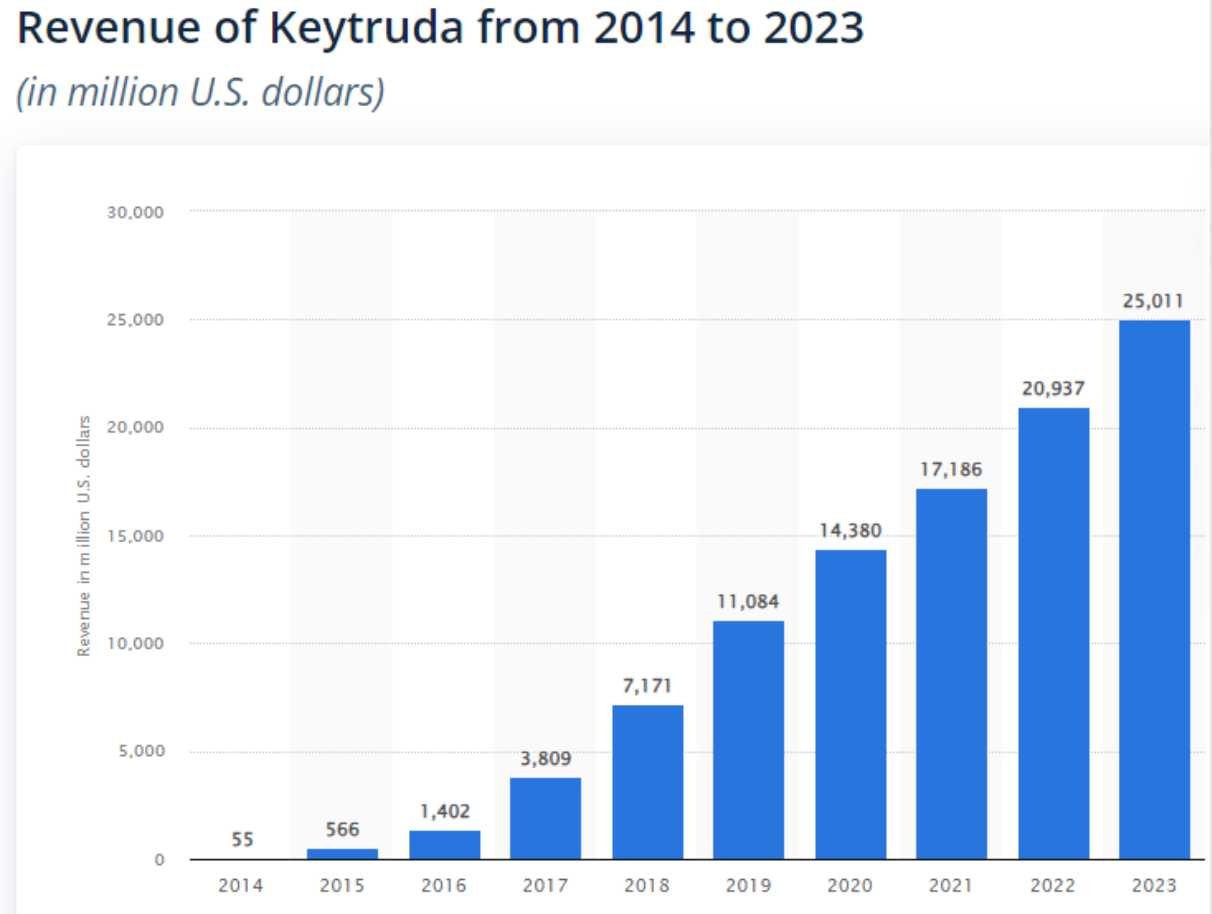
Pembrolizumab



Common Offenders

Therapy	MOA	Study	Population	Intervention	Results
Carvedilol	Antioxidant activity preventing mitochondrial damage	Avila MS. J Am Coll Cardiol. 2018 (CECCY trial)	Anthracycline naïve HER2-negative breast cancer patients due to receive AC-T (N =200)	Carvedilol (C) up to 25 mg BID started before treatment & continued x 6 mos vs. placebo (P)	Carvedilol had no impact on the incidence of early onset of LVEF reduction (14.5% (C) vs. 13.5% (P), P=1.0). However C resulted in a significant reduction in troponin levels and diastolic dysfunction.
Nebivolol	Antioxidant activity and nitric oxide mediated peripheral vasodilation	Kaya. Int J Cardiol. 2013	Breast cancer patients receiving AC or CEF (N = 45)	Nebivolol (N) 5 mg daily started 1 week before treatment & continued x 6mos vs. placebo (P)	LVEF preserved in treatment group but not placebo group at 6 months N: LVEF 65.6% -> 63.8% P: LVEF 66.6% -> 57.5% (P = 0.01)
Enalapril	Free radical scavenger and RAS inhibition	Cardinale. Circulation. 2006	Patients with troponin I > 0.07 after high dose chemo (N = 114)	Targeted enalapril (E) 20 mg/day 1 month after chemo & continued x 1 yr	LVEF preserved in treatment group but not placebo group at 1 year E: LVEF 61.9% -> 62.4% P: LVEF 62.8% -> 48.3%
		Cardinale. Eur J Cancer. 2018 (ICOS-ONE)	Patients at 21 Italian hospitals on anthracyclines (N = 273) – 88% women with 76% havin breast cancer	To see if timing of when enalapril (E) up to 10 mg BID x 1 year is started makes an impact (before troponin elevation or once elevation was seen) and evaluation of serial troponin monitoring	The incidence of troponin elevation was 23% in the prevention and 26% in the troponin-triggered group (p = 0.50). Consider a troponin-triggered strategy to initiate treatment with E to minimize cardiotoxicity.
Valsartan	RAS inhibition	Nakamae. Cancer. 2005	Untreated NHL due for CHOP (N=40)	Randomized to 80 mg/day valsartan (V) or placebo (P)	CHOP induced increases in the LVEDD, QTc interval/dispersion, and in brain/ atrial natriuretic peptides. Significantly prevented all these changes except for the elevation in atrial natriuretic peptide

Historical development of cancer therapies

- **1949** first FDA approved chemotherapy was mustard gas for the treatment of Hodgkin lymphoma
- **1950** 5-FU developed as chemotherapy for colorectal cancer
- **1960** development of combination regimens for lymphomas
- **1974** doxorubicin is found to be active against breast cancer
- **1990** development of targeted therapies including trastuzumab
- **2000** development of immunotherapy
- **2017** first use of CAR-T therapy

Hypertension from chemotherapy