

THE HISTORY OF CANCER: FROM HALSTED'S RADICAL SURGERY TO TARGETED THERAPIES

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THE IMPACT OF CANCER IN U.S.

- 1/3 women and half of men will develop cancer
- In 2018, 600,000 will die of cancer
- 25% of all deaths are due to cancer

- *(CNN) September 12, 2018*
 - By the end of the century, cancer will be the No. 1 killer globally
 - WHO [International Agency for Research on Cancer](#).

CANCER
WHERE WE HAVE BEEN;
WHERE WE ARE;
WHERE WE ARE GOING

Karkinos: from Greek work for 'crab'

Onkos: Greek term for a mass or a burden

CANCER: WHERE WE STARTED

- **400 BC- Hippocrates :**
 - Cancer “best left untreated, since patients live longer that way”
- **130 A.D- Galen :** “Excess of black bile causes cancers”
 - Bleeding and purging rituals
 - Unchallenged for over 1300 years
- **1761- Giovanni Morgagni:** Autopsies relate illness to pathologic findings
- **1761: John Hill** published “Cautions against the Immoderate Use of Snuff”
 - Lip, mouth, and throat cancer
- **1761: Percival Pott**

WHAT CAUSES CANCER?



1761: Percival Pott noted a marked rise in scrotal cancer in chimney sweeps in London

- ✓ Orphan boys starting age 4-5
- ✓ Irritation from chimney soot
- ✓ First to identify cause and effect

1875: Child labor laws

- ✓ Cancer incidence disappeared

WHAT CAUSES CANCER?

- 1914: Francis Carter Wood:
“We have learned nothing, therefore, about the real cause of cancer or its actual nature. We are where the Greeks were.”
- 1915: Cancer produced by applying coal tar to rabbit skin
- 1918: Sarcoma in chickens caused by a virus
- 1950s: Occupational
- 1950: “Smoking and Carcinoma of the Lung; Preliminary Report”
- 1992: BRCA 1 and 2 genes identified
- Ongoing: ? Obesity, exercise, diet, supplements

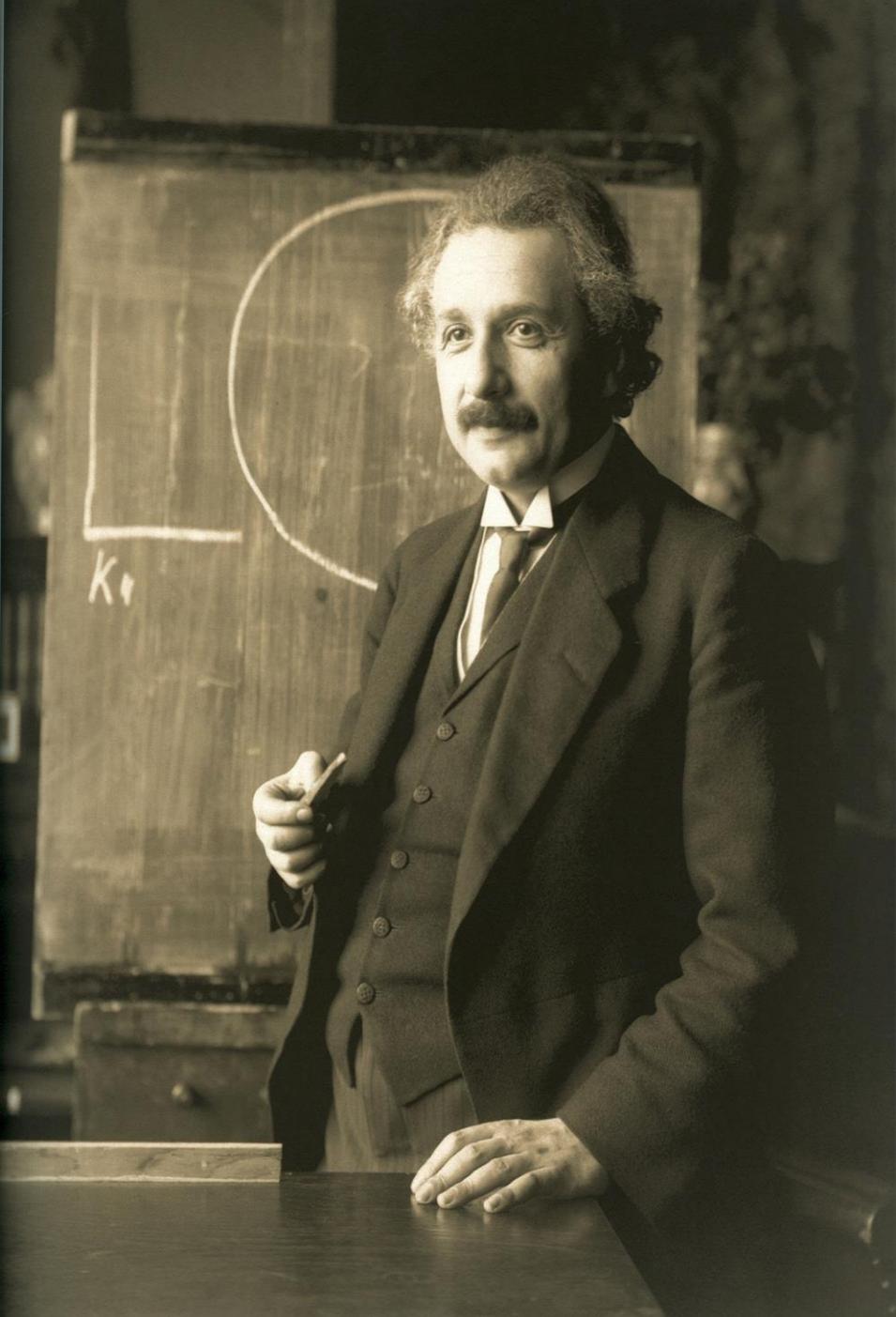
THE EVOLUTION OF CANCER CARE

Surgery

Chemotherapy

Radiation





"Imagination is more important than knowledge. For knowledge is limited, whereas **imagination** embraces the entire world, stimulating progress, giving birth to evolution."

ALBERT EINSTEIN

CANCER TREATMENT: SURGERY



- “A chance to cut is a chance to cure.”
- “Heal with steel.”

AMBROISE PARE (1510-1590)



- French barber surgeon
- “Je le pansai, Dieu le guerit”
(I bandaged him and God healed him)
- Introduced ligating arteries in amputations
(instead of cauterization with red-hot iron)
- 1572: As a Huguenot, his life was saved during St Bartholomew’s Day Massacre when King Charles IX locked him in a clothes closet.

ANESTHESIA: NO MORE SURGERY=PAIN

1846

First public display of general anesthesia

Dr. William Morton

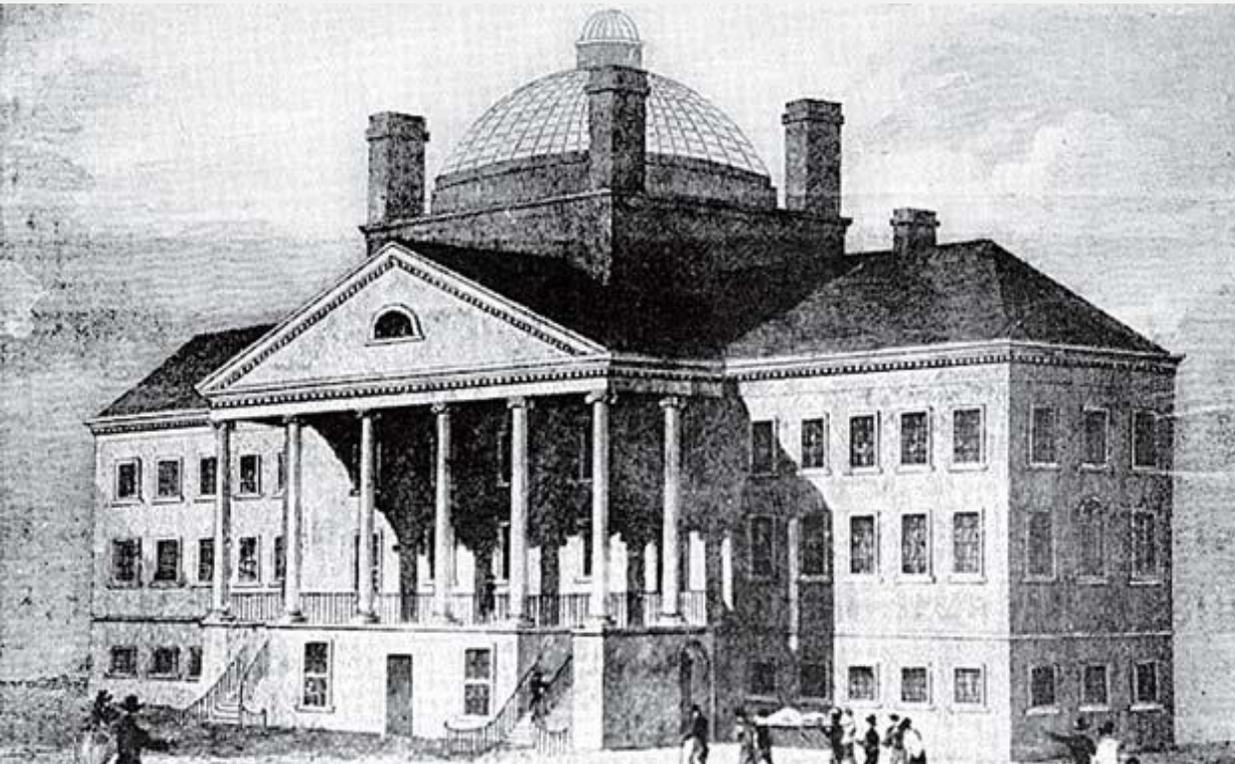
“The Ether Dome”

Massachusetts General Hospital



MGH: Built in 1811, designed by Charles Bulfinch

ETHER DOME: Operating room from 1821-1867



MASSACHUSETTS GENERAL HOSPITAL TODAY





THEODOR BILLROTH (1829-1894)



Austrian surgeon

Father of abdominal surgery

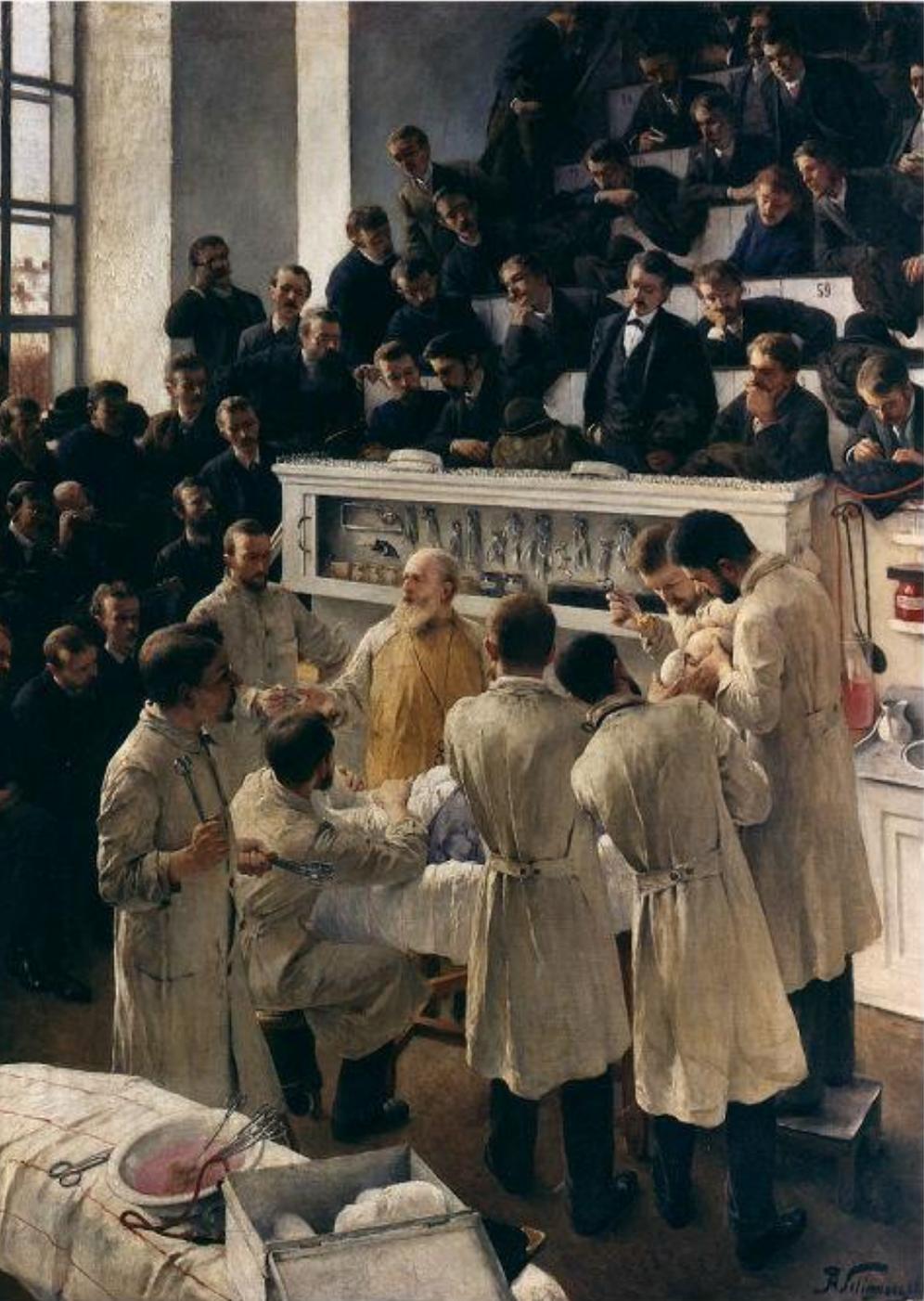
Firsts:

1855: First to resect rectal cancer

1872: First esophagectomy

1873: First laryngectomy

1881: First gastrectomy for cancer



THEODOR BILLROTH

"It is one of the superficialities of our time to see in science and in art two opposites. **Imagination** is the mother of both."

THEODOR BILLROTH



Introduced sharing information:

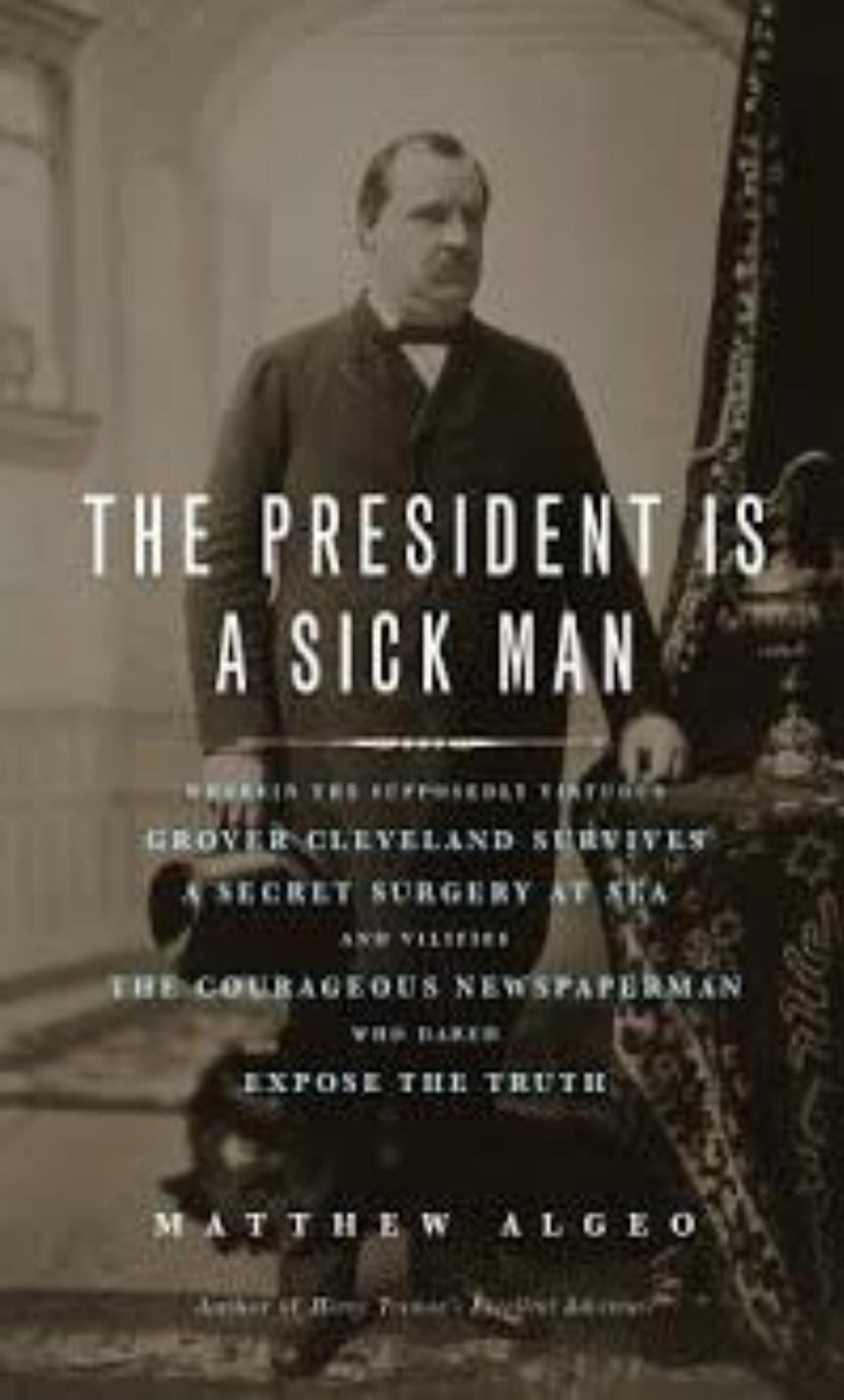
- Patient selection, surgical techniques
- Discussion of mortality and morbidity
- Publish all results



Statistics are like women; mirrors of purest virtue and truth, or like whores to use as one pleases.

(Theodor Billroth)

PRESIDENT GROVER CLEVELAND (1837-1908)



THE PRESIDENT IS A SICK MAN

- July 1, 1893, he boarded a friend's yacht
- Then not seen for 5 days.
- Secretly, doctors removed a cancerous tumor from his upper jaw.
- Truth revealed 24 years later.
- Most memorable quote: "Tell the truth."
- 2011 book is first full account of events.

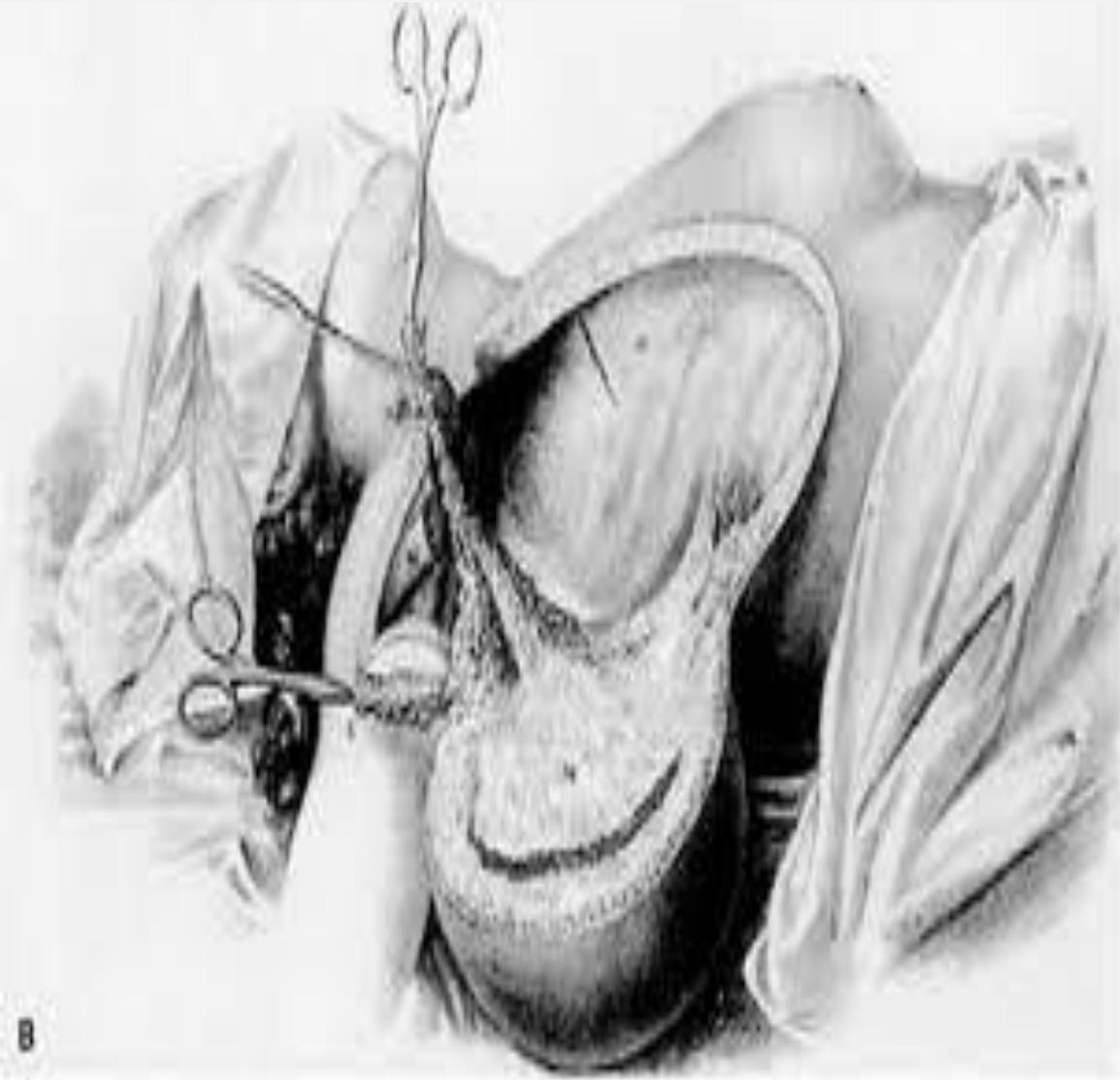
**DR. WILLIAM
HALSTED
(1852-1922)**



“Father of Modern Surgery”

- Firsts:
 - Began first modern surgical residency
 - Temperature charts on medical records
 - Emergency blood transfusion (on his sister) and one of first gallstone surgeries (on his mother)
 - Use of cocaine for local and spinal anesthesia
 - Use of rubber gloves in surgery

DR. WILLIAM HALSTED: RADICAL MASTECTOMY “AVOID MISTAKEN KINDNESS”



Initial series:

- Large wounds healed by granulation
- All patients had lymphedema, restricted arm movement
- Chronic pain

Eventually, he was first to promote
“safe surgery”

WILLIAM HALSTED'S RADICAL MASTECTOMY:

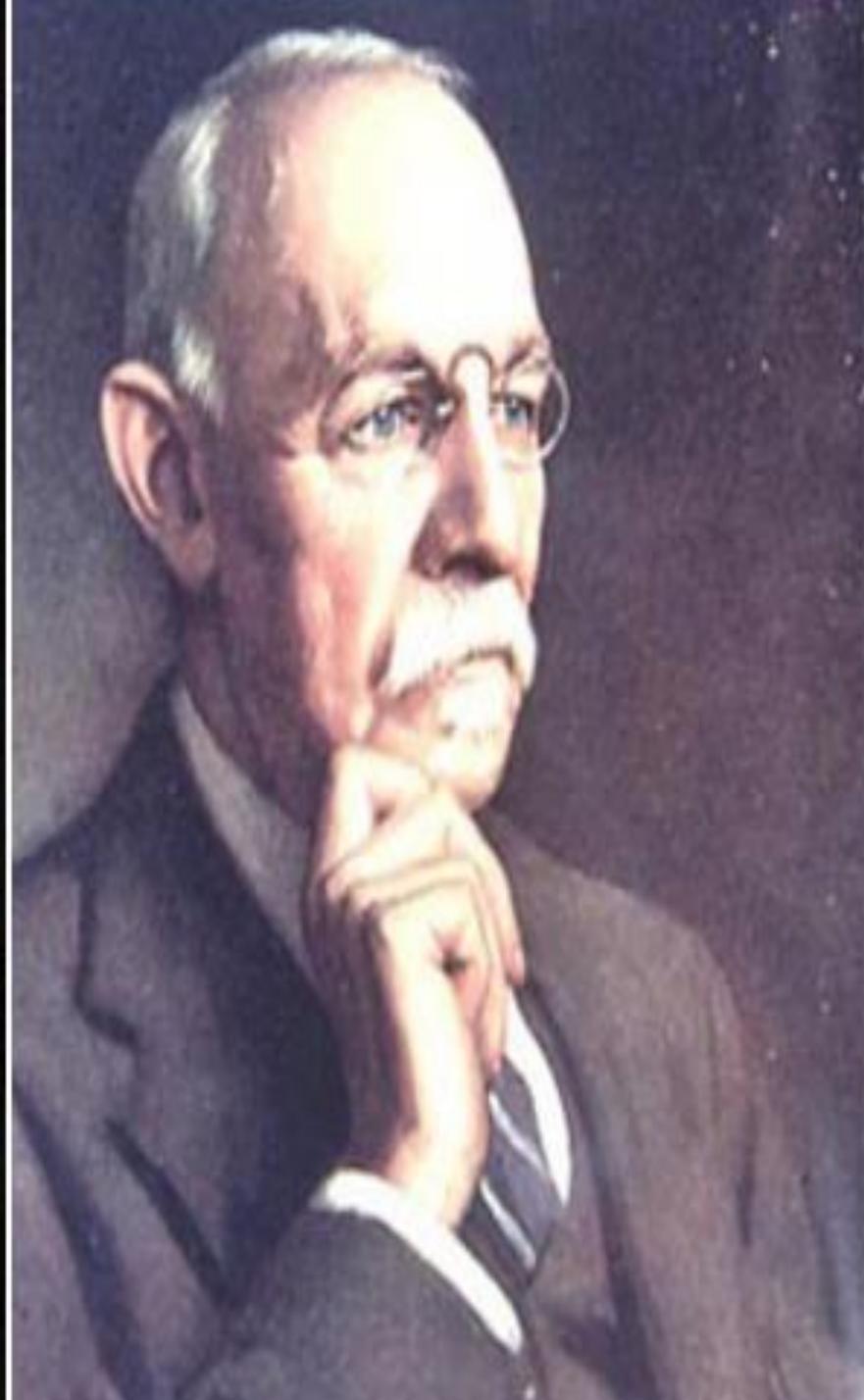
Johns Hopkins Hospital

1896: Reported on 50 patients:

- 3-year chest recurrence of 20%
- No surgical deaths
- 5-year survival of 40%



Dr. Halsted's First Operation in the New Surgical Amphitheatre in 1904



The only weapon with which the
unconscious patient can
immediately retaliate upon the
incompetent surgeon is
hemorrhage.

— *William Stewart Halsted* —

**“Diseases desperate grown
By desperate appliance are relieved,
Or not at all”**

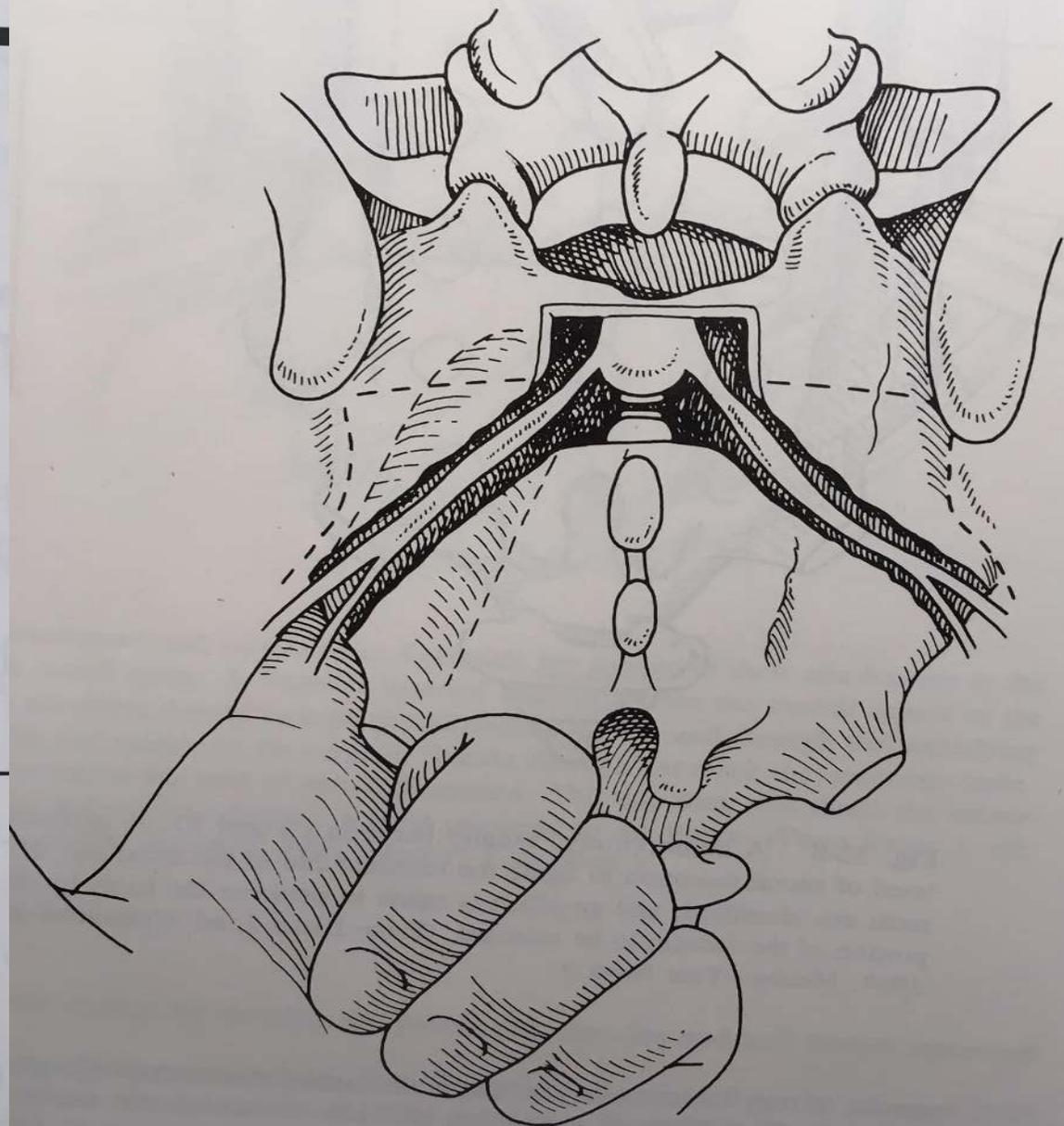
WILLIAM SHAKESPEARE
HAMLET ACT 4, SCENE 3 (CLAUDIUS

CHAPTER 32

Resection of Pelvic Recurrence

PETER S. TURK

HAROLD J. WANEBO



AVOIDING MISTAKEN KINDNESS

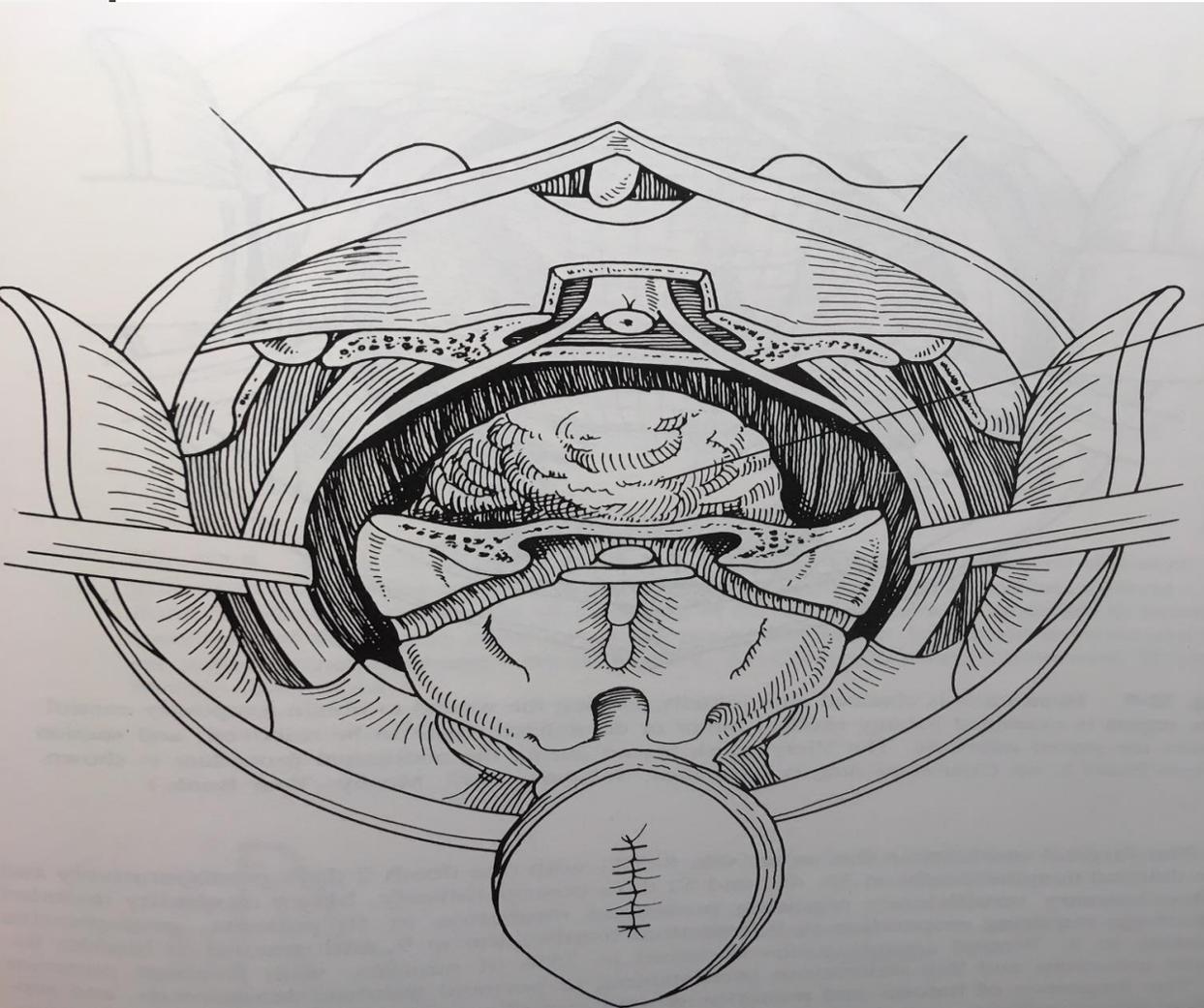


Fig. 32-7 The sacrum, pelvic sidewalls, and tumor are removed en bloc, along with the indicated. (From Bauer J, ed: *Colorectal* s

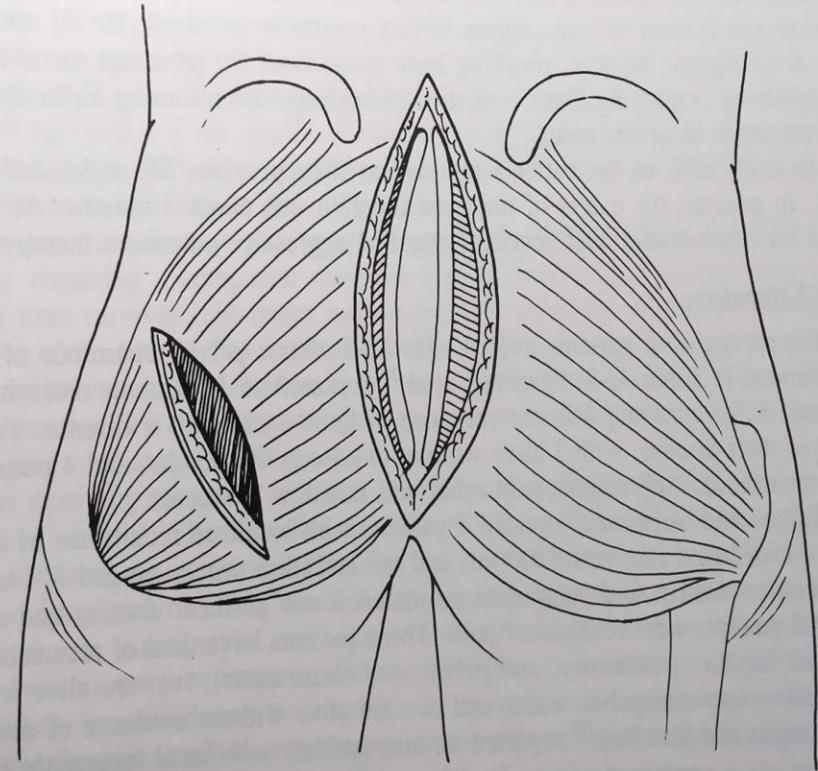


Fig. 32-9 If the fascial origin of the gluteus maximus has been preserved or if there is adequate muscle close to midline, the muscles are approximated to midline, forming a new pelvic

CANCER TREATMENT: CHEMOTHERAPY



CANCER TREATMENT: CHEMOTHERAPY

1600s: physician Gideon Harvey called chemists “the most impudent, ignorant, flatulent, fleshy and vainly boasting sort of mankind.”

1917: soldiers exposed to mustard gas had bone marrow failure

- Banned by Geneva Protocol, 1925

1942: Goodman and Gilman, at Yale Medical School

- First used nitrogen mustard against lymphoma

1937: Lucy Willis in India identified the vitamin folic acid.

- Infusion could restore normal blood cells in vitamin-deficiency

1947: Sidney Farber used anti-folate on acute leukemia in children

DR. SIDNEY FARBER



Trained in medicine in Heidelberg and Freiburg, Harvard

1929: First full-time pathologist at Children's Hospital,
Boston

1946: inspired to focus on most hopeless diagnosis:

Childhood leukemia: "it could be measured"

He injected patients with folic acid...

hastening their deaths

1947: new version of antifolate Aminopterin - blocking
chemical reaction needed for DNA replication

- First chemotherapy to prove effective in cancer
- Initial reaction: disbelief and resistance

FARBER'S FIRST LAB: THE BASEMENT





“It has been said the purpose of life is to spend it on something that outlives you.

No man finds his ultimate end in himself, but does so by sharing with others.”

SIDNEY FARBER, MD

Isolated Pelvic Perfusion for Unresectable Cancer Using a Balloon Occlusion Technique

Peter S. Turk, MD; James F. Belliveau, PhD; James W. Darnowski, PhD; Marc C. Weinberg, MD; Luke Leenen, MD, PhD; Harold J. Wanebo, MD

Previously irradiated recurrent pelvic malignancy is refractory to most treatment modalities. Ten patients with local recurrences (six with rectal cancer; three, anal cancer; one, anorectal melanoma) were treated with a total of 12 courses of isolated pelvic perfusion chemotherapy (12 multiple agents) using standard hemodialysis technology. Aortic and inferior vena caval occlusion was maintained via transfemoral balloon catheters, with a single intraperitoneal balloon disruption. Mean pelvic-systemic drug concentration ratios were 9.8:1 for fluorouracil, 4.8:1 for cisplatin, and 4.4:1 for mitomycin C. Results were three partial responses (two patients subsequently underwent resection) and three minor responses, all in patients with a visible primary tumor. Pelvic pain was relieved in six of eight symptomatic patients (mean duration, 4 months). Using limited access,

treatment of the primary tumor, is effective as shown for palliation in most cases. Nevertheless, most patients survive these palliative efforts and die of local progressive disease, with uncontrolled pain, tenesmus, or a frequent hospital discharge related to an externally draining abscess rather than of systemic metastases.

Regional pelvic chemotherapy by means of isolated perfusion for unresectable malignant neoplasms was first described by Creech et al⁴ in 1959, and the technique has been modified by several authors.⁵⁻⁷ Despite various innovations, with significant response rates, isolated perfusion has not seen widespread use owing to technical complexity. Recently, Wile and Smolin⁵ described treatment of 27 patients with refractory pelvic cancer using hyperthermic pelvic isolation-perfusion of

†Five minutes after infusion
 ‡Extrapolated for time 0 minutes, intravenous bolus 20-117 mg
 §Extrapolated for time 0 minutes, intravenous bolus 10 mg/m².³⁰

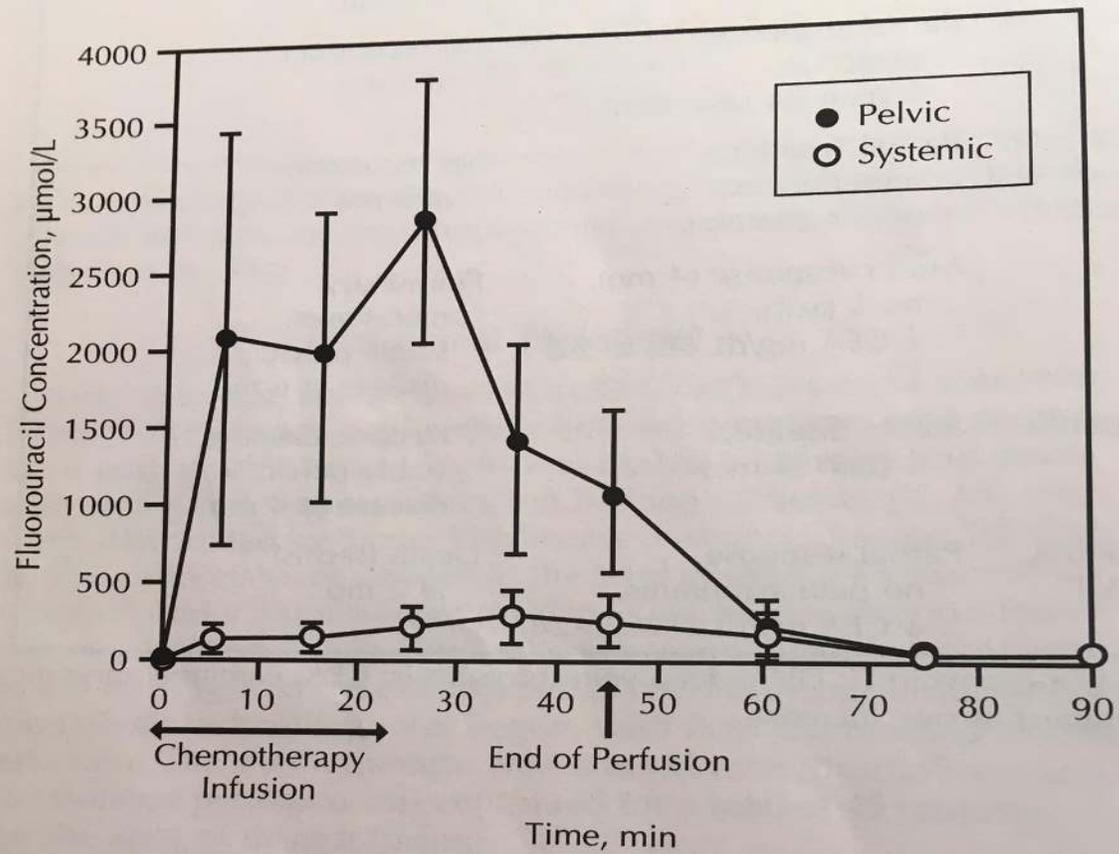


Fig 3.—Fluorouracil mean concentration (\pm SD) over time during isolated pelvic perfusion (12 courses included, 1100 to 2000 mg/m²).

three patients, a minor response. Patient 6, who presented with a massive bilateral inguinal recurrence from anorectal melanoma, had a partial response after two multiple-agent perfusions, with pathologic regression of the inguinal adenopathy (although disease persisted in the iliac nodes on microscopic examination), allowing for surgical resection. Patient 7 presented with painful

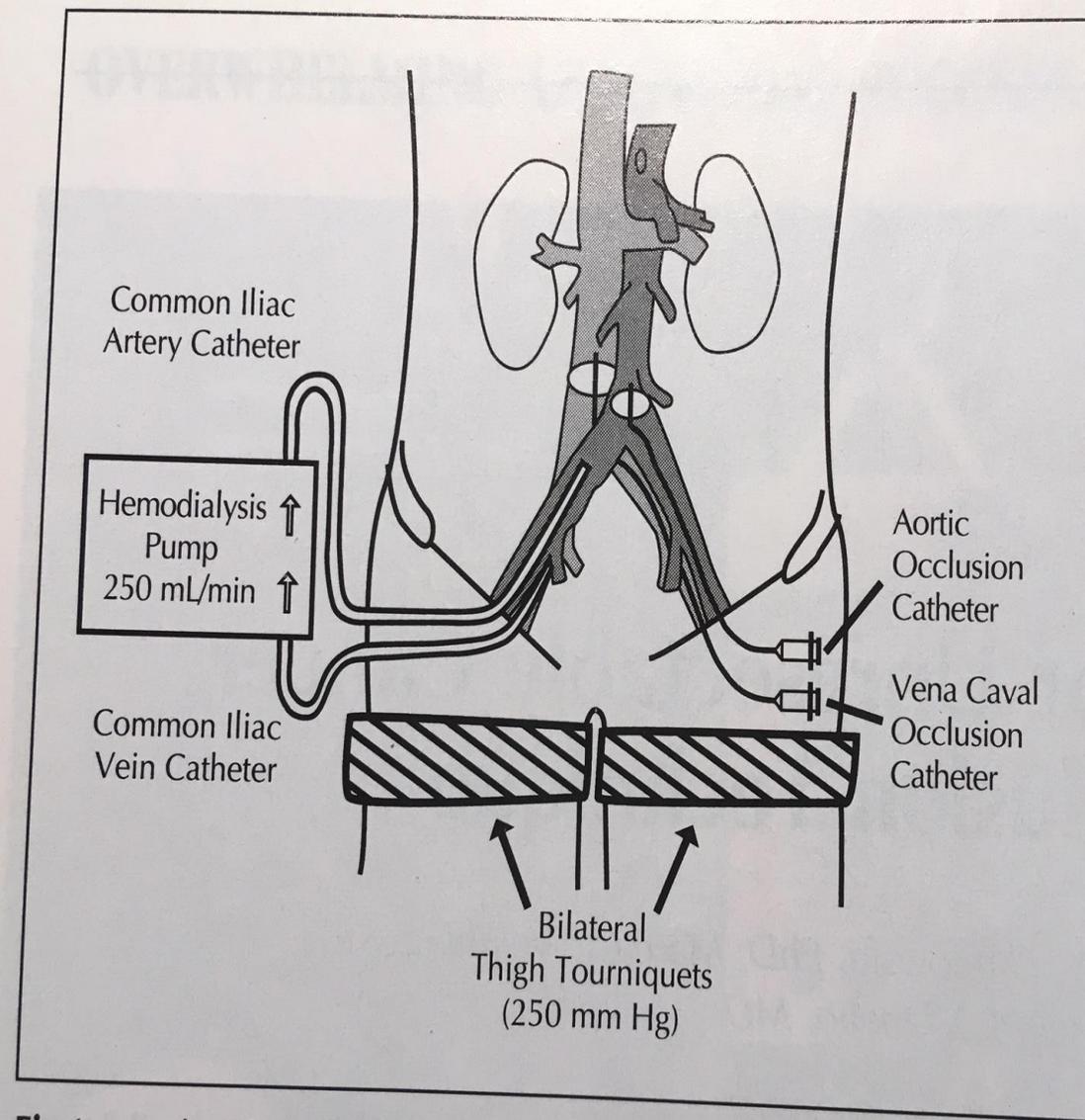


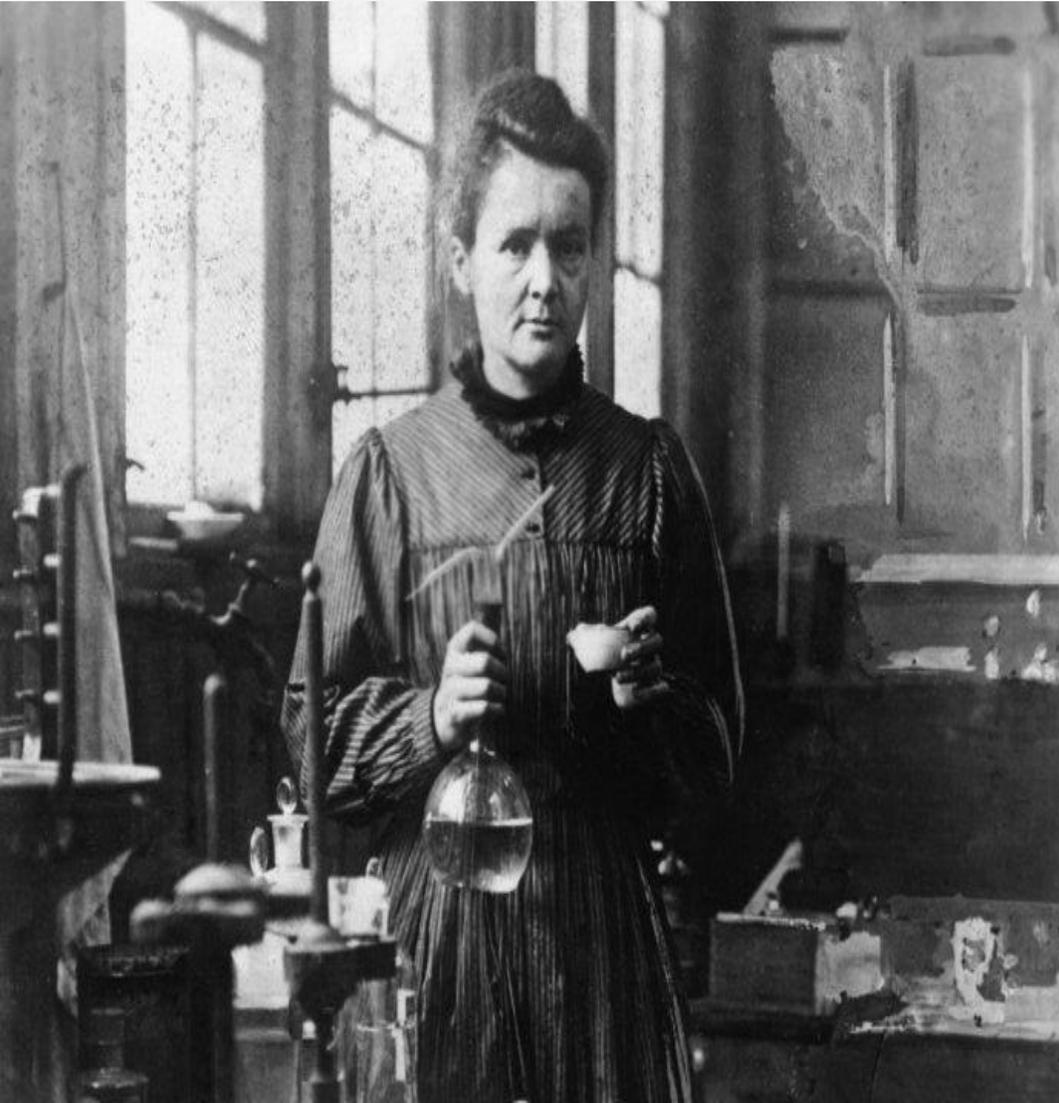
Fig 1.—Isolated pelvic perfusion incorporating transfemoral access and vascular isolation, and the extracorporeal circuit using standard hemodialysis technology.

CANCER TREATMENT: RADIATION



DANGER
RADIATION

MARIE CURIE (1867-1934)



Developed theory of radioactivity

Developed techniques for isolating isotopes

Discovered two elements (Polonium, Radium)

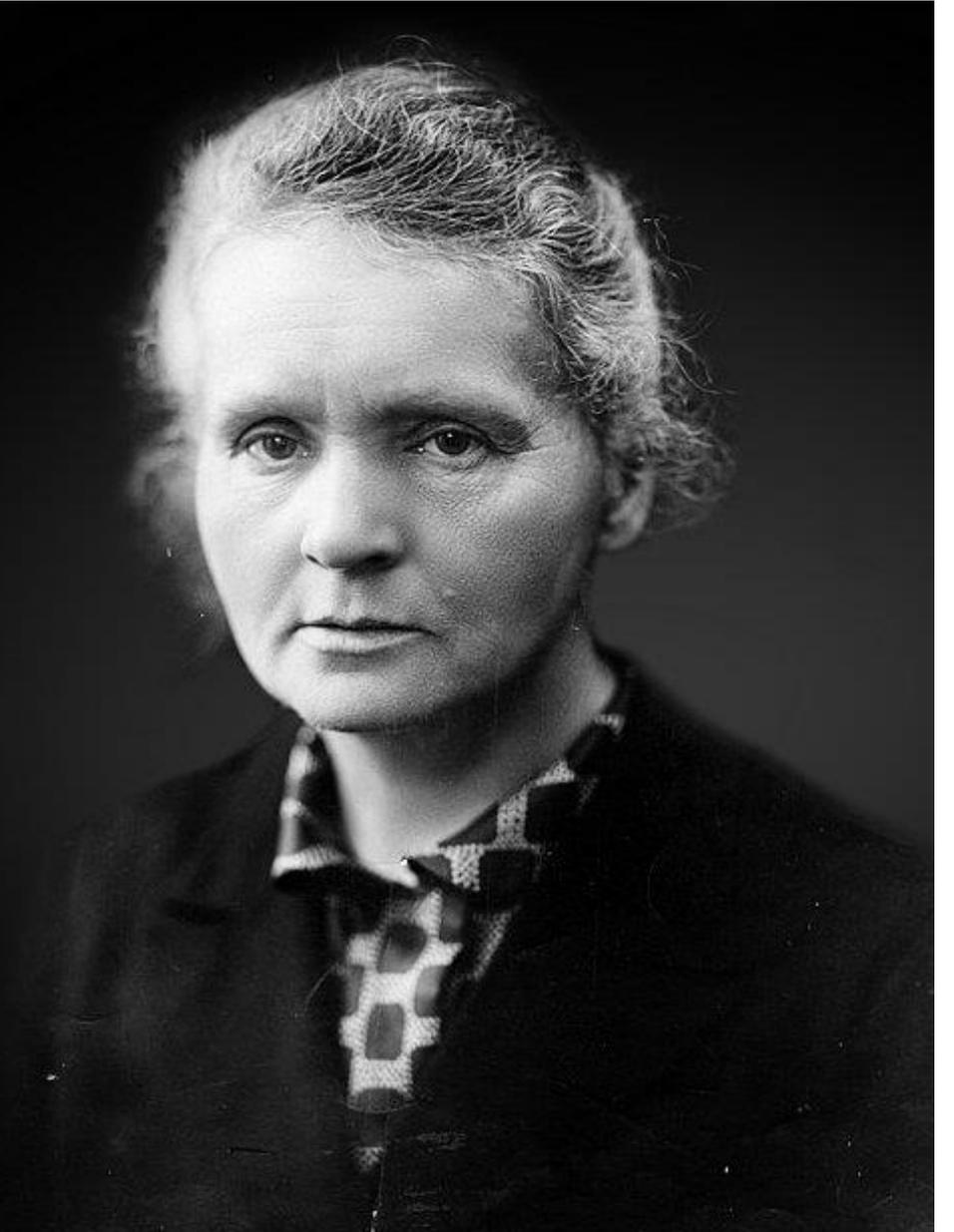
First woman to win Nobel Prize

- Only person to win in 2 sciences
- Curie family legacy: 5 Nobel Prizes

Died of aplastic anemia from radiation exposure

Nothing in life is to be feared,
it is only to be understood.
Now is the time to understand
more, so that **we may fear less.**

– *Marie Curie*



CANCER TREATMENT: RADIATION

- 1900: first used to treat cancer
- Soon discovered it could cause cancer
- Current methods:
 - Conformal radiation therapy (CRT)
 - Intensity-modulated radiation therapy (IMRT)
 - Gamma Knife
 - Intraoperative radiation



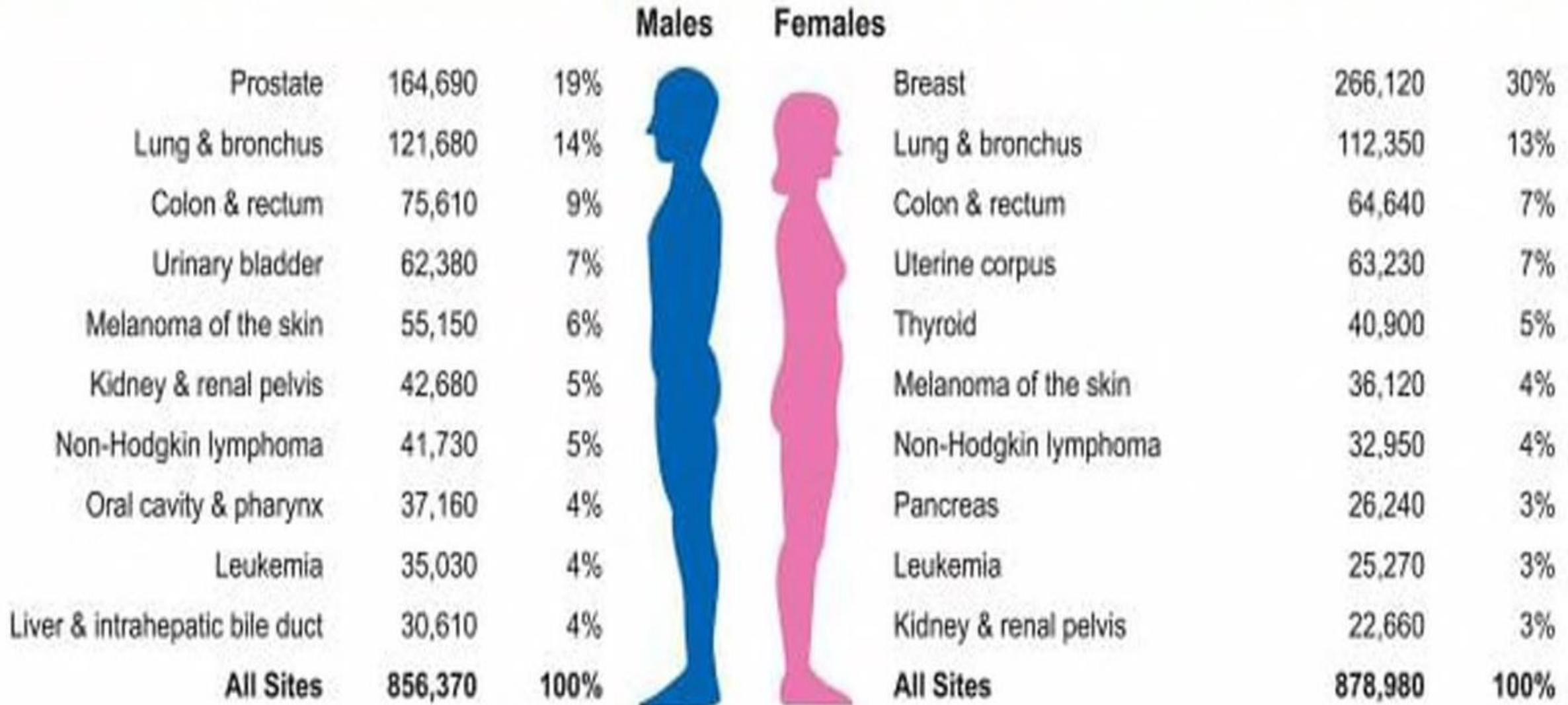
BREAST CANCER

PANCREAS CANCER

MELANOMA

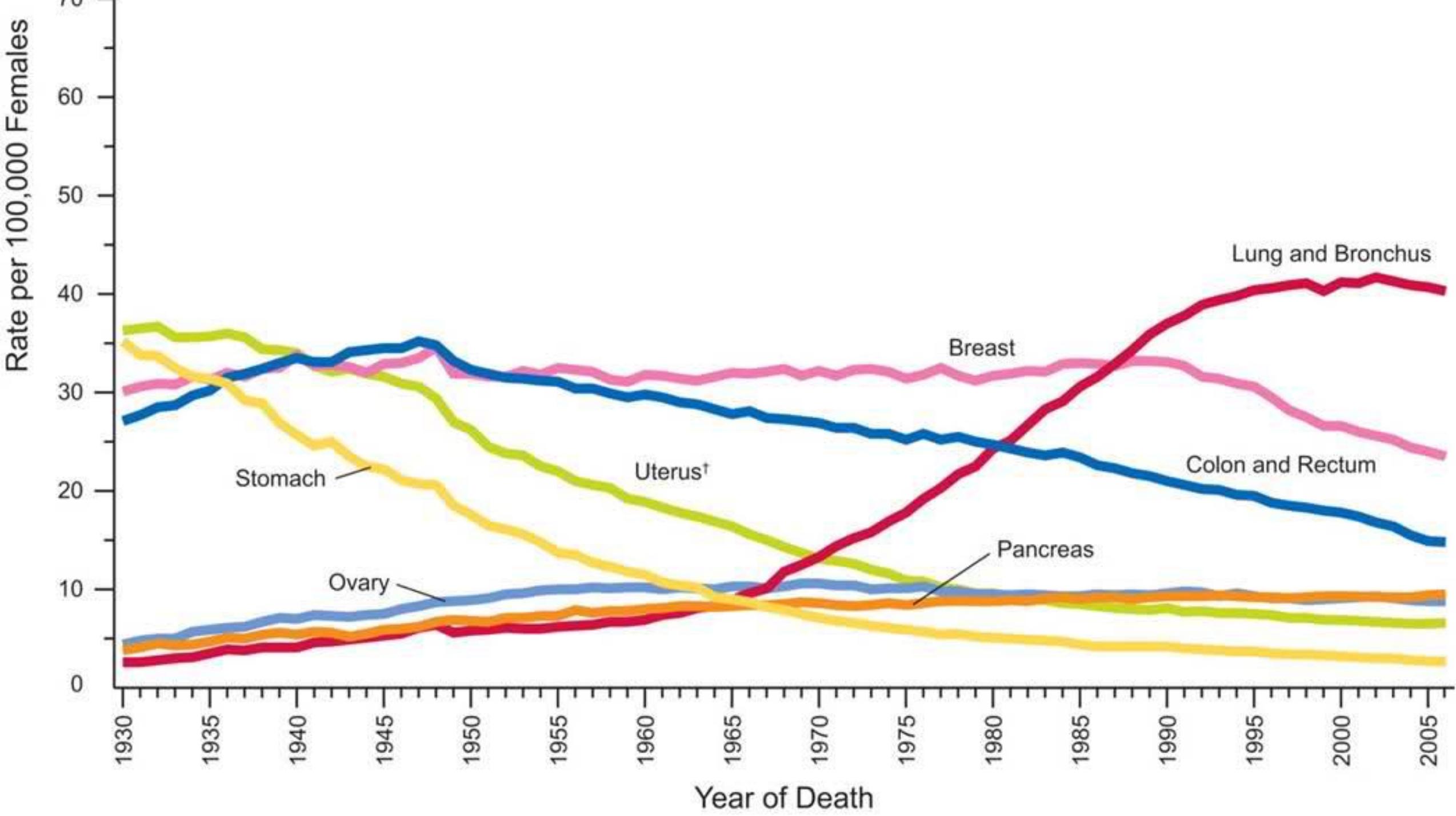
CANCER INCIDENCE IN US, 2018

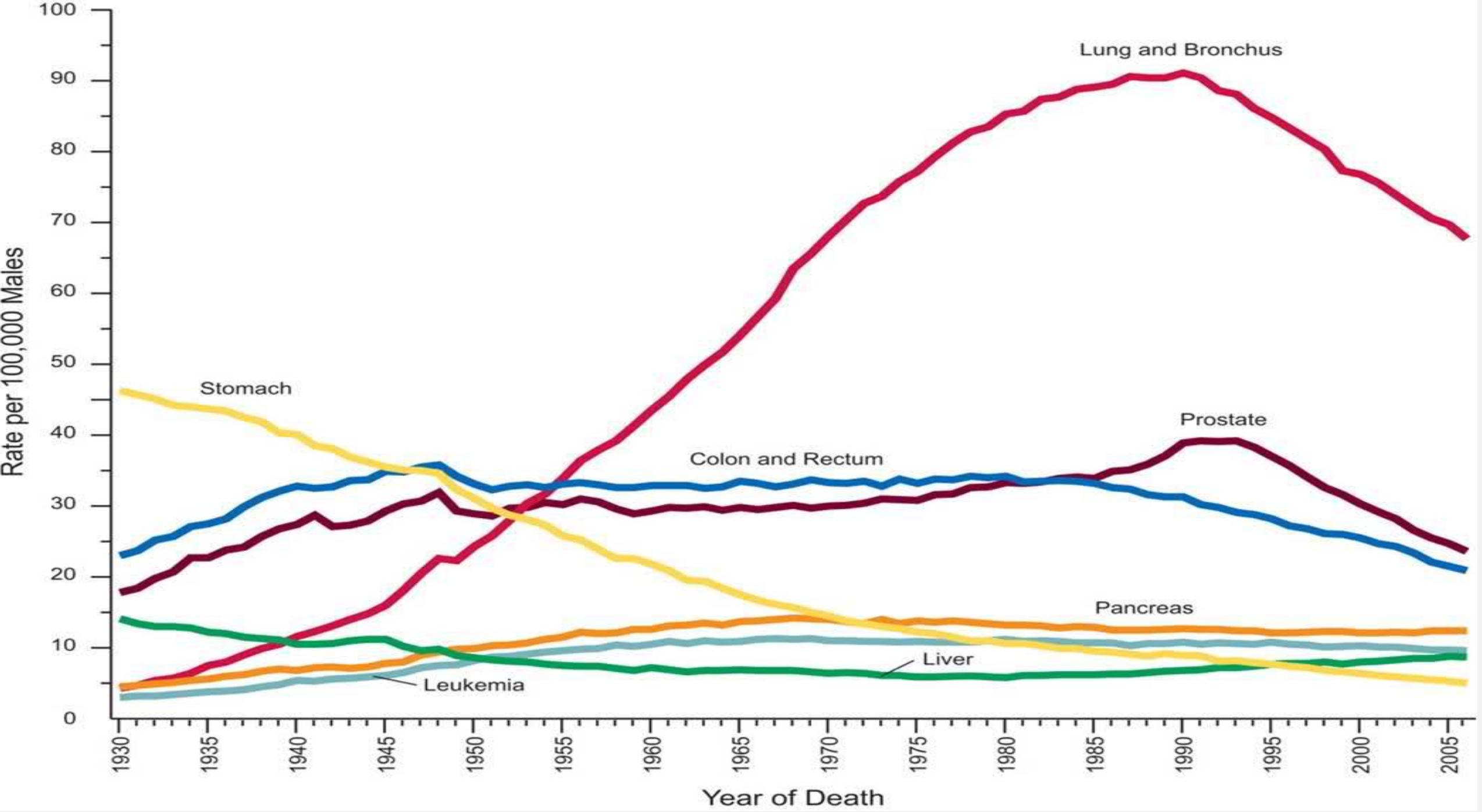
Estimated New Cases



MORTALITY TRENDS

- **Lung, colorectal, breast, and prostate cancer:**
 - Nearly half of all cancer deaths
 - Decreased 36% between 1991-2015
- **Stomach cancer:**
 - Since 1930, death rate has gone from 40 → 3 per 100,000
- **Pancreatic cancer:**
 - Death rate is stable over last 40 years: 11 per 100,000



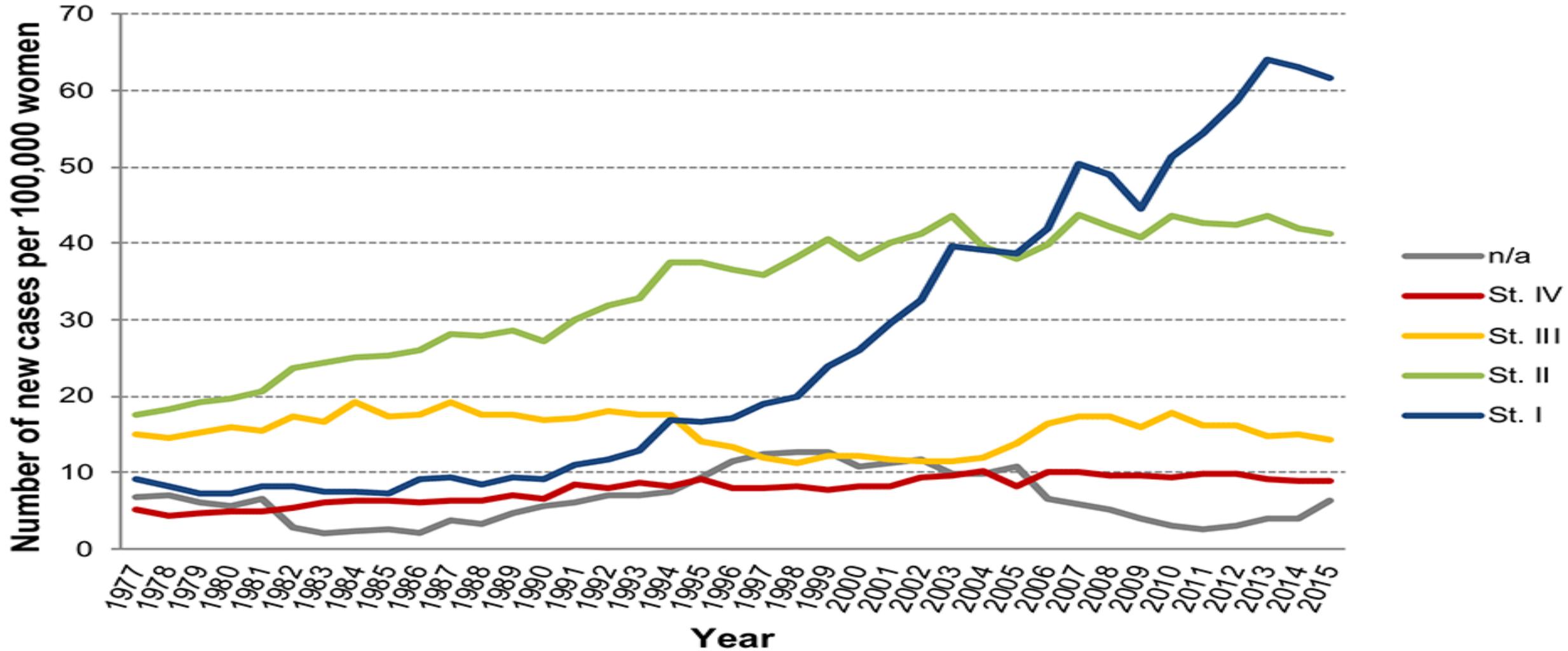


EVOLUTION OF BREAST CANCER TREATMENT

- 1896: Radical mastectomy
- 1930: Radiotherapy added
- 1937: Ultra-radical mastectomy
- 1969: Dedicated mammography units
- 1970-80s: Breast conservation
- 1975: Chemotherapy
- 1978: Tamoxifen
- 1995: BRCA 1 and 2
- 1996: Sentinel lymph node biopsy
- 1998: Herceptin
- 2010: Nipple-sparing mastectomy, oncoplastic techniques
- 2018: TailoRx trial for Oncotype DX; non-surgical trials

BENEFIT OF MAMMOGRAM, EARLY DETECTION

C50 – incidence according to clinical stages – women

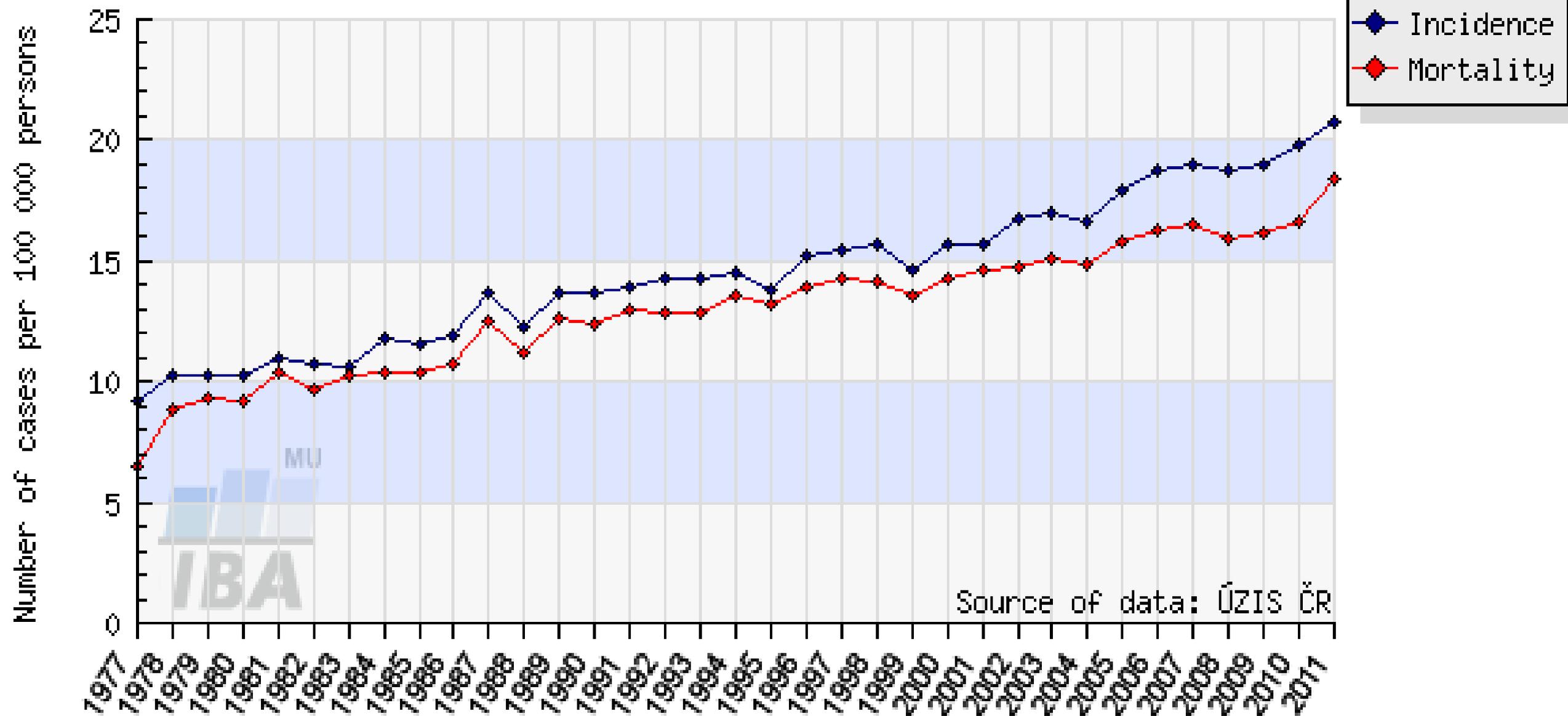


PANCREAS CANCER

- 3% of all cancers
- Overall 5 year survival rate 7%
- Most patients present unresectable
- Surgery “Whipple operation”
 - Since 1935

C25 - Malignant neoplasm of pancreas

Time trend



Analysed data: N(inc)=52500, N(mor)=46996

<http://www.svod.cz>

**“IT'S HARD TO RAISE AWARENESS OF
PANCREATIC CANCER - PEOPLE WHO GET IT
DON'T LIVE LONG ENOUGH.”**

**RANDY PAUSCH
AUTHOR OF "LAST LECTURE"**

MELANOMA

6% of male cancers, 4% of female cancers

Fastest growing in incidence

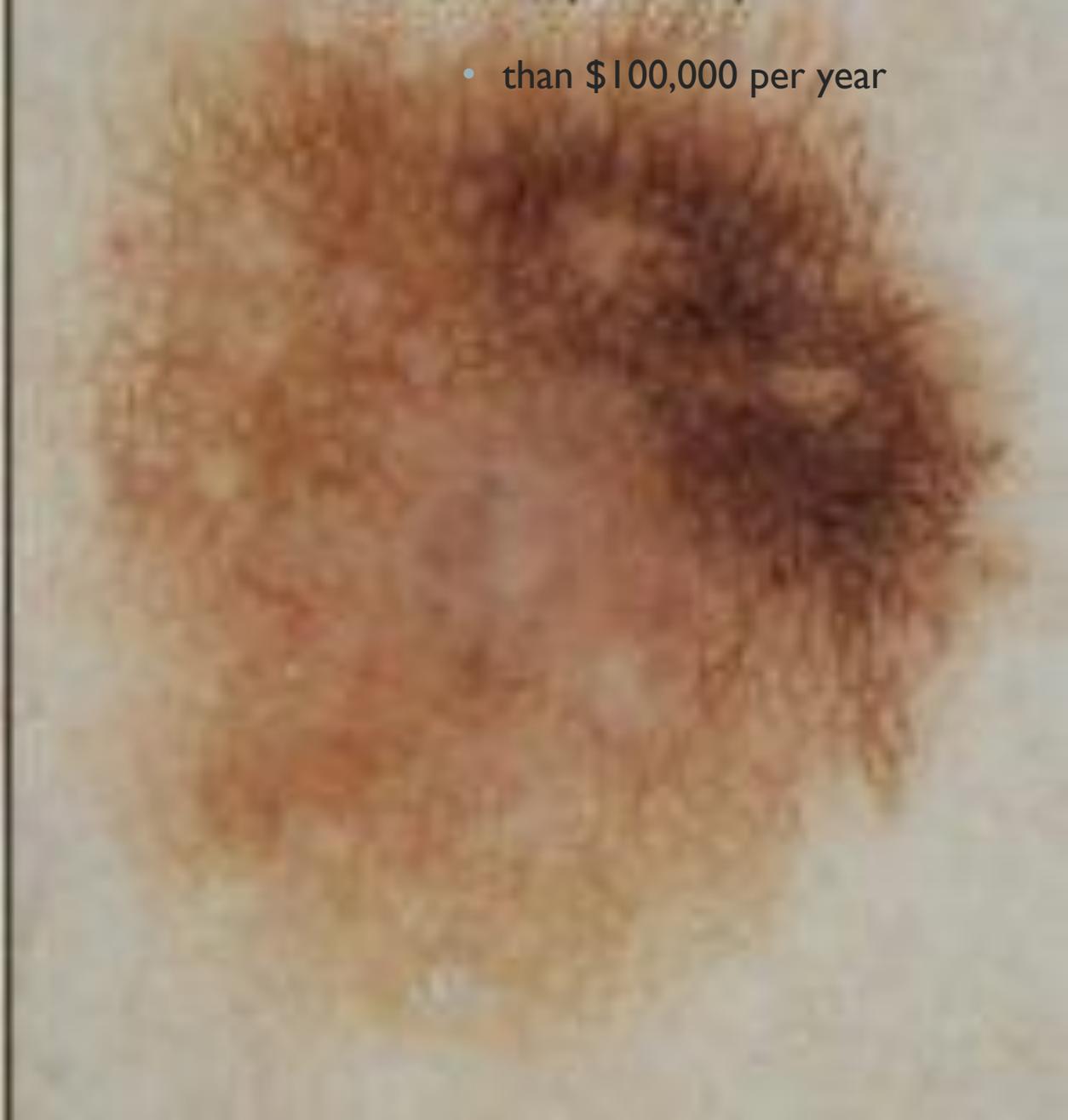
5 year Survival:

- ✓ 99% if localized
- ✓ 63% if involving lymph nodes
- ✓ 10% with distant spread

Melanoma Cancer



Nevus (Mole)



- than \$100,000 per year

“METASTATIC MELANOMA GIVES CANCER A BAD NAME”

- **91,270 new cases in US in 2018**
- **9,320 deaths from metastatic melanoma**
- **Not responsive to chemotherapy or radiation**
- **Immune therapy...**

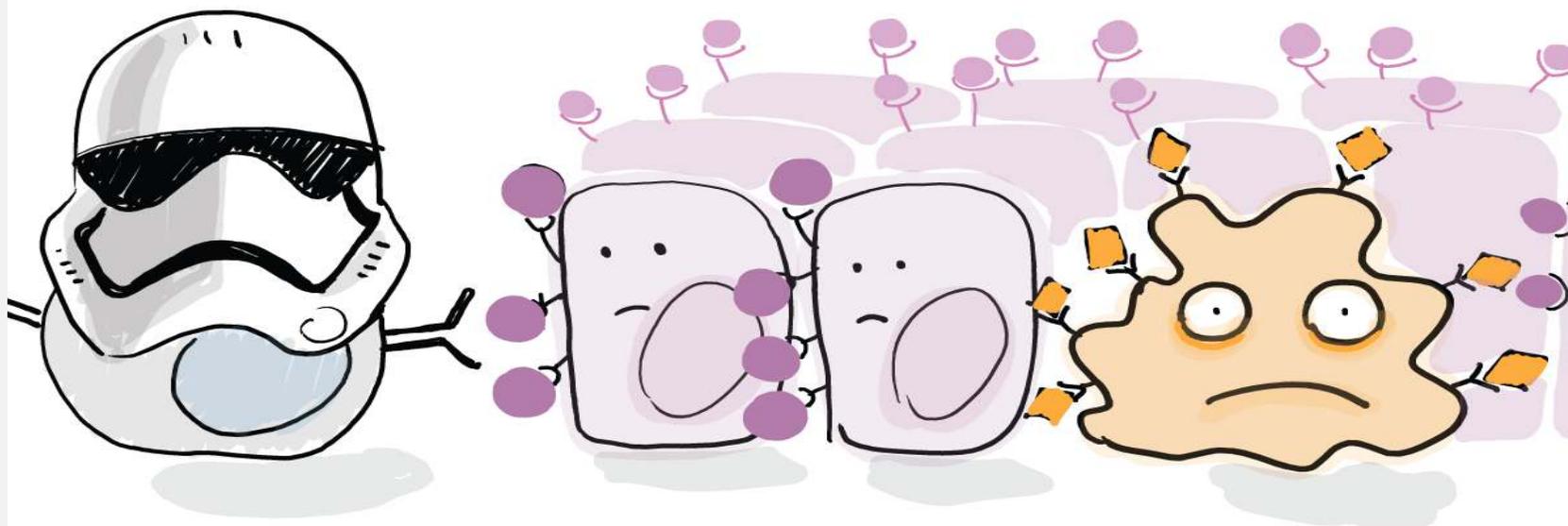
“In solving a problem of this sort, the grand thing is to be able to reason backwards. That is a very useful accomplishment, and a very easy one, but people do not practice it much.”

SHERLOCK HOLMES
SIR ARTHUR CONAN DOYLE'S
A STUDY IN SCARLET

THE FOURTH LEG OF THE STOOL

AWAKEN THE FORCE WITHIN

Immunotherapy brings a new hope
to cancer treatment



New immunotherapy drug behind Jimmy Carter's cancer cure

Former president given pembrolizumab, one of the most promising new drugs in the treatment of cancer



Jimmy Carter:

- July 2015: Announced metastatic melanoma
- Treated with surgery, radiation, Keytruda
- December 2015: Announced “cure”

PEMBROLIZUMAB (KEYTRUDA)

TARGETED THERAPIES

Human monoclonal antibodies

- ✓ Part human/part mouse
- ✓ Identical proteins, made in the lab
- ✓ Activate the immune system
- ✓ Suffix “-umab”

James Allison and Tasuku Honjo win 2018 Nobel Prize in Medicine

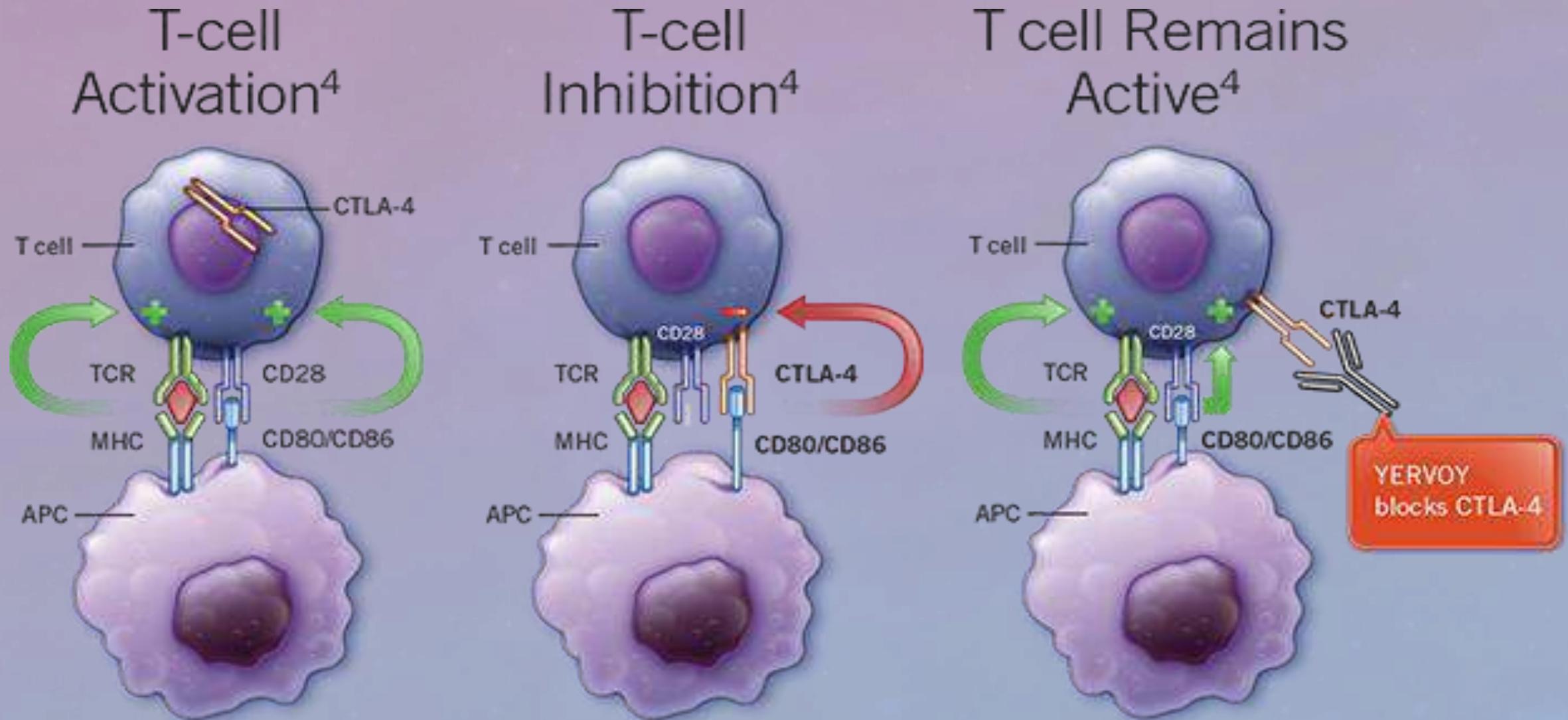
OCTOBER 1, 2018

Research studying a protein that functions as a brake on the immune system.

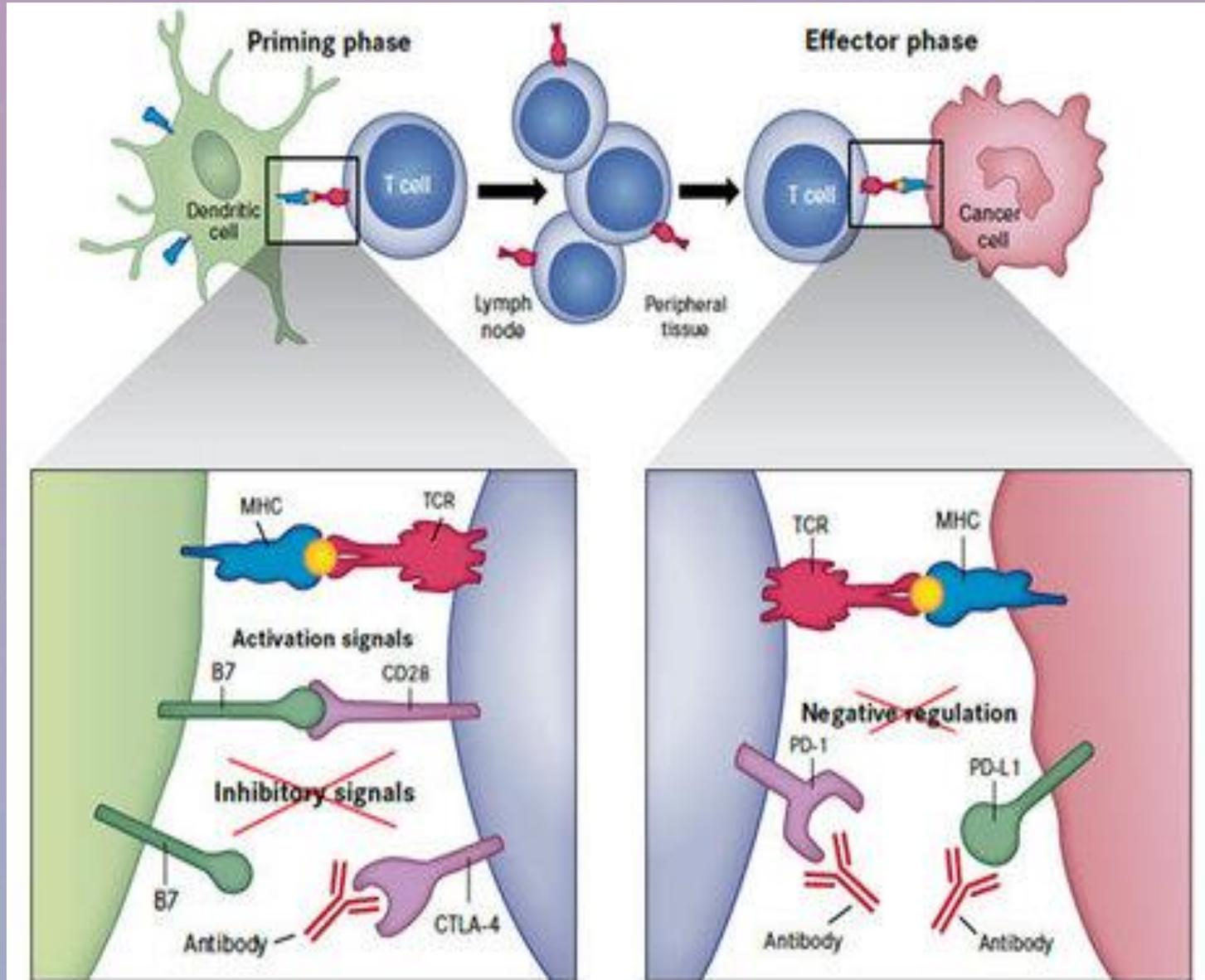
Releasing the brake allowed immune system to attack cancer cells, the immune checkpoint theory, has “revolutionized cancer treatment and has fundamentally changed the way we view how cancer can be managed.”



YERVOY (IPIILIMUMAB) BINDS TO CTLA-4

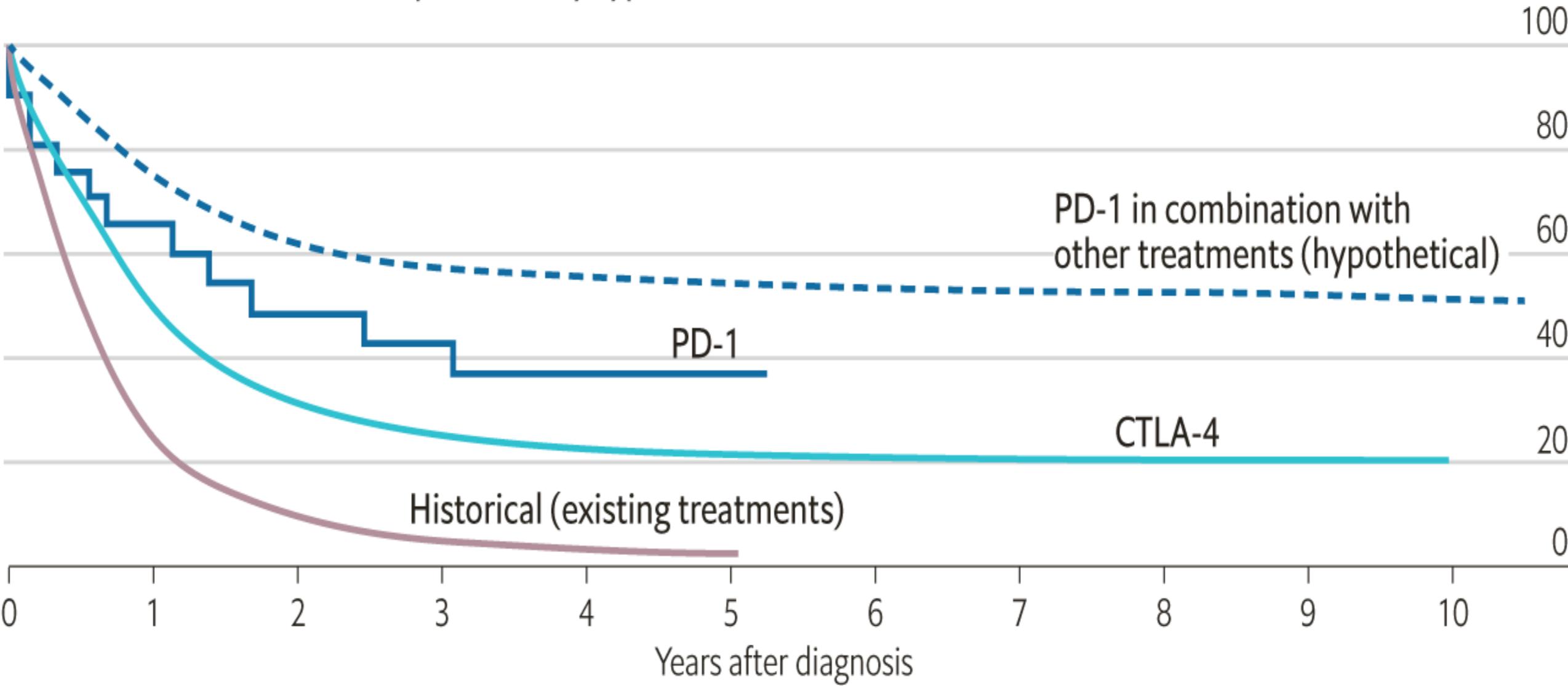


OPDIVO: NIVOLUMAB (ANTI-PD-1 IMMUNE CHECKPOINT INHIBITOR)



Stepping up

Survival rates of melanoma patients, by type of treatment, %



Sources: AACR 2016; J Clin Oncol

RESEARCH!!

CHECKPOINT INHIBITOR TRIALS FOR TNBC BREAST CANCER

FIRST LINE:

IMpassion 130: chemo +/- atezolizumab for untreated TNBC

Phase I and 2 trials with avelumab and nivolumab as monotherapy

ADJUVANT:

SWOG 21418 and A-BRAVE: pembrolizumab and avelumab after chemo

KEYNOTE-522: randomizes pembrolizumab vs. placebo with chemo

NeoTRIPaPDL1: randomizes chemo +/- atezolizumab

METASTATIC:

KEYNOTE-355: first line pembrolizumab

KEYNOTE-119: pembrolizumab with chemo as second line



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IMMUNE-RELATED ADVERSE EVENTS

A Case of Nivolumab-Induced Bullous Pemphigoid: Review of Dermatologic Toxicity Associated with Programmed Cell Death Protein-1/Programmed Death Ligand-1 Inhibitors and Recommendations for Diagnosis and Management
Adriana T. Lopez, Larisa Geskin

Trifluridine/Tipiracil (TAS-102) in Refractory Metastatic Colorectal Cancer: A Multicenter Register in the Frame of the Italian Compassionate Use Program
Chiara Cremolini, Daniele Rossini, Erika Martinelli et al.

Global Acceptance of Biosimilars: Importance of Regulatory Consistency, Education, and Trust
Eduardo Cazzop, Ira Jacobs, Ali McBride et al.

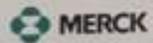
PRECISION MEDICINE CLINIC: MOLECULAR TUMOR BOARD

EM14-ALK Rearrangement and its Therapeutic Implications

KEYTRUDA
(pembrolizumab) injection 100 mg

IS YOUR PATIENT A CANDIDATE
FOR **KEYTRUDA**?

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“As Drug Costs Soar, People Delay Or Skip Cancer Treatments”

- Treating melanoma patients with Keytruda, costs [\\$152,400](#) a year.
- One-quarter of all cancer patients chose not to fill a prescription due to cost, according to a 2013 study in [The Oncologist](#)

- “The promise of immunotherapy currently has been realized as the fourth major method in cancer therapy for lung, bladder, colon cancer and melanoma.”
- “Immunotherapy finally has landed at the doorstep and is about to cross the threshold... and join the list of therapies that put the Halsted hypothesis and mastectomy into the rear view mirror.”

De La Cruz and Czerniecki, Ann Surg Oncol, October, 2018

WINNER OF THE PULITZER PRIZE

THE
EMPEROR
OF ALL
MALADIES



A BIOGRAPHY OF CANCER

SIDDHARTHA
MUKHERJEE

*'A tale of hopes, dreams and pain—sharp disappointment.
Cancer has a master storyteller'* *Independent*

