Canada Life™ Reinsurance

THE **THICK** & THIN OF MELANOMA

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GREAT-WEST LIFECO INC.

Agenda

- Importance in Underwriting
- Clinical Picture

1.3 million people are living with melanoma in the US

Machine learning can detect melanomas using a cell phone

- Staging
- Treatment and Follow-up

Sentinel lymph node biopsy identifies regional spread

Follow-up includes an annual skin examination for life

- Long-term Outcomes
- Case studies

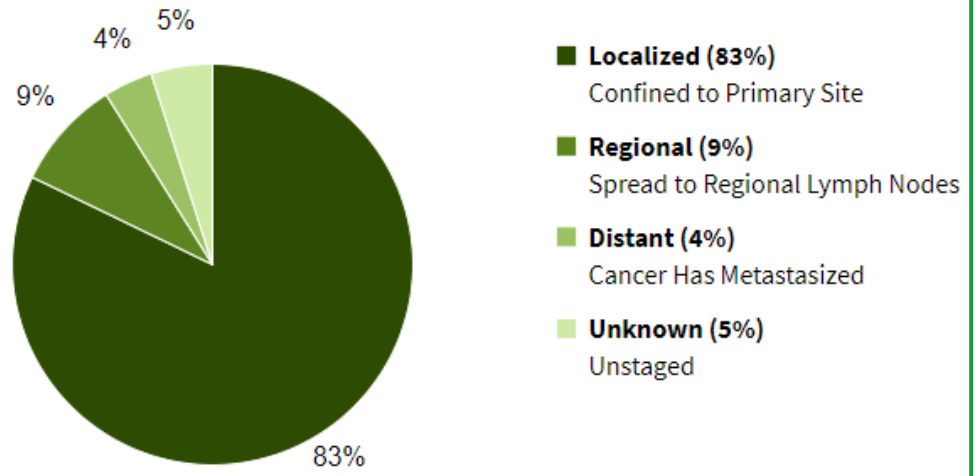
Tumor **thickness** is the single most important factor in survival

In thin melanoma most deaths occur after 5 years

- Questions

Melanoma and underwriting – 1.3 million cases

	Common Types of Cancer	Estimated New Cases 2021	Estimated Deaths 2021
1.	Breast Cancer (Female)	281,550	43,600
2.	Prostate Cancer	248,530	34,130
3.	Lung and Bronchus Cancer	235,760	131,880
4.	Colorectal Cancer	149,500	52,980
5.	**Melanoma of the Skin**	**106,110**	**7,180**
6.	Bladder Cancer	83,730	17,200



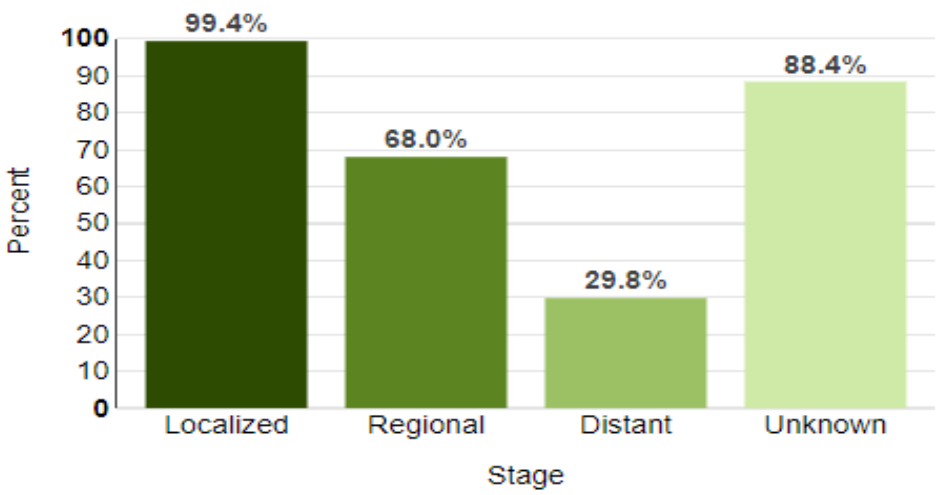
Melanoma of the skin represents 5.6% of all new cancer cases in the U.S.

Median Age At Diagnosis

65

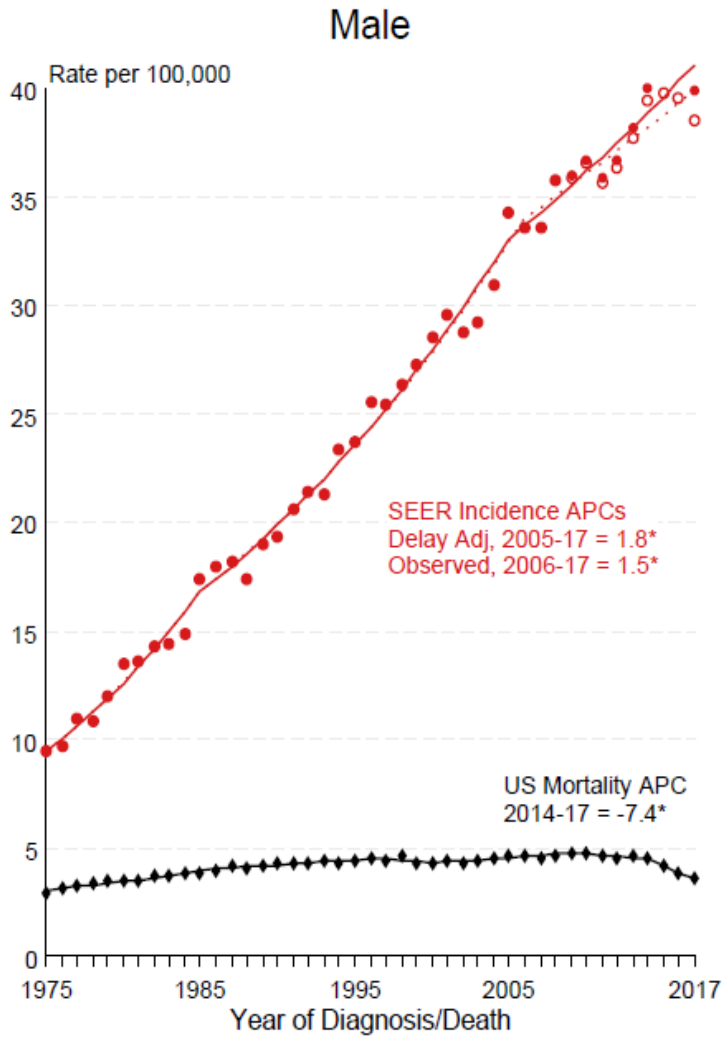
Median Age At Death

71



SEER Cancer Stat Facts: Melanoma of the Skin. National Cancer Institute. Bethesda, MD

Steeply rising incidence and very gradually declining mortality



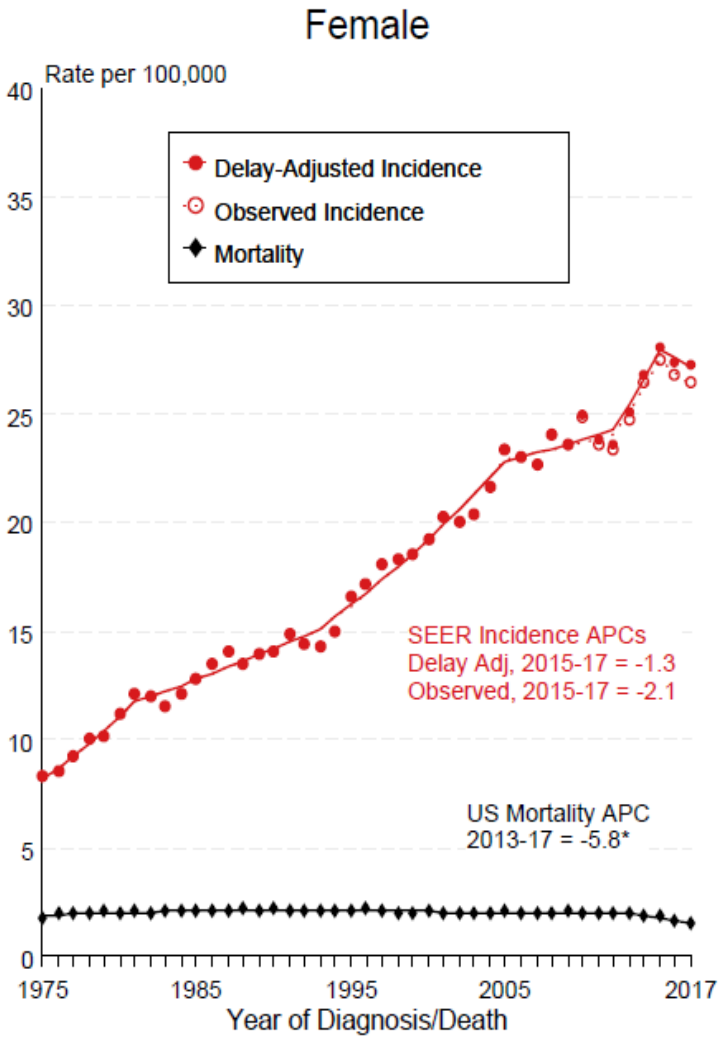
High Awareness
Increasing Screening

enable

80% to 85% of
Melanomas to be
detected at
an early stage

improving

long-term survival.



Howlader N, SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD

Risk Factors

- Excessive exposure to ultraviolet (UV) radiation
  - -Natural sunlight
  - -artificial means like indoor tanning beds

- Sensitive Skin
  - -sun-sensitive skin that burns or freckles easily
  - -presence of multiple (>50) atypical or large moles

- Personal or family history of melanoma

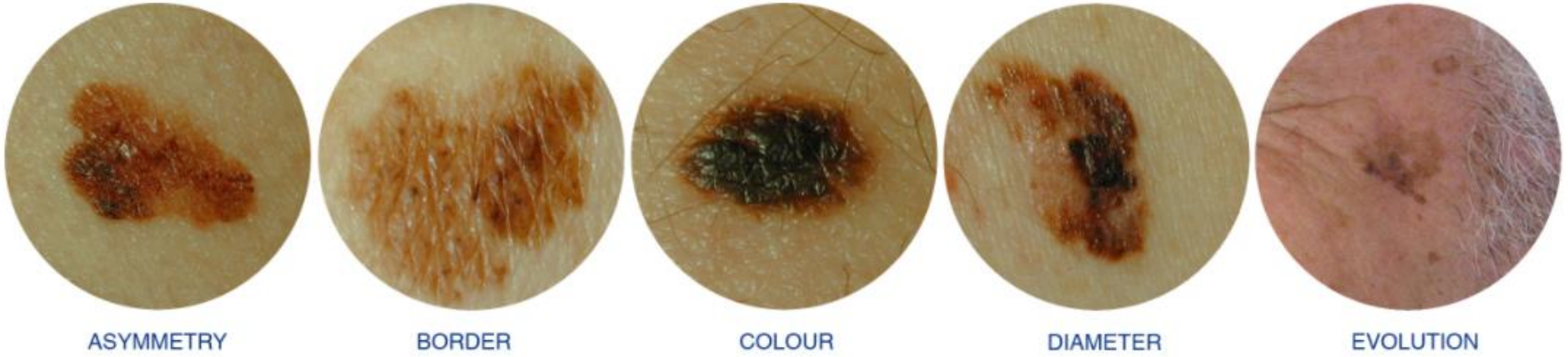
- Genetic syndromes - familial atypical multiple mole melanoma (FAMMM) syndrome (previously called dysplastic nevus syndrome)

Clinical Picture

Melanoma usually presents as a change in a previously existing mole or the appearance of a newly developed atypical mole

Detected by the patient first

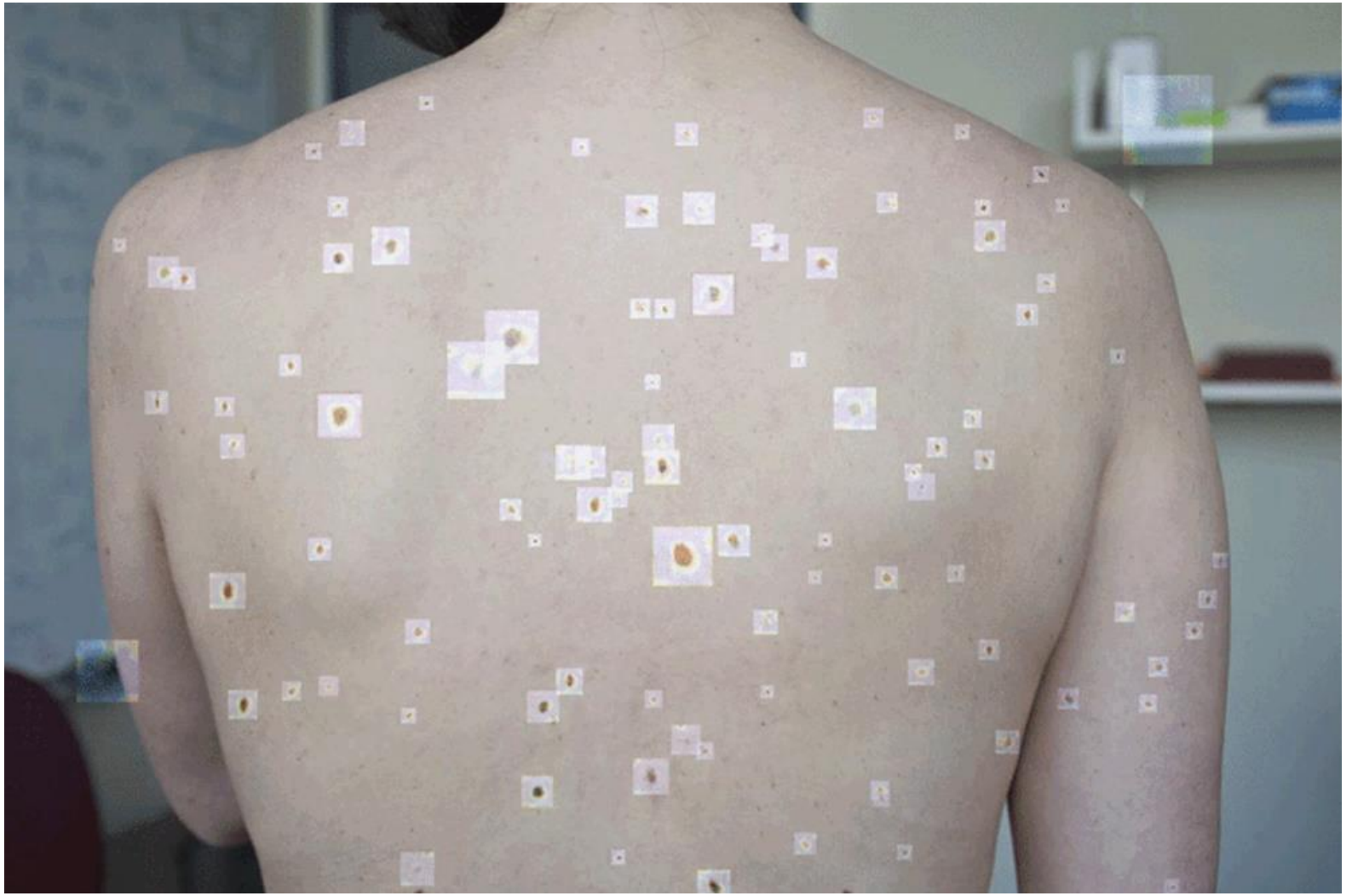
Clinician correlates the atypical features



Diagnosed by the pathologist

Images: Melanoma Institute Australia

Machine learning can help detect melanoma using a cell phone



An automated system detects, and analyzes all pigmented skin lesions in real time

An algorithm determines the suspiciousness of individual pigmented lesions and marks them

yellow = **consider** inspection

red = **requires** inspection or referral to dermatologist)

Soenksen, Luis R., et al. “Using Deep Learning for Dermatologist-Level Detection of Suspicious Pigmented Skin Lesions from Wide-Field Images.” *Science Translational Medicine*, vol. 13, no. 581, Feb. 2021, p. eabb3652.

Histological significance

Superficial spreading

(70%)

Usually arise from atypical nevi

exhibit a flat, spreading growth pattern

are less invasive

Nodular

(15%)

Grow vertically downward into the skin layers

display aggressive growth

frequent lymph node metastasis

Lentigo maligna

(4-10%)

found among older individuals on sun exposed areas

more benign course and

less propensity to metastasize

Acral lentiginous

(5-10%)

Frequently occur on the palms, soles, or beneath the nail beds

Aggressive growth

with poor long-term outcomes

Images: Melanoma Institute Australia

Work up and management

- A thorough clinical examination and investigations like chest X-ray or CT scan done to identify regional and distant spread.

- Sentinel lymph node biopsy (SLNB) procedure is carried out to identify pathologically positive lymph nodes which may be clinically occult, if a melanoma is more than 1mm thick.

- Newer studies have found that SLNB status is the most important prognostic factor even in thin melanoma (up to 1mm thin) and clearly identifies patients at higher risk of late recurrence.

Staging and its implications

- AJCC staging manual is used to categorize melanomas based on the tumor depth (T), nodal involvement (N), metastasis (M) and certain high-risk features like ulceration (a/b)

TNM categories are then grouped together to create TNM stages (I, II, III, IV) and subdivided (A, B, C, D) into IA, IB, IIA, IIB, IIC, IIIA, IIIB, IIIC, IIID, and IV.

- T0 (unknown primary)
- T1 (< = to 1mm)
- T2 (1.1mm to 2mm)
- T3 (2.1mm to 4mm)
- T4 (more than 4mm)

- Subdivided based on absence/presence of ulceration into **a , b**

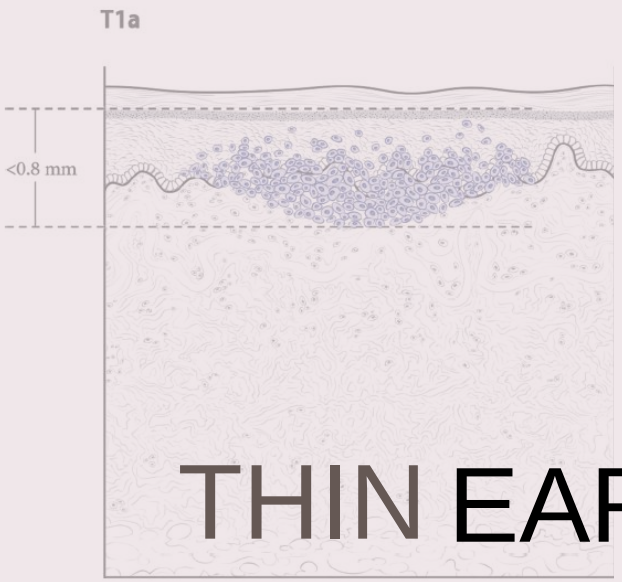
- N0 (no nodes involved)
- N1 (one node involved)
- N2 (two or three nodes)
- N3 (four or more nodes)

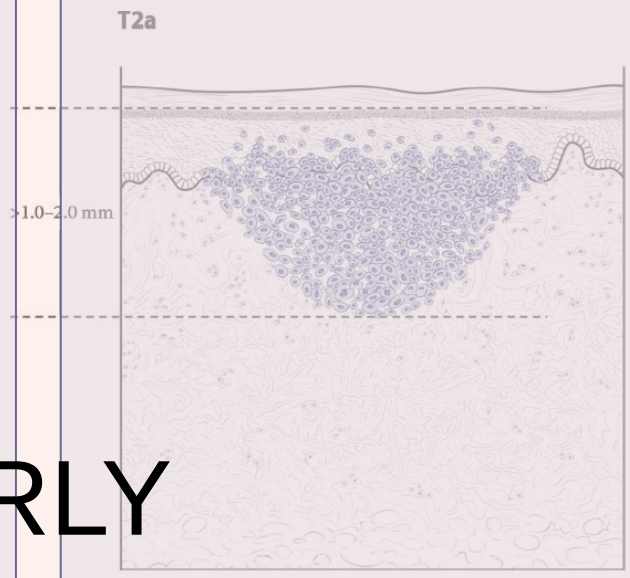
- Subdivided based on type of nodal deposits into **a, b, c**

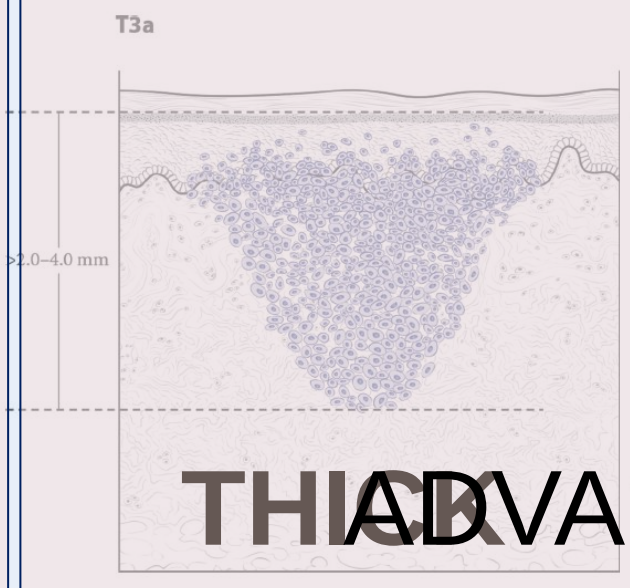
- M0 (distant metastasis absent)
- M1 (distant metastasis present)

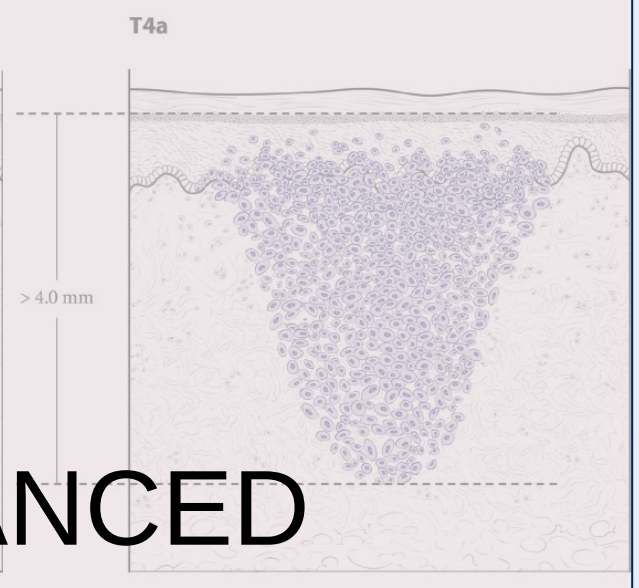
- subdivided based on the organ site involved into organ name suffix

Tumor thickness is the single most important factor in patient survival



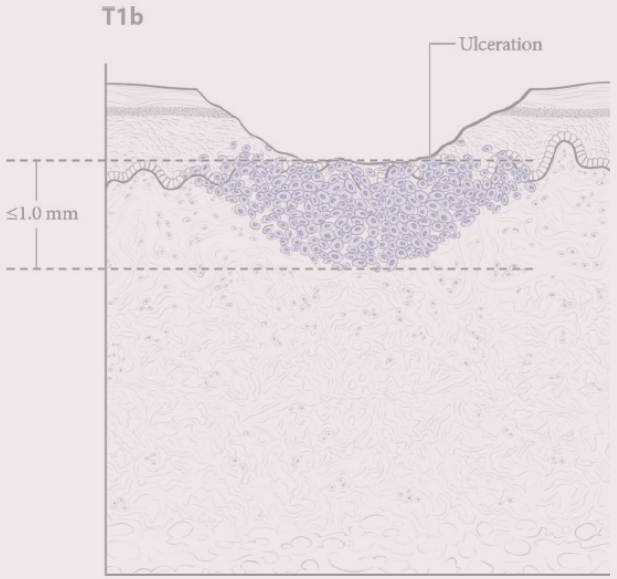


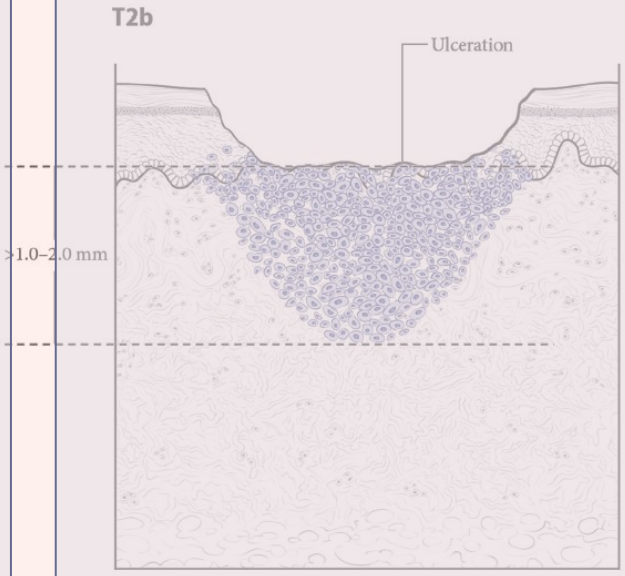


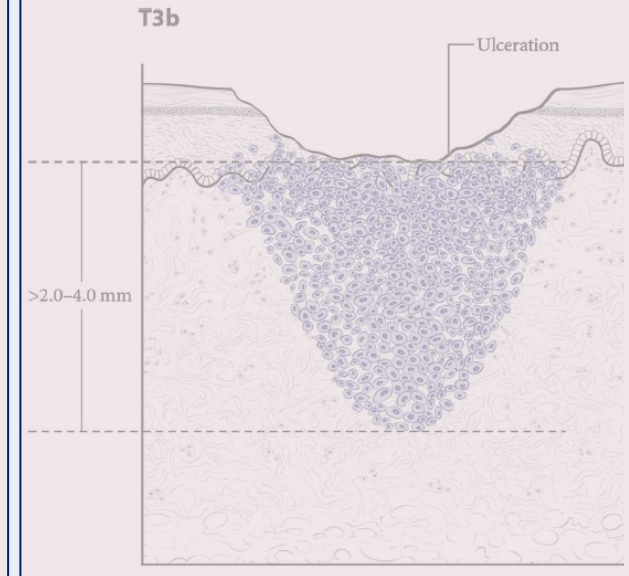


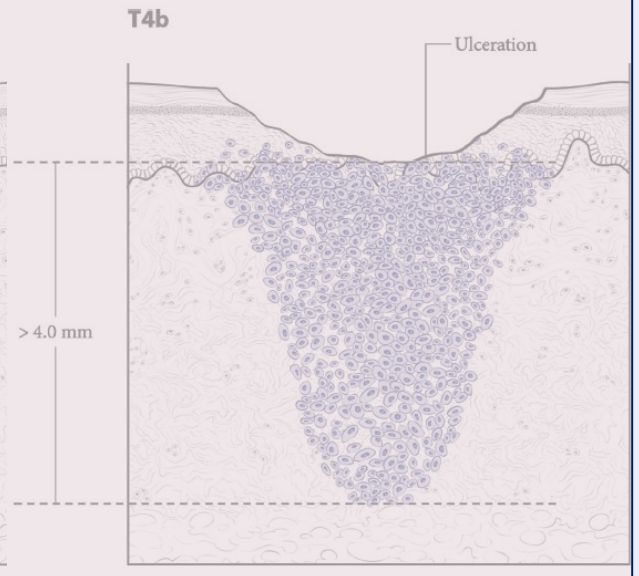
THIN EARLY

THICK ADVANCED







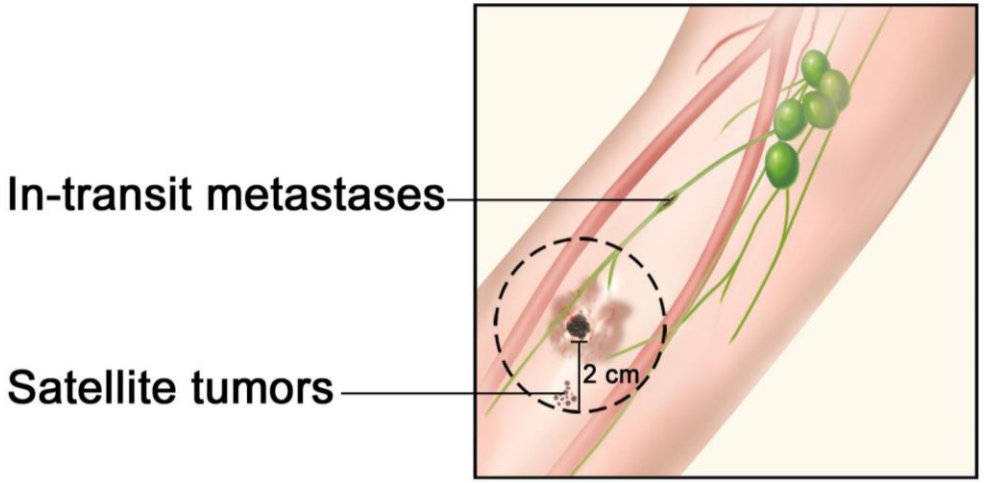


Images: AJCC 8th edition

Even microscopic tumor burden in the SLNB signifies worse prognosis

Apart from lymph node count N status is determined by

- In-transit metastases (between the primary tumor and regional lymph nodes)
- Satellite (adjacent to a primary melanoma)
- microsatellite metastases



Regional metastasis via intra-lymphatic spread indicates a very high risk of recurrence.

This upstages the melanoma to stage III

Treatment and Follow-up

- Surgery is the definitive treatment for early-stage melanoma

- Wide local excision with complete lymph node dissection (CLND) in patients with positive sentinel lymph node biopsy results is considered the mainstay of treatment.

- Treatment of advanced disease combines surgery with immunotherapy, and in some cases radiotherapy.

- Oncolytic virus therapy – a virus is injected into the tumor.

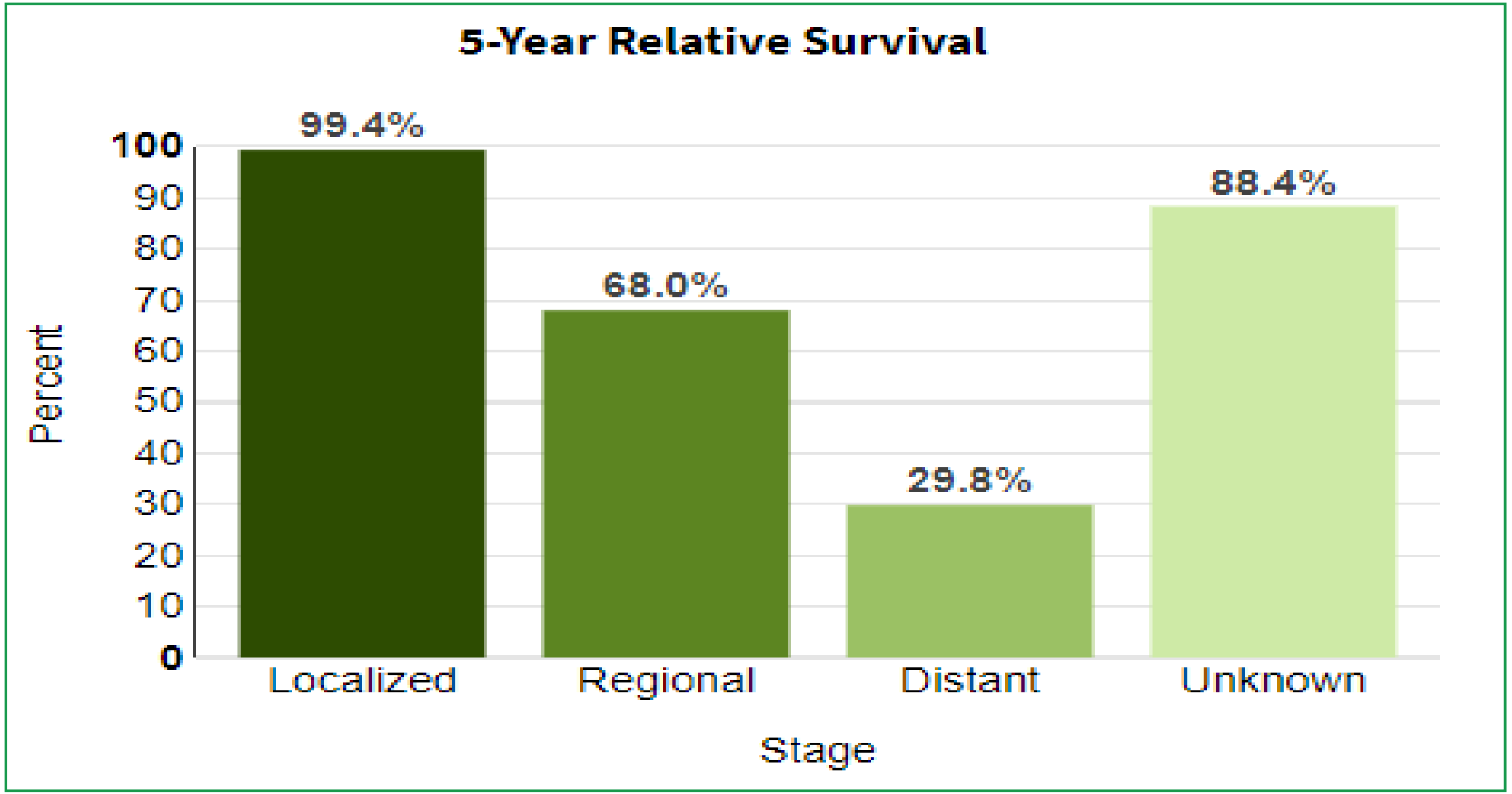
The National Comprehensive Cancer Network (NCCN) recommends that

- stage 0 in-situ melanoma should include at least an annual skin examination for life

- stage IA should include a history and physical examination every 3-12 months for 5 years and then annually as clinically indicated and at least an annual skin examination for life.

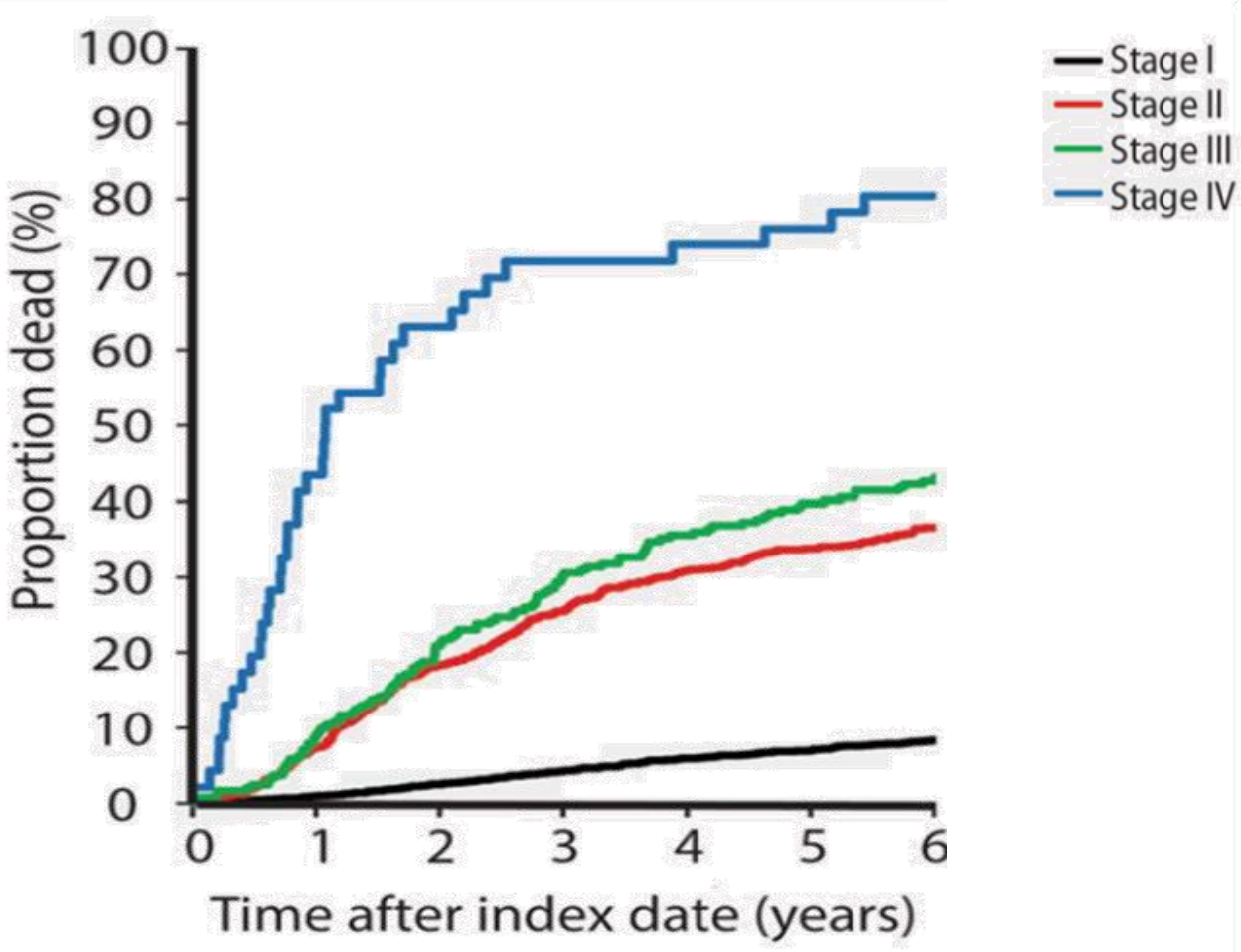
- stage IB and above should additionally include CT scans to actively screen for recurrent /metastatic disease

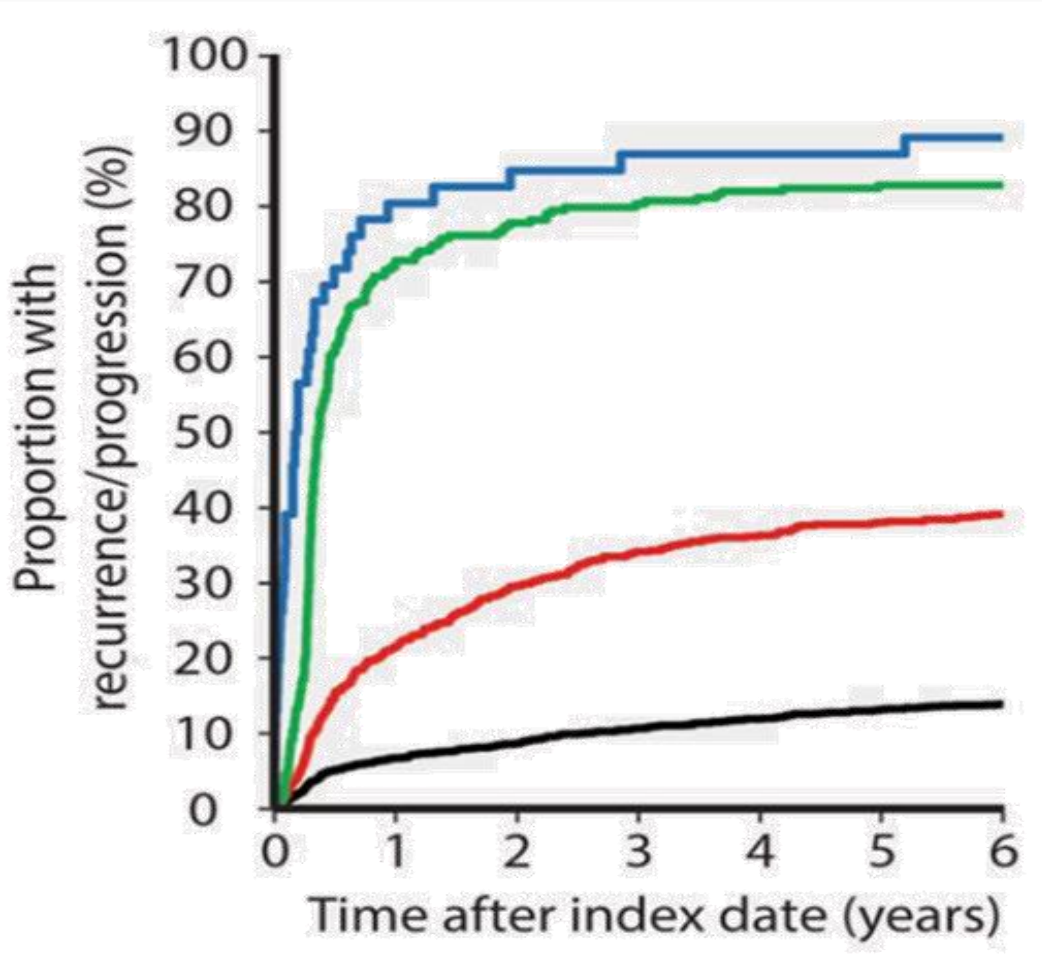
Risk assessment



Sweden Registry Data - 6 years of follow-up

For stage II patients, the 5-year survival rate was lower than expected and similar to stage III





Rockberg, Julia, et al. “Epidemiology of Cutaneous Melanoma in Sweden-Stage-Specific Survival and Rate of Recurrence: Epidemiology of Cutaneous Melanoma in Sweden.” *International Journal of Cancer*, vol. 139, no. 12, Dec. 2016, pp. 2722–29.

US SEER Data – 10 years of follow-up

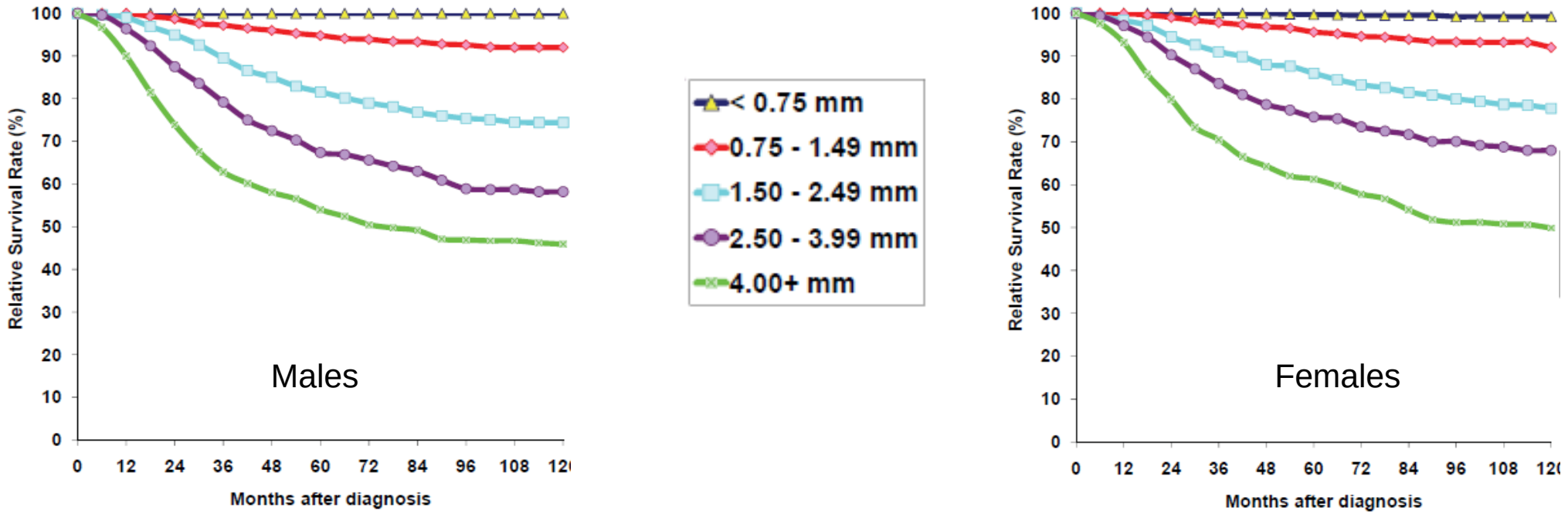
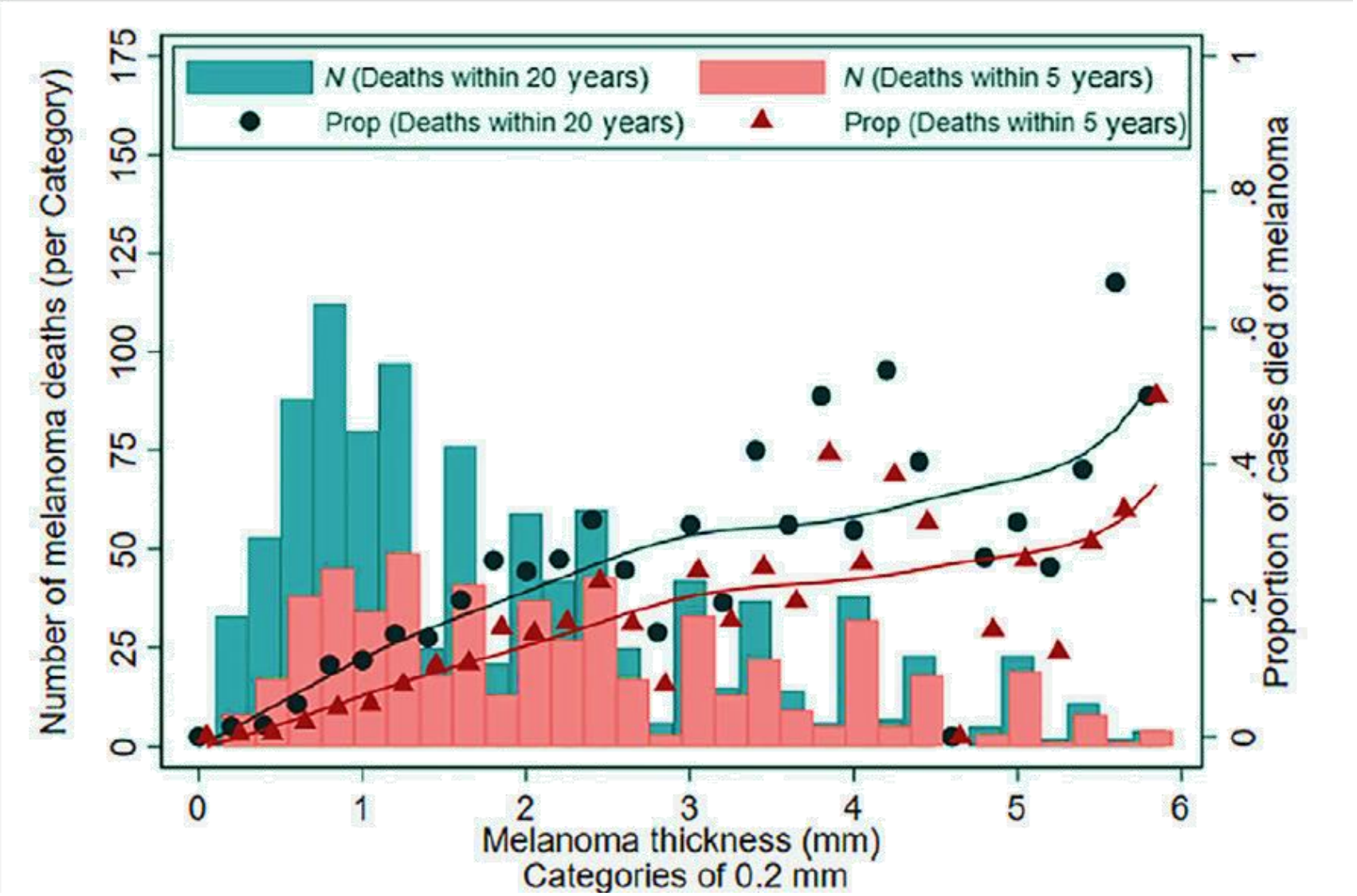


Table II. Deaths and proportion dead from invasive melanoma limited to skin by thickness category within 10 years of diagnosis, SEER 13 Registry, 1992-2013

Melanoma depth	# Melanomas	% All T	# Dead at 10 yrs	% Dead at 10 yrs (95% CI)
T1N0M0 (0.01-1.00 mm)	35,509	72.0%	1072	3.0% (2.8%-3.2%)
T2N0M0 (1.01-2.00 mm)	7879	16.0%	974	12.4% (11.6%-13.1%)
T3N0M0 (2.01-4.00 mm)	3948	8.0%	985	25.0% (24.0%-25.9%)
T4N0M0 (>4.00 mm)	1983	4.0%	629	31.8% (29.3%-34.2%)
All T N0M0 melanomas	49,319	100.0%	3660	7.4% (7.2%-7.7%)

Howlader N, SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD

Australia Registry Data – 20 years of follow-up



For melanomas <1.0 mm, most deaths occurred between 5 and 20 years after diagnosis,

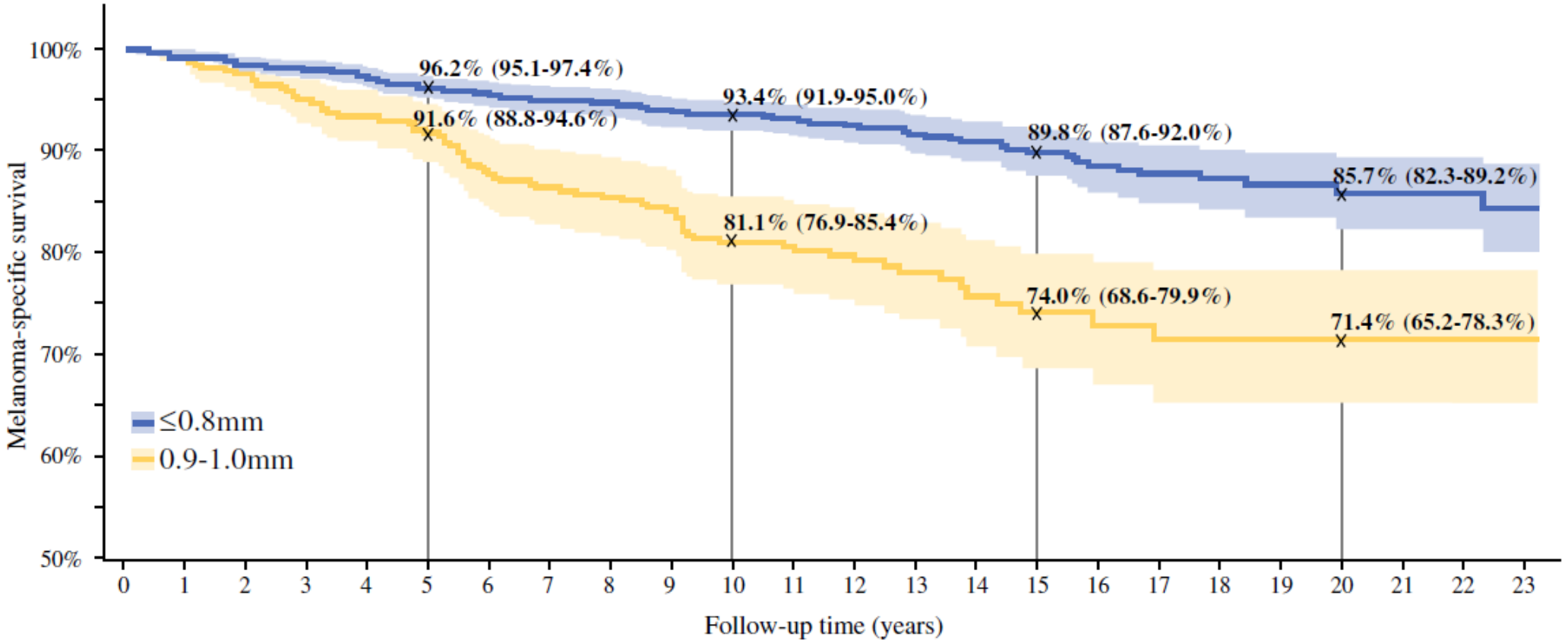
whereas

for thicker melanomas most deaths occur within the first 5 years.

Baade, Peter D., et al. “Long-term Deaths from Melanoma According to Tumor Thickness at Diagnosis.” *International Journal of Cancer*, vol. 147, no. 5, Sept. 2020, pp. 1391–96.

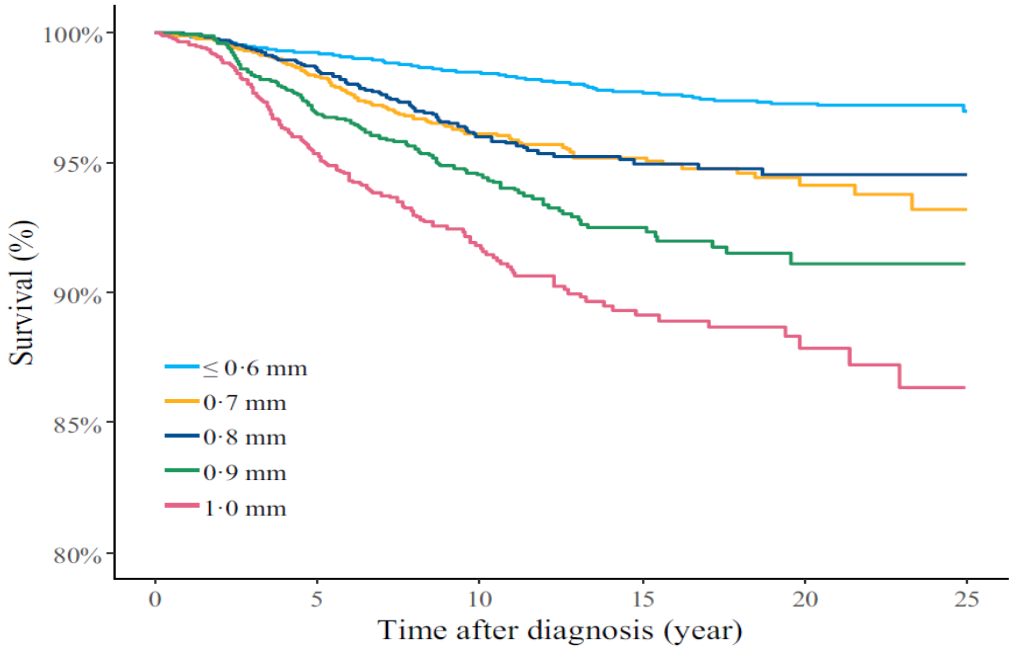
Melbourne Registry Data – 23 years follow-up

Melanoma-specific survival for tumor thickness <0.8 mm versus tumor thickness 0.9–1.0 mm (n = 1489)



Lo, Serigne N., et al. “Long-Term Survival of Patients with Thin (T1) Cutaneous Melanomas: A Breslow Thickness Cut Point of 0.8 Mm Separates Higher-Risk and Lower-Risk Tumors.” Annals of Surgical Oncology, vol. 25, no. 4, Apr. 2018, pp. 894–902. DOI.org (Crossref), doi:10.1245/s10434-017-6325-1.

Long-term survival of thin (<1mm or T1) melanomas



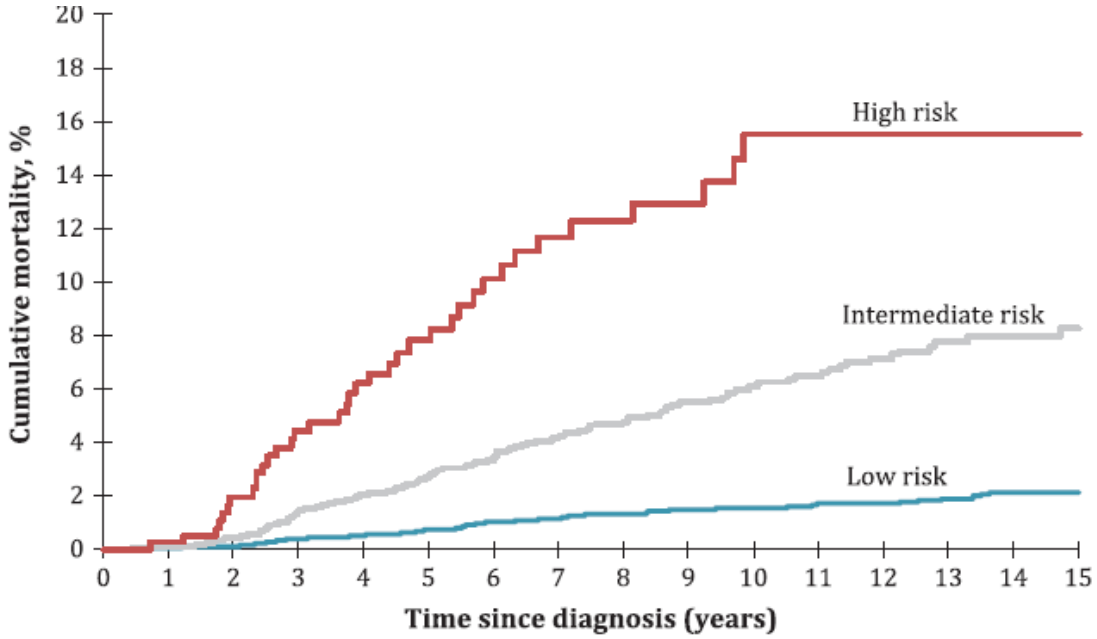


Table IV. T1 melanoma deaths with and without ulceration, SEER 13 Registry, 1992-2013

	Total		Ulcerated		Not ulcerated	
Melanoma thickness	# Melanomas	# Dead at 10 yrs (%)	# Melanomas	# Dead at 10 yrs (%)	# Melanomas	# Dead at 10 yrs (%)
0.01-0.25 mm	6060	184 (3.0%)	112	23 (20.5%)	5948	161 (2.7%)
0.26-0.50 mm	14,926	279 (1.9%)	139	26 (18.7%)	14,787	253 (1.7%)
0.51-0.75 mm	8809	282 (3.7%)	126	18 (14.3%)	8683	264 (3.0%)
0.76-1.00 mm	5669	327 (5.8%)	164	20 (12.2%)	5505	307 (5.6%)
0.01-1.00 mm	35,509	1072 (3.0%)	541	87 (16.1%)	34,968	985 (2.8%)

Isaksson, K., et al. “Survival in 31 670 Patients with Thin Melanomas: A Swedish Population-based Study*.” *British Journal of Dermatology*, vol. 184, no. 1, Jan. 2021, pp. 60–67. .

Lyth, J., et al. “Prognostic Subclassifications of T1 Cutaneous Melanomas Based on Ulceration, Tumour Thickness and Clark’s Level of Invasion” BJD , vol. 168, no. 4, Apr. 2013, pp. 779–86.

Case Study I

A 45-year-old male applied for $5 million in May 2021

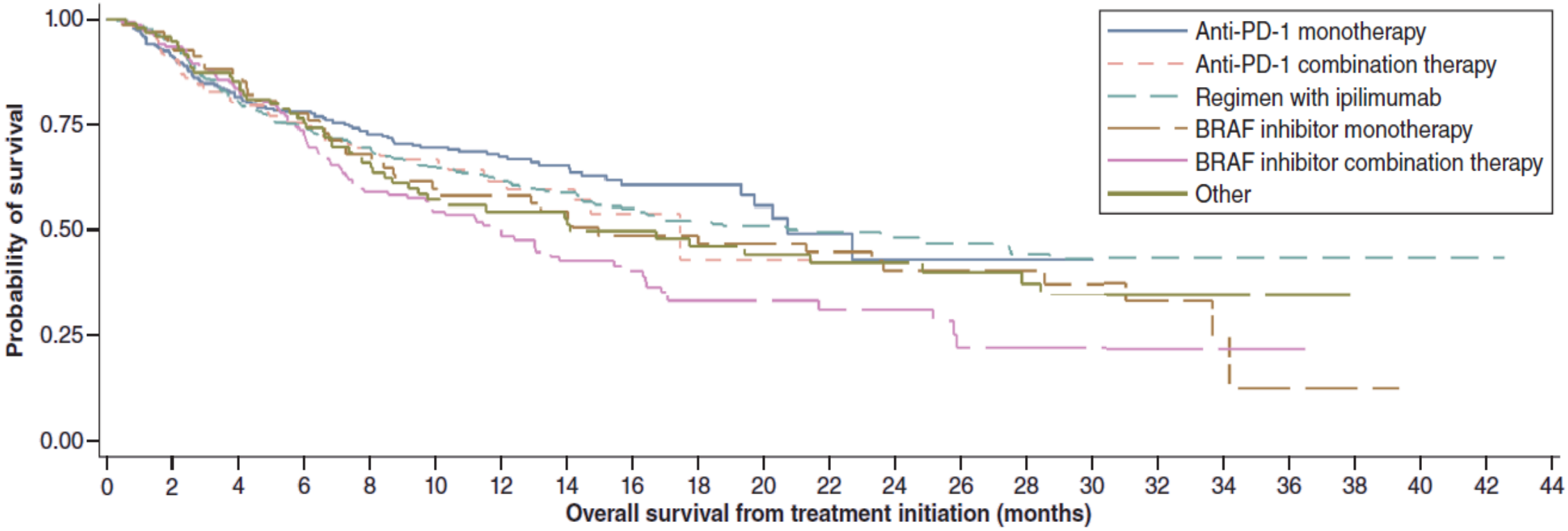
May 2015 - Malignant melanoma, nodular type stage 3A Breslow thickness 1.6 mm, non-ulcerated 2SLN + (micro-metastases) Clark's level IV, Good follow-up

May 2010 - Back Melanoma, stage III, 1 pos LN, IFN alpha treatment , left axillary node dissection CXR N 6/2010 MRI brain normal.

June 2010 CT chest - single, very small somewhat ill-defined low attenuation lesion within periphery of the junction R & L hepatic lobes 5 x 8 mm. indeterminate etiology, no definite findings of metastatic disease related to melanoma.

Advanced Melanoma (pathologic stage III or IV, First/Recurrence)

Median overall survival from immunotherapy initiation was 18.8 months (n=1140)



Whitman, Eric D., et al. “Treatment Patterns and Outcomes for Patients with Advanced Melanoma in US Oncology Clinical Practices.” Future Oncology, vol. 15, no. 5, Feb. 2019, pp. 459–71. DOI.org (Crossref), doi:10.2217/fon-2018-0620.

Case Study II

A 53-year-old female applying for 900,000 in Mar 2021

History of moles and biopsies > being proactive - nevi and tags > all benign

Bumps on forehead and left ear for years

In June 2017 - Left Ear helix – Lesion - Melanoma - superficial spreading

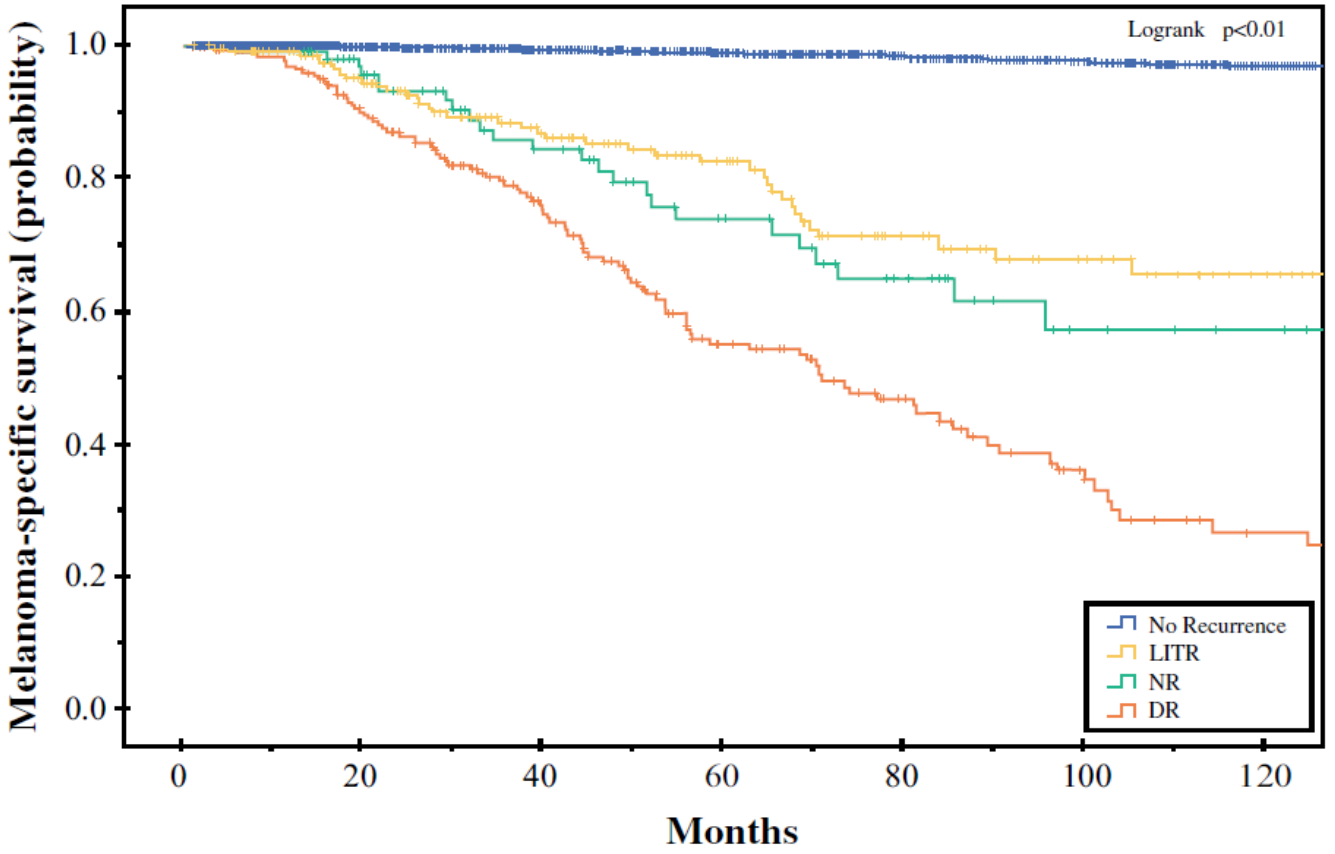
T2aN0M0

Non-ulcerated

Sentinel node negative

Excellent follow up

10.4% of negative SLNB patients and 33.0% positive SLNB patients developed recurrences. (n=6305)



LITR local or in-transit recurrence, NR nodal recurrence, DR distant recurrence

Thomas, Daniel C., et al. "Recurrence of Melanoma After a Negative Sentinel Node Biopsy: Predictors and Impact of Recurrence Site on Survival." *Annals of Surgical Oncology*, vol. 26, no. 7, July 2019, pp. 2254–62.

Key Learnings

1.3 million people are living with melanoma in the US

Sentinel lymph node biopsy identifies regional spread

Follow-up includes an annual skin examination for life

Tumor thickness is the single most important factor in survival

In thin melanoma most deaths occur after 5 years

Questions