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MELANOOM STUDIEDAG

M.be

16-12-2017

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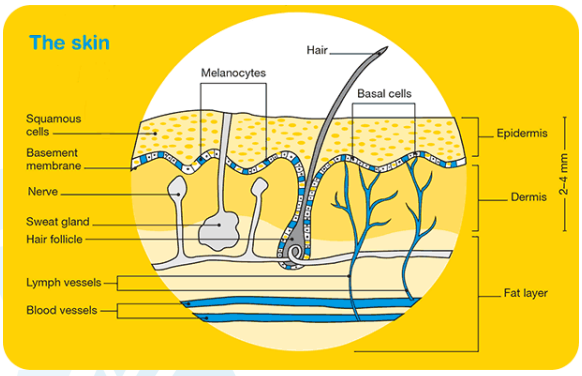
De huid en huidkanker



Basal Cell	Squamous Cell	Melanoma
1 RANK	2 RANK	3 RANK
Most common form of skin cancer	Second most common skin cancer	Accounts for less than 2% of skin cancer cases
DISCOVERY	DISCOVERY	DISCOVERY
Usually discovered in areas exposed to the sun	Sometimes spreads to other parts of the body, but almost all cases are curable	Melanoma may develop as a new mole or in a preexisting mole
Rarely spreads, very rarely fatal	WHO: Rarely appears before age 50	Causes the vast majority of skin cancer deaths
WHO		WHO
Anyone - people who are at highest risk have fair skin, blond or red hair, & blue, green, or grey eyes	Majority of skin cancers in African-Americans are squamous cell	One of the most common cancers in people younger than 30

Myth Buster: we are all at risk for skin cancer even if you always tan

Created by

livesunsmart.org
FB/Twitter LiveSunSmart

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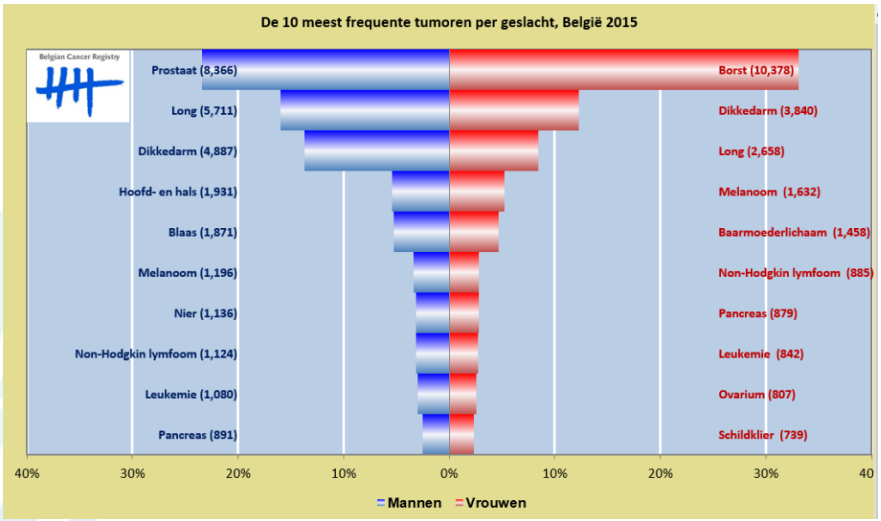
Meest voorkomende kankers in België



Belgisch Kankerregister – Cancer Facts Sheet
http://www.kankerregister.org

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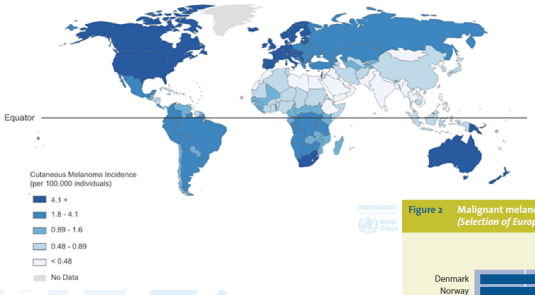
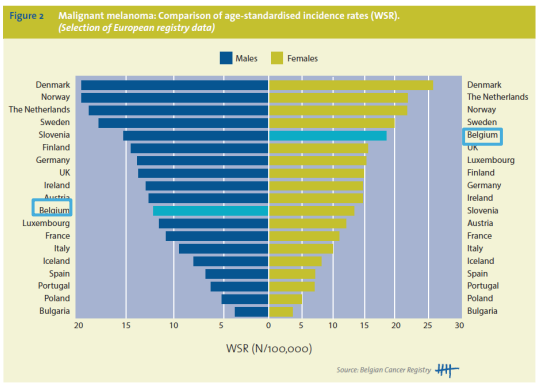
Geografische spreiding risico op melanoom





Belgisch Kankerregister – Cancer Facts Sheet
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Melanoma: Epidemiology, Risk Factors, and the Role of Adaptive Pigmentation. Horrell E, et al. DOI: 10.5772/58994

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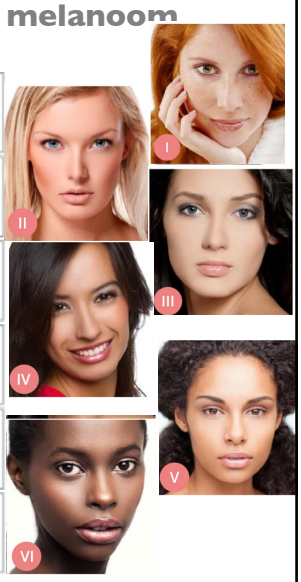
Fototype correleert met risico op melanoom

		Skin characteristics	Hair	Eyes
1		**Type 1** Pale skin, which often burns and rarely tan	Blonde, brown or red	Blue, brown, green, grey
2		**Type II** Fair skin (European), Usually burns, sometimes tans	Light or dark	Blue, brown, green, grey or hazel
3		**Type III** Light intermediate or dark skin European. Rarely burns, usually tan	Brown	Blue, brown, green, grey or hazel
4		**Type IV** Mediterranean / olive skin. Rarely burns often tans	Dark brown or black	Black, blue, brown or green
5		**Type V** Naturally brown skin.	Dark brown or black	Black or brown
6		**Type VI** Very dark brown or Black skin.	Black	Dark brown or black



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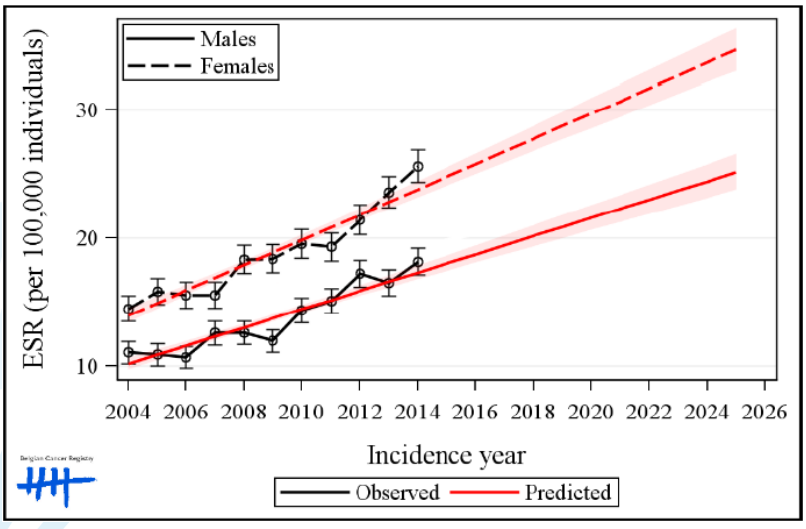
Te verwachten evolutie risico op melanoom



Belgisch Kankerregister – Cancer Incidence Projections in Belgium 2015 to 2025
http://www.kankerregister.org/media/docs/publications/IncidenceProj2015-2025_finaal_171120.pdf

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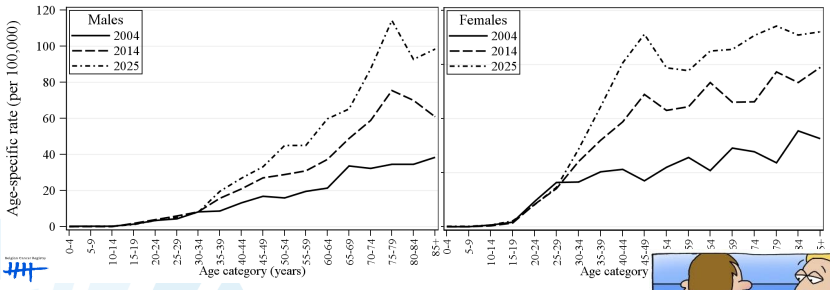
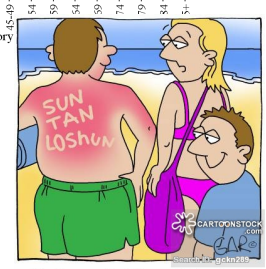
Te verwachten evolutie risico op melanoom



Toenemende levensverwachting
Outdoor activities
Ozon depletie
Veranderde kledingsstijl
Immuunsuppressie
Ioniserende straling
…



"Darling, you should have asked me to put sun tan lotion on your back and not the kids!"

Donaldson MR et al Semin Cutan Med Surg 30:3-5, 2011

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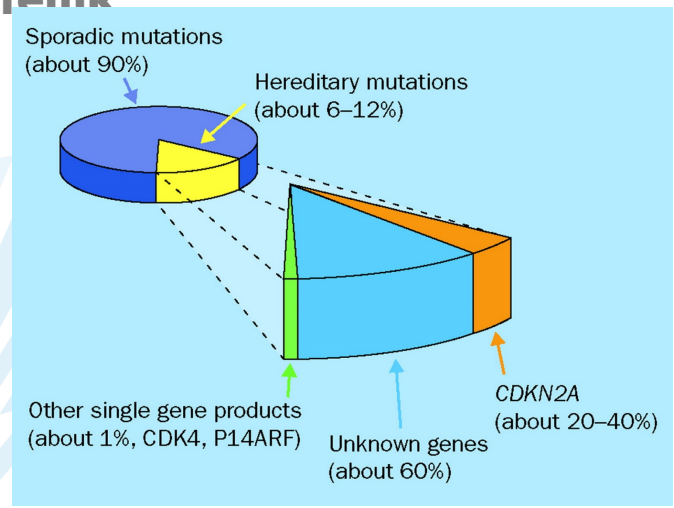
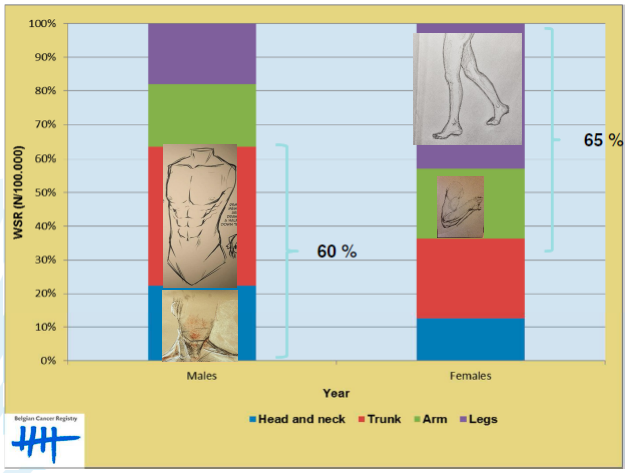
Melanoom is meestal niet erfelijk



Frequenste locatie verschilt bij mannen en vrouwen



Belgisch Kankerregister – Cancer Facts Sheet Maligne Melanoom
http://www.kankerregister.org

Diagnose melanoom
Verschillende subtypes

Superficieel spreidend melanoom
Acraal lentigineus melanoom
Lentigo maligna melanoom
Nodulair melanoom
Mucosaal
Desmoplastisch
Nevoid
…

=> Geen onafhankelijke prognostische waarde

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Ziektestadiëring in functie van risico

- Klinisch onderzoek
- Indien mogelijkheid van verdere ziekte-uitbreiding:
  - Echografie afvoerende lymfeklieren, punctie bij verdachte bevindingen
  - Foto longen en echografie buik
  - Bloedname met LDH
- Bij hogere stadia, zeker bij lymfeklieraantasting
  - CT borstkas/buik of PET-CT

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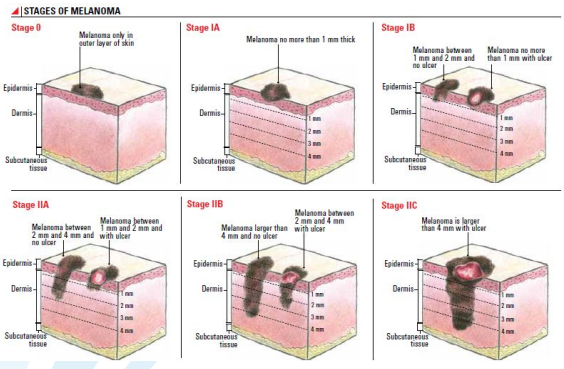
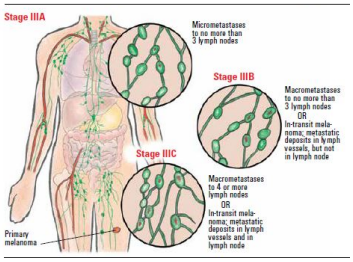
Stadiëring melanoom - TNM

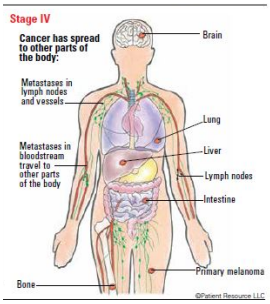
Tumor: tumordiepte

Node: lymfeklier (-aant

Metastasis: uitzaaiing





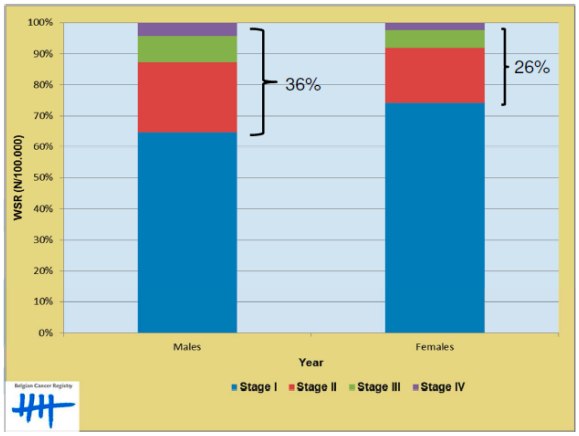


Balch CM et al J Clin Oncol 27:6199-6206, 2009

Verdeling TNM stadia bij diagnose melanoom in België

ELSEVIER

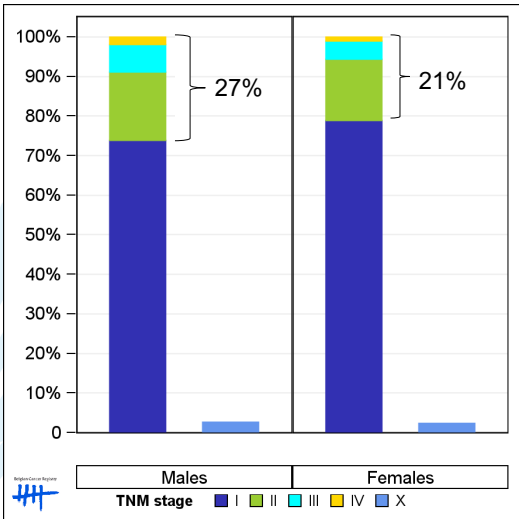
A Prime minister managed to attract elderly men in a Belgian Euromelanoma campaign



Belgisch Kankerregister – Cancer Incidence in Belgium 2011, presented at BADO meeting Brussels 2013

del Marmol V et al Eur J Cancer, Vol 45 (9), 2009, 1532 - 1534

Melanoom wordt de laatste jaren vaker in stadium I gedetecteer



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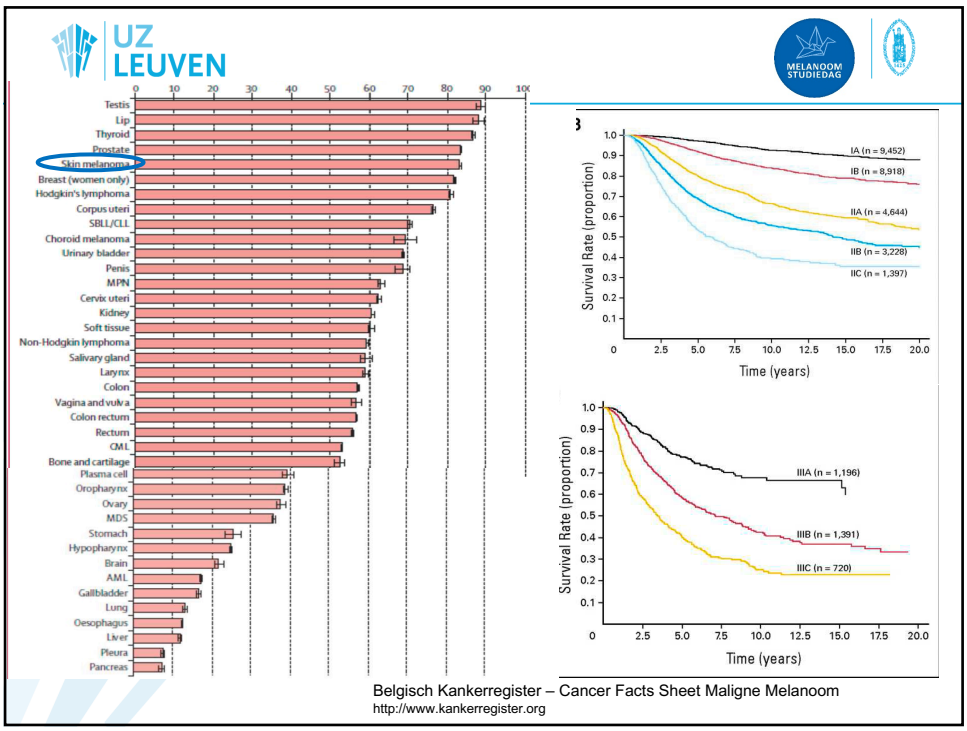

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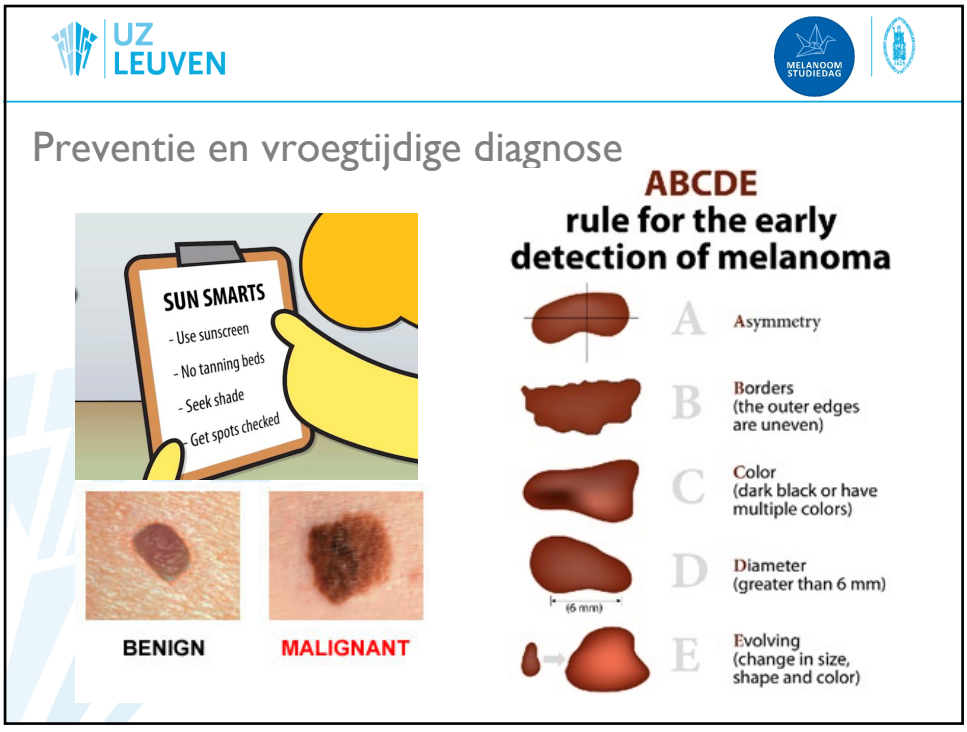

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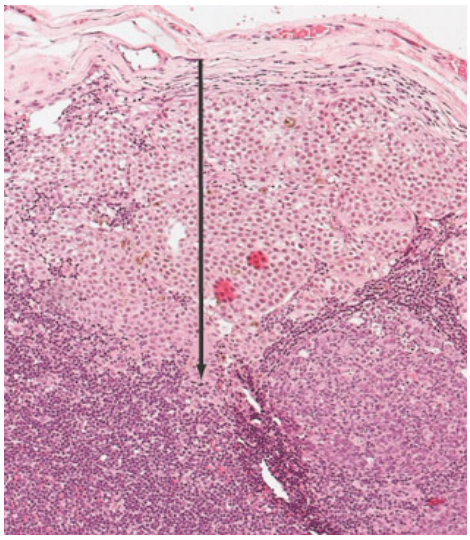
Diagnose + stadiëring melanoom
Microscopisch onderzoek

Breslow-dikte
Ulceratie
Aantal celdelingen (/mm²)
Bloed/lymfevatinvasie
Microsatellieten
Infiltrerende immuuncellen (TILs)

Kleuringen

Tumor type	CK	VIM	S-100	CD45
Carcinoma	+	-	-	-
Sarcoma	-	+	-	-
Lymphoma	-	-	-	+
Melanoma	-	-	+	-



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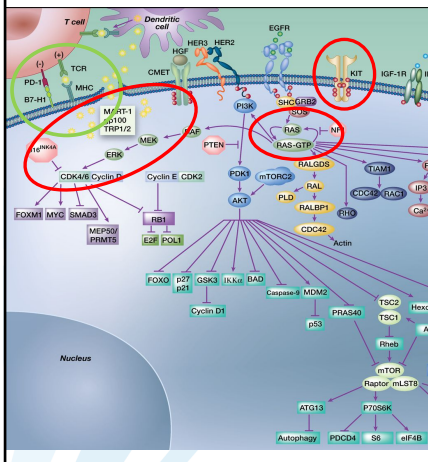
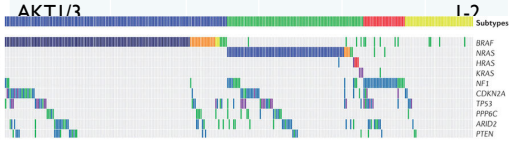
Diagnose melanoom
Moleculair onderzoek



Sullivan R J et al. Clin Cancer Res 2013;19:5283-5291
Davies MA et al Oncogene 2010, 29, 5545-5555

Frequency (%) of mutations in kinase signaling pathways in melanoma subtypes

	cutaneous	acral	Mucosal	uveal	Not specified
BRAF	**40-60**	**15-20**	**3-5**	**<1**	
NRAS	**15-25**	**10-15**	**5-15**	**<1**	
c-KIT (mut)	**<2 (CSD 2-17)**	**10-20**	**15-20**	**<1**	
ERBB4					10-20
PTEN					10-30
PIK3CA					1-2
AKT1/3					1-2



Nature Reviews | Clinical Oncology

The Cancer Genome Atlas Network. *Cell* **161**, 1681–1696 (2015

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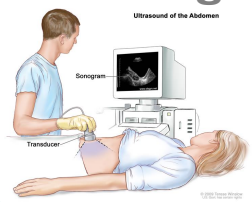
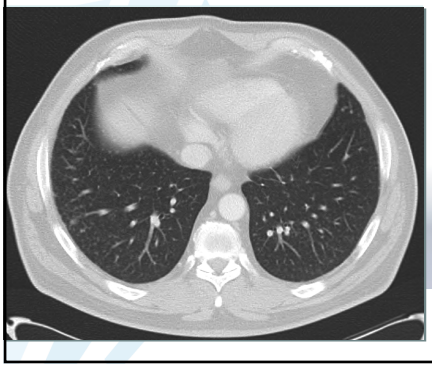
Medische beeldvorming

- Rx / Echografie
- CT vs PET-CT
- (PET)-MRI





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Medische beeldvorming

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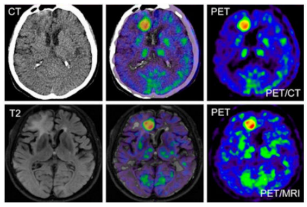

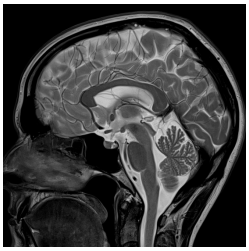

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Primaire behandeling = heelkunde

Tumor dikte	Laterale marges	Dieptes
In situ	0,2 cm of 0,5 cm	Onderhuids vet
≤ 1 mm	1 cm	> Fascia
> 1 mm	2 cm	> Fascia
Satelliet-noduli cutaan	3 cm	> Fascia
Satelliet-noduli subcutaan	3 cm	< Fascia

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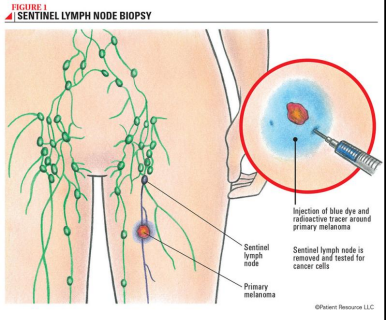
Schildwachtklier-procedure = Sentinel-procedure

- Gevoeligheid voor detectie lymfekliermetastasen
  Sentinel > echo > PET
  > CT > klinisch onderzoek
- 15-20 % van de sentinels = positief
- Klieruitruiming bij positieve sentinel ?
  - Kans op positiviteit andere klieren +/- 20%
  - Geen bewezen impact op overleving
  - prognostische informatie vs nevenwerkingen



Spanknebel, Am J Surg Pathol 2012

Schildwachtklier-procedure = Sentinel-procedure

Te overwegen zodra Breslow-dikte > 1 mm
Of >0,75 mm met additionele risicofactoren (ulceratie, hoge mitotische index)

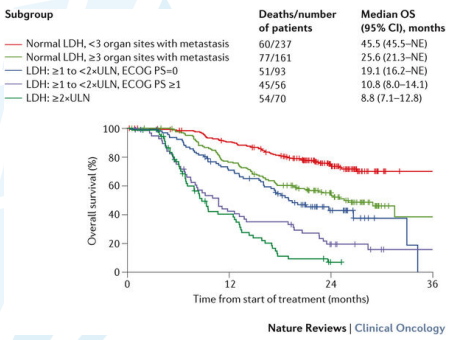
Frequentie (%) van positieve en negatieve SNB volgens Breslow dikte

Breslow dikte	Aantal patiënten	SNB pos. n (%)	SNB neg. n (%)
	3377	548 (16.2)	2829 (83.8)
≤ 1.00	735 (21.8)	45 (6.1)	690 (93.9)
1.01 – 2.00	1421 (42.1)	166 (11.7)	1255 (88.3)
2.01 – 4.00	845 (25)	214 (25.3)	631 (74.7)
≥ 4.00	376 (11.1)	123 (32.7)	253 (67.3)

White, Ann Surg Oncol 2011

Labo-onderzoeken

- Milde afwijkingen zijn doorgaans niet relevant
- Significante LDH-verhoging heeft een belangrijke prognostische waarde bij stadium 4 melanoom => 'tumormerker'



Nature Reviews Clinical Oncology **14**, 463–482 (2017)

Completformule
Ionogram
Nierfunctie
Leverfunctie
LDH

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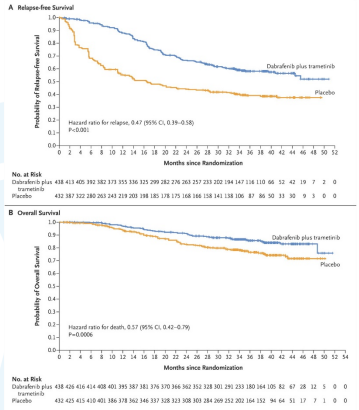
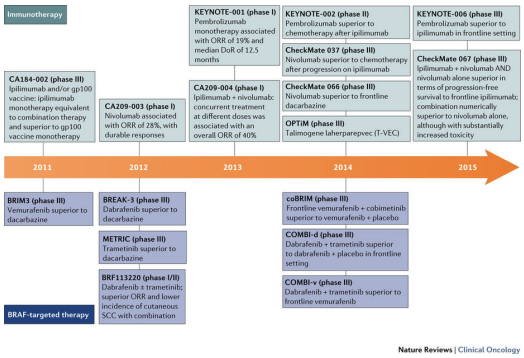
Systeemtherapie

- Adjuvant vs Stadium IV



Long GV et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1708539



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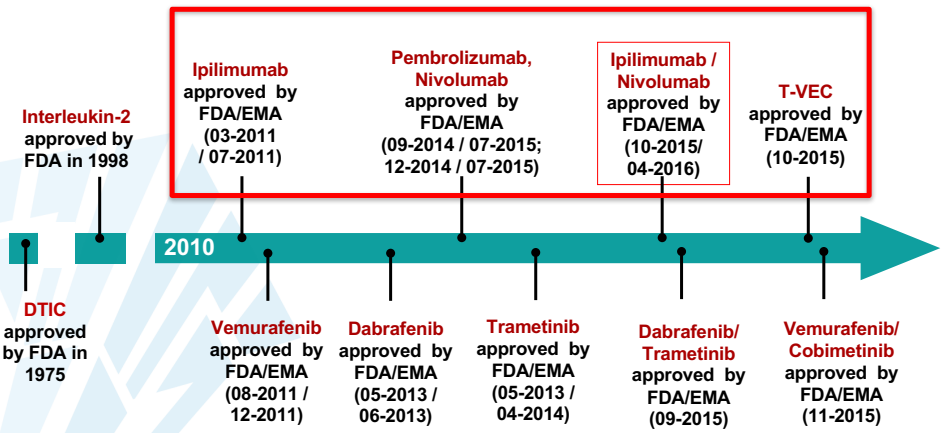
Systeemtherapie: Goedgekeurde behandelingen



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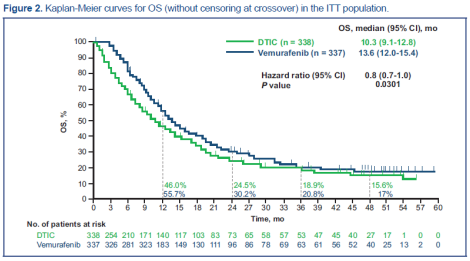
Systeemtherapie: Goedgekeurde behandelingen sinds 2011

Agent	Mechanism	FDA-approved indications
Targeted therapies		
Vemurafenib	BRAF inhibitor	As monotherapy and in combination with cobimetinib for $BRAF^{V600E/K}$-mutant disease
Dabrafenib	BRAF inhibitor	As monotherapy and in combination with trametinib for $BRAF^{V600E/K}$-mutant disease
Trametinib	MEK inhibitor	As monotherapy and in combination with dabrafenib for $BRAF^{V600E/K}$-mutant disease
Cobimetinib	MEK inhibitor	In combination with vemurafenib for $BRAF^{V600E/K}$-mutant melanoma
Immunotherapies		
Ipilimumab	Anti-CTLA-4 antibody	As monotherapy and in combination with nivolumab
Pembrolizumab	Anti-PD-1 antibody	As a monotherapy
Nivolumab	Anti-PD-1 antibody	In combination with ipilimumab, or as monotherapy
Oncolytic viral therapy		
Talimogene laharparepvec	Modified oncolytic herpes virus	Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after surgery

1.CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell-death protein 1.

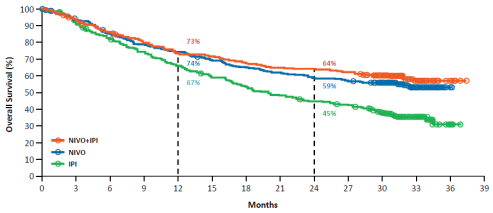
Nature Reviews Clinical Oncology **14**, 463–482 (2017)

Figure 2. Kaplan-Meier curves for OS (without censoring at crossover) in the ITT population.



CI, confidence interval; DTIC, dacarbazine; ITT, intent-to-treat.

Chapman P et al abstract SMR 2015



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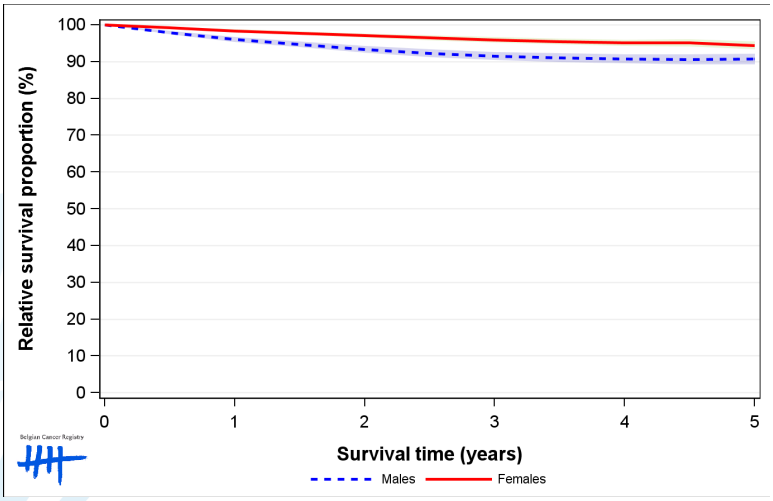
Prognose melanoom (België 2011-2015)



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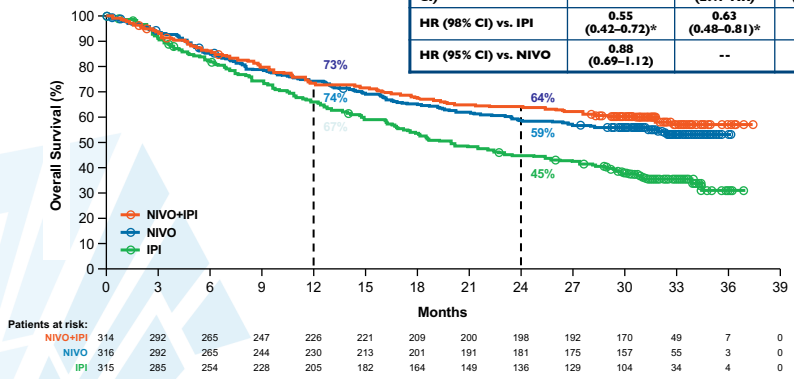
Prognose van stadium IV melanoom is sterk verbeterd

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Larkin J NEJM 2015 CA209-067
Database lock: Sept 13, 2016, minimum f/u of 28 months

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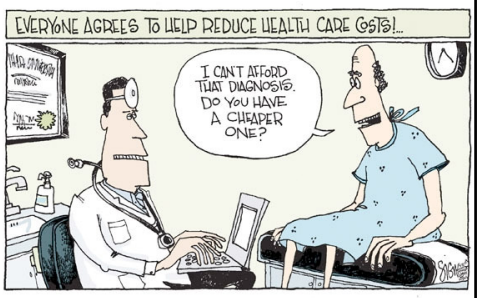
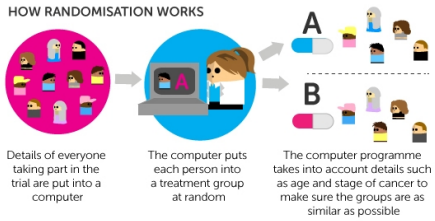
Bijwerkingen

- Klinisch
- Praktisch
- Financieel



- Temporeel aspect: niet enkel graad 3 toxiciteit is relevant!



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Changing the face of melanoma … the modern melanoma patient

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