Kanker bij kinderen en adolescenten

Anne Uyttebroeck
Kinderhemato-oncologie

PEV 12-12-2023

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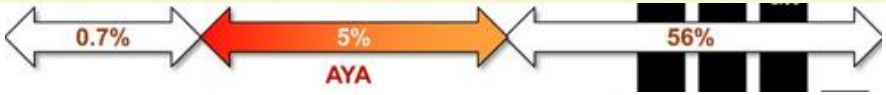
Leeftijdgerelateerde incidentie kanker



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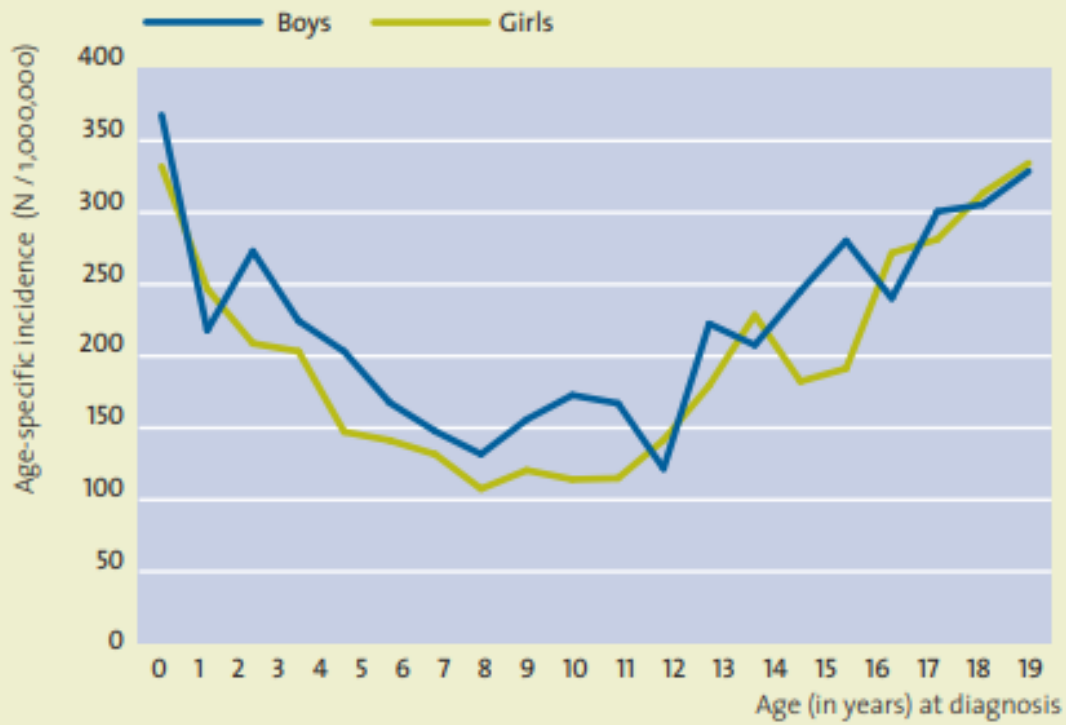
Leeftijdgerelateerde incidentie kanker

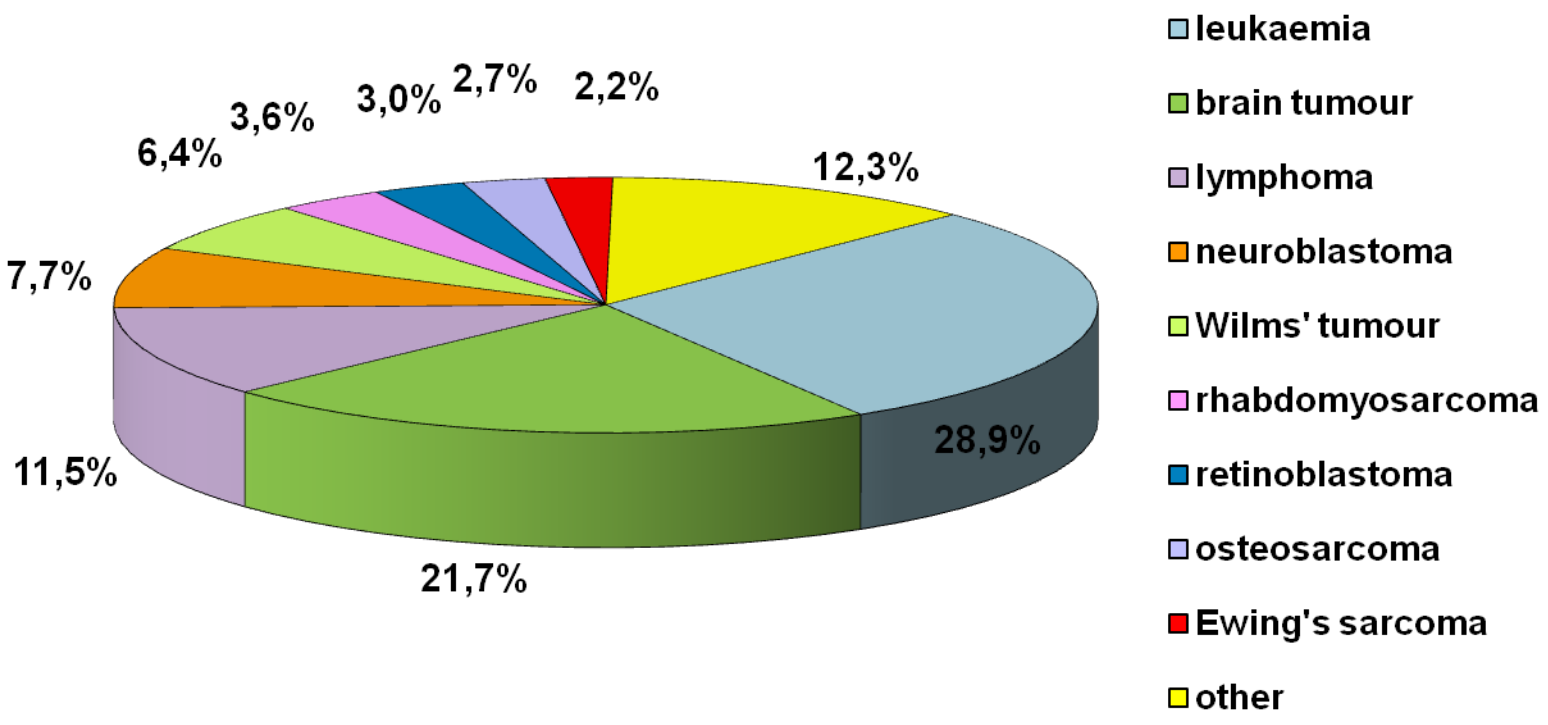
Every year,
about 340 children
(0-14 years)
and 180 adolescents
(15-19 years) are
diagnosed with a
malignancy

Figure 4 Cancer in children and adolescents: Age-specific incidence rate by sex, Belgium 2010-2016



Source: Belgian Cancer Registry

Type of childhood cancer



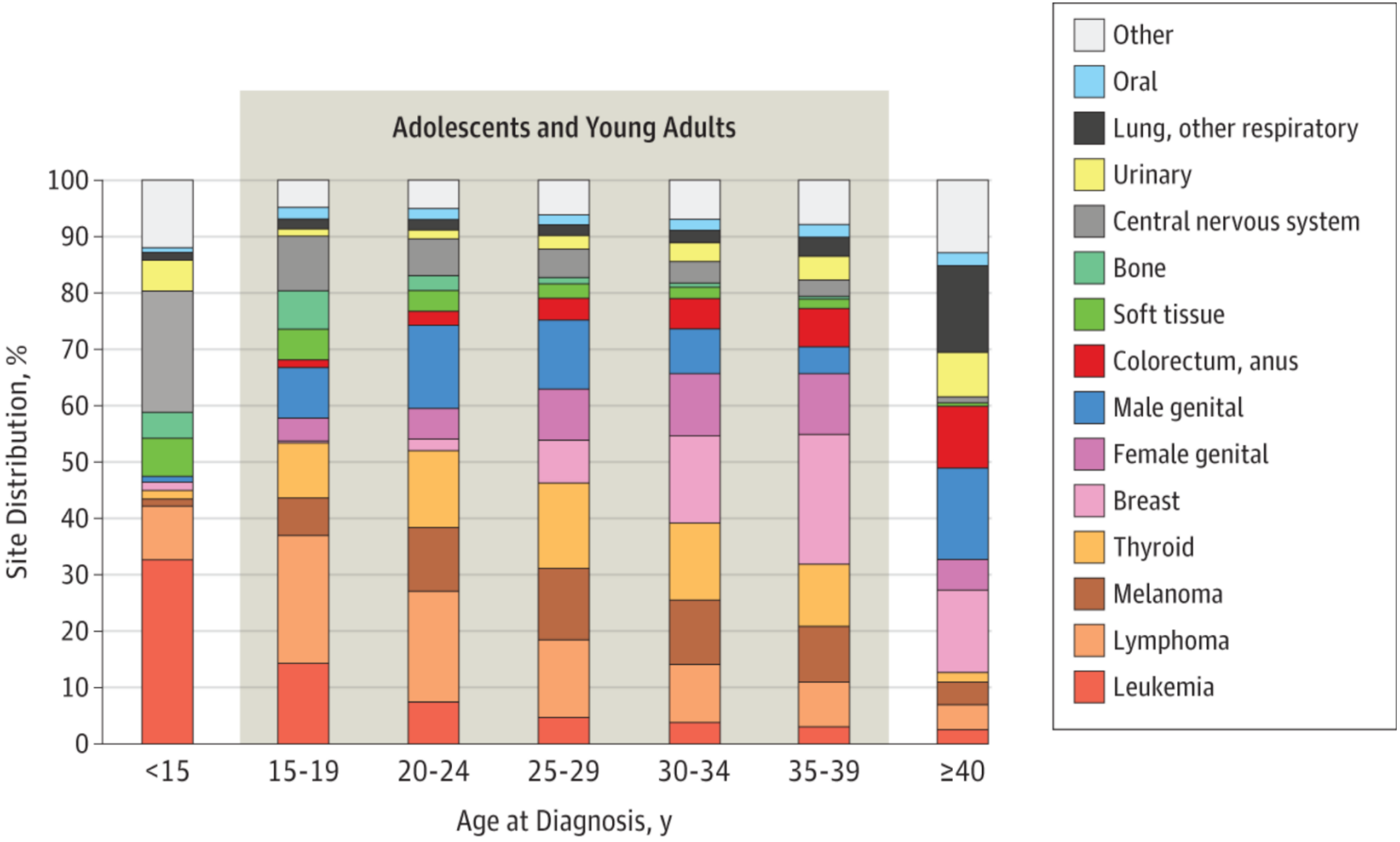
Pizzo P, Principles and practice of pediatric oncology 2002

Life stages

Neo-natal	Pediatric	AYA	Adult	Geriatric

Adolescents: 10-19 jaar
AYAs: 15-39 jaar

Cancer site distribution by age



JAMA Pediatr. 2016;170(5):495-501. doi:10.1001/jamapediatrics.2015.4689

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Etiologie kinderkanker

- GEEN
- Sporadische events

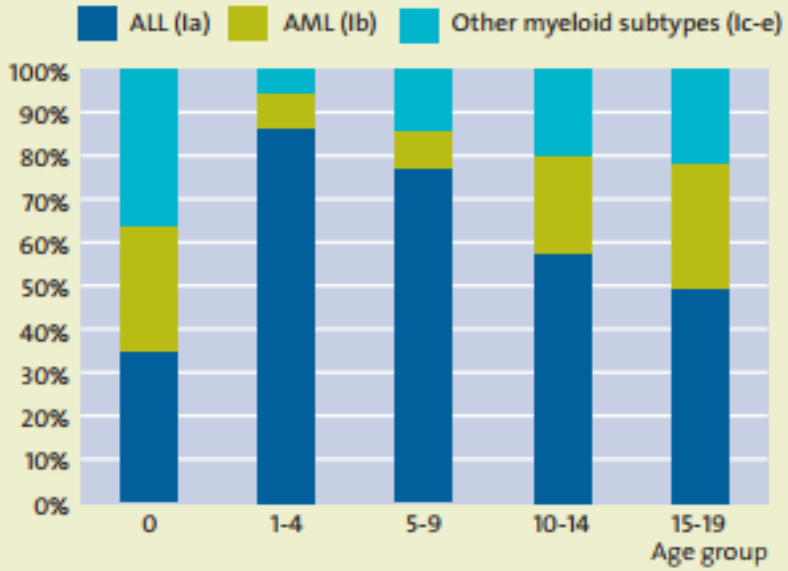
- Genetische predispositie <10%
  - Li-Fraumeni syndroom
  - Ataxia telangiectasia
  - Turner syndroom
  - Beckwitt-Wiedemann
  - Down syndroom
  - Neurofibromatosis NF1
  - Fanconi

Leukemie

- **Akute leukemie**
- *Chronische leukemie zeer zeldzaam in kinderen*

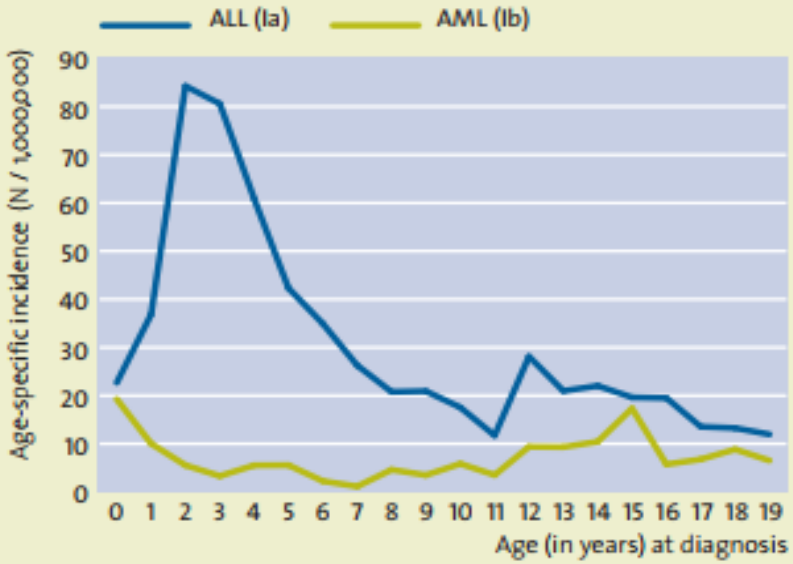
➢ Akute lymfoblasten leukemie ALL
➢ Akute myeloblasten leukemie AML

Figure 15 Leukaemias, myeloproliferative diseases, and myelodysplastic diseases by age group, Belgium 2010-2016



Source: Belgian Cancer Registry

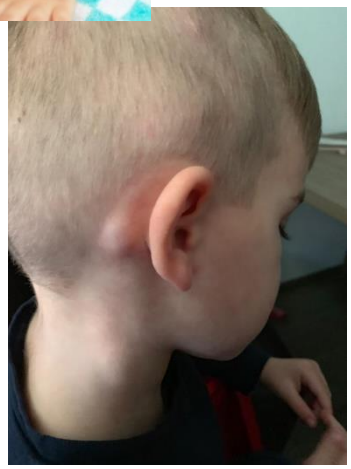
Figure 16 Age-specific incidence rates for ALL (Ia) and AML (Ib), Belgium 2010-2016

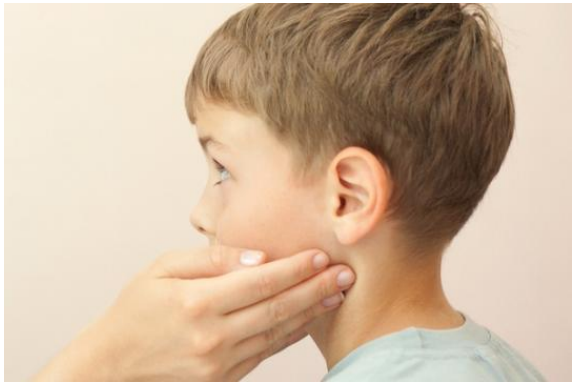


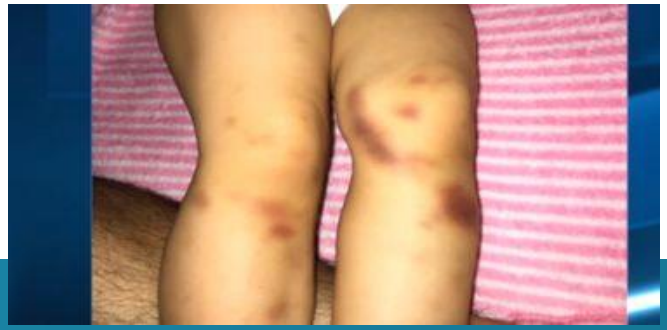
Source: Belgian Cancer Registry

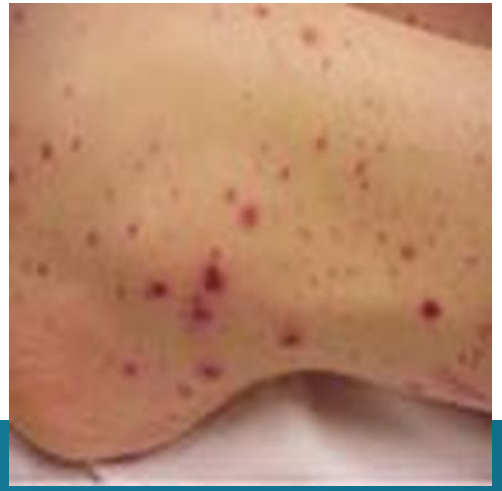
Symptomen & Kliniek

- algemene malaise
  - futloos
  - hangerig
- infecties, aanslepende koorts
- bleekheid
- klieren
- botpijn
  - nachtelijk!
  - manken
- bloedingsneiging
  - huid
  - tandvlees
- vergrote lever
- vergrote milt



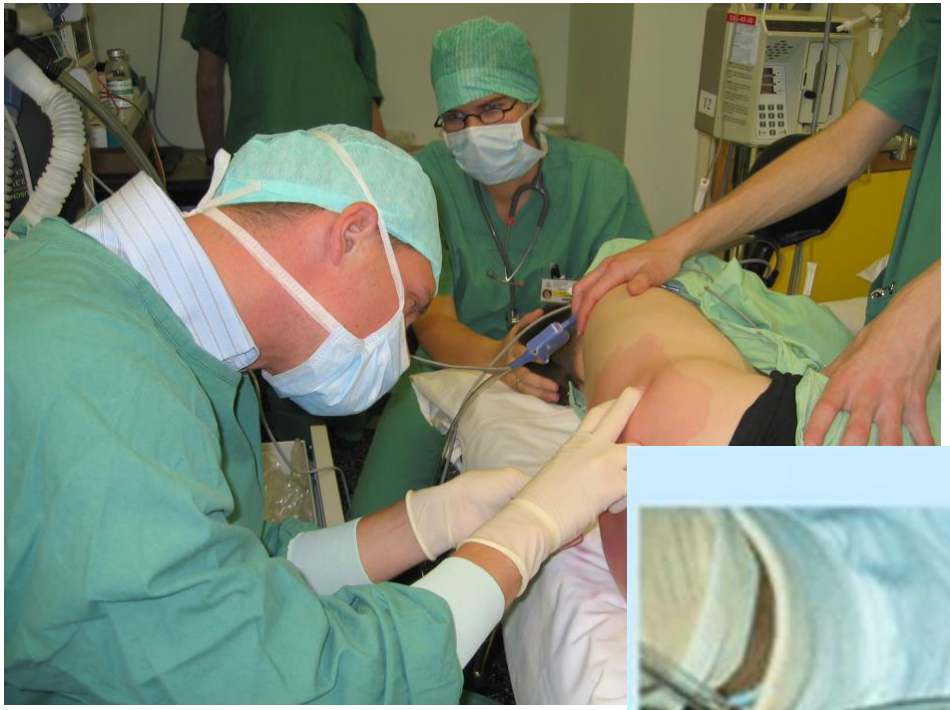


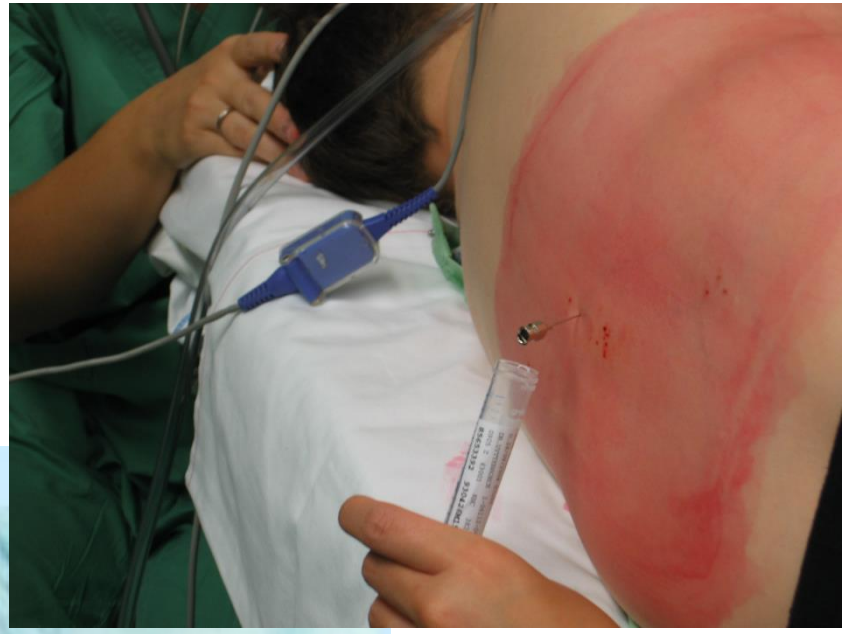


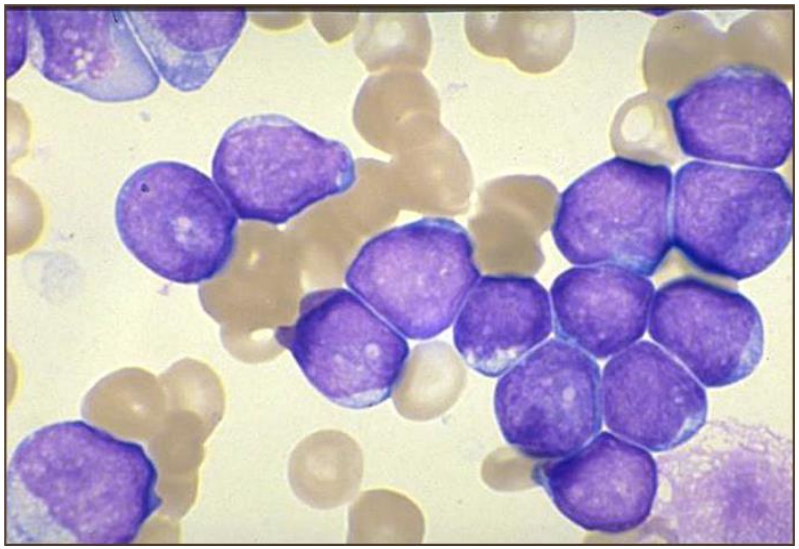


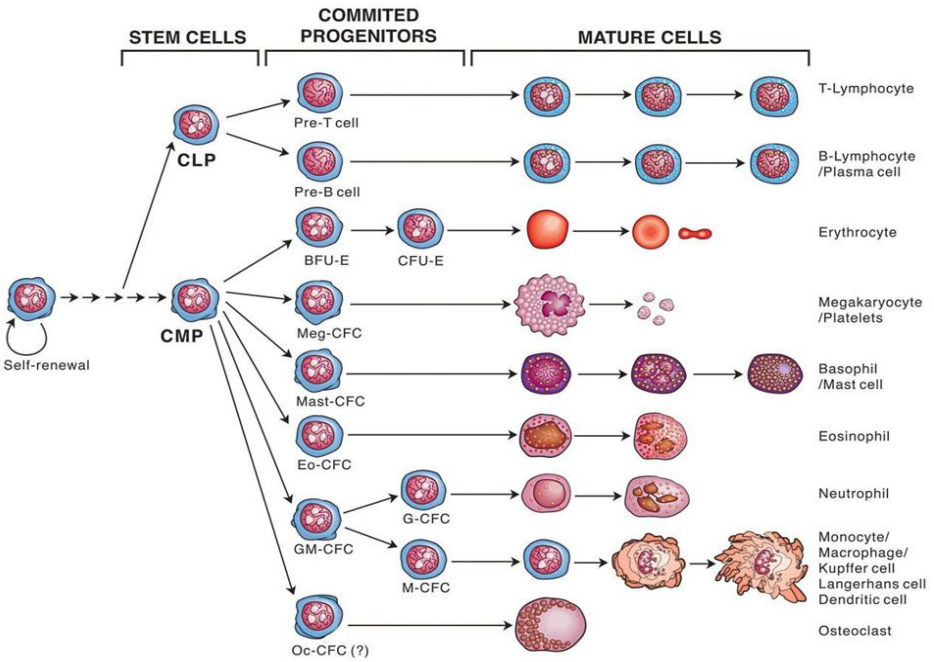
Diagnostiek

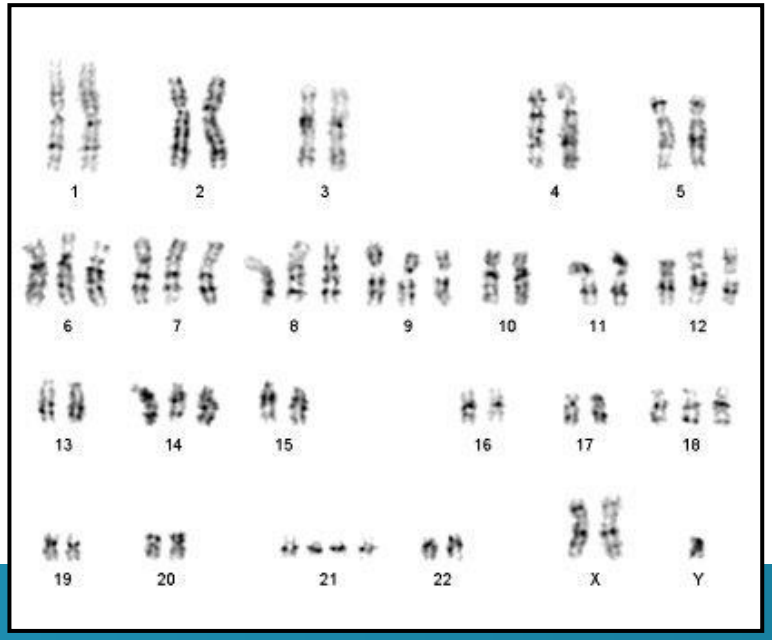
- Beenmergonderzoek onder anesthesie
- Lumbale punctie








STEM CELLS
COMMITED PROGENITORS
MATURE CELLS
Pre-T cell
CLP
Pre-B cell
BFU-E
CFU-E
Self-renewal
CMP
Meg-CFC
Mast-CFC
Eo-CFC
G-CFC
GM-CFC
M-CFC
Oc-CFC (?)
T-Lymphocyte
B-Lymphocyte /Plasma cell
Erythrocyte
Megakaryocyte /Platelets
Basophil /Mast cell
Eosinophil
Neutrophil
Monocyte/ Macrophage/ Kupffer cell Langerhans cell Dendritic cell
Osteoclast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X
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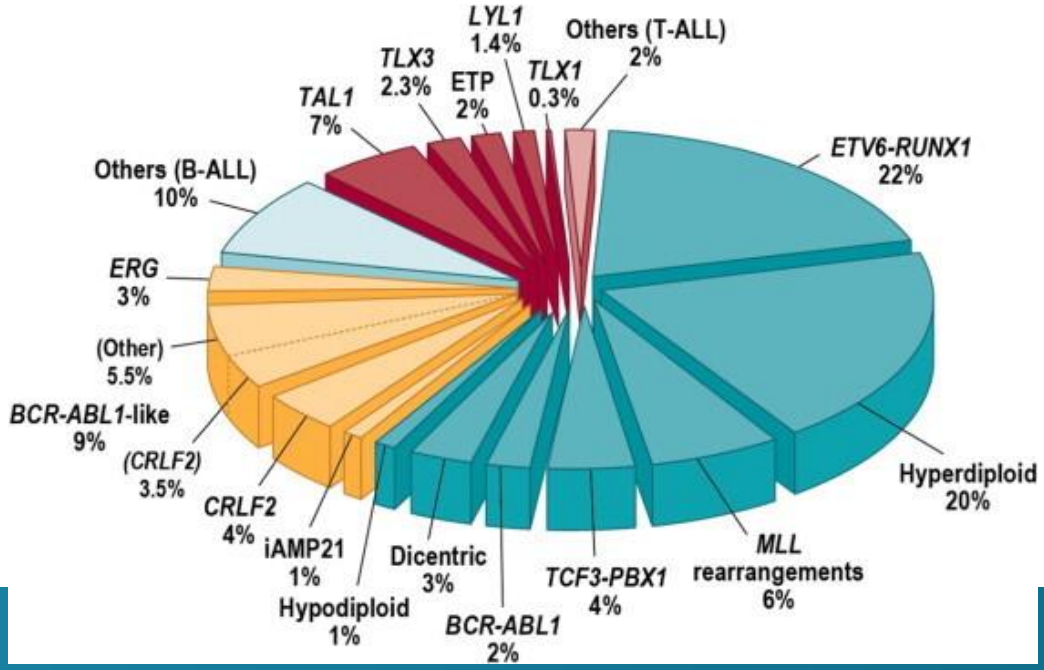
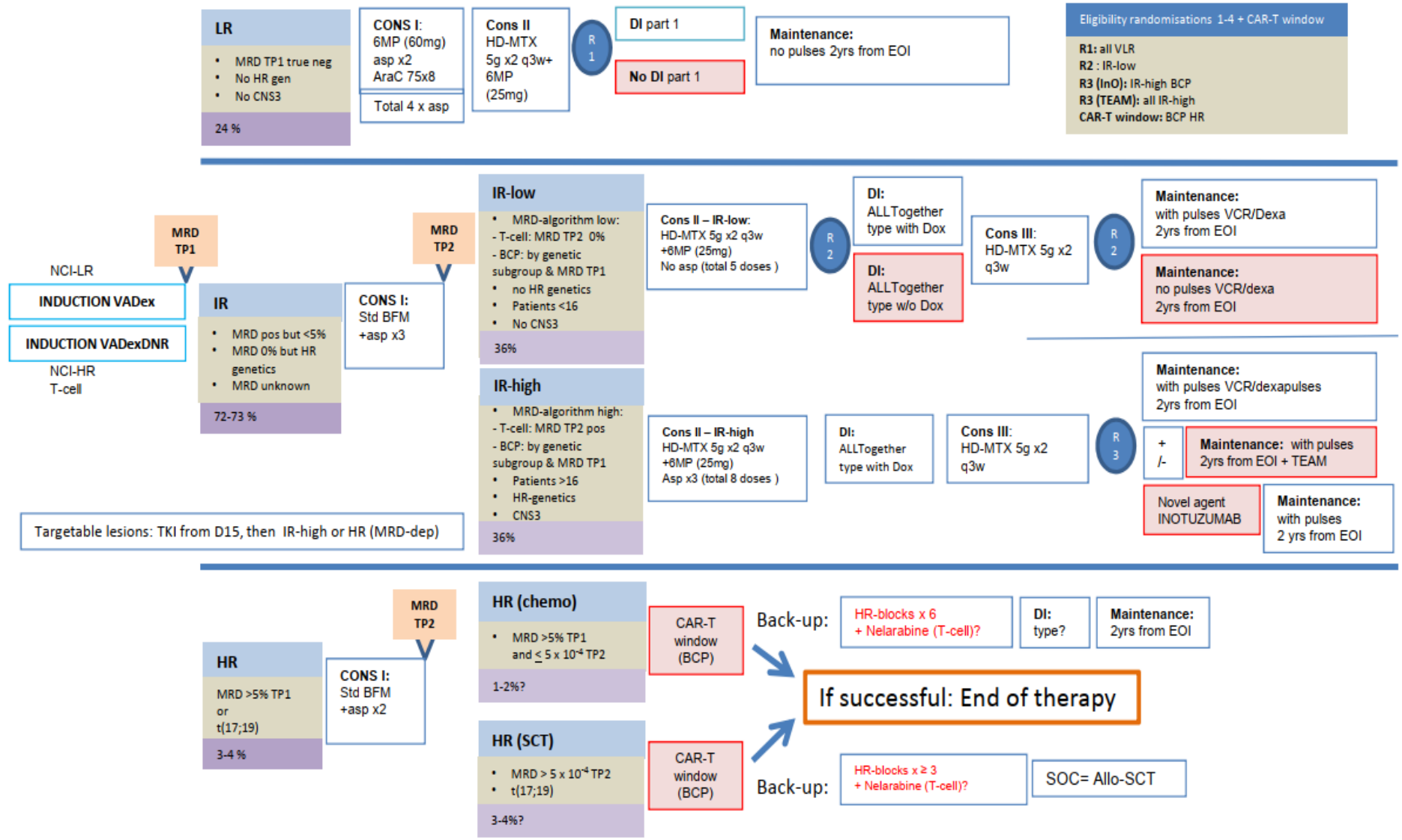

LYL1 1.4%
Others (T-ALL) 2%
TLX3 2.3%
ETP 2%
TLX1 0.3%
TAL1 7%
ETV6-RUNX1 22%
Others (B-ALL) 10%
ERG 3%
(Other) 5.5%
BCR-ABL1-like 9%
(CRLF2) 3.5%
CRLF2 4%
iAMP21 1%
Hypodiploid 1%
Dicentric 3%
BCR-ABL1 2%
TCF3-PBX1 4%
MLL rearrangements 6%
Hyperdiploid 20%

Behandeling

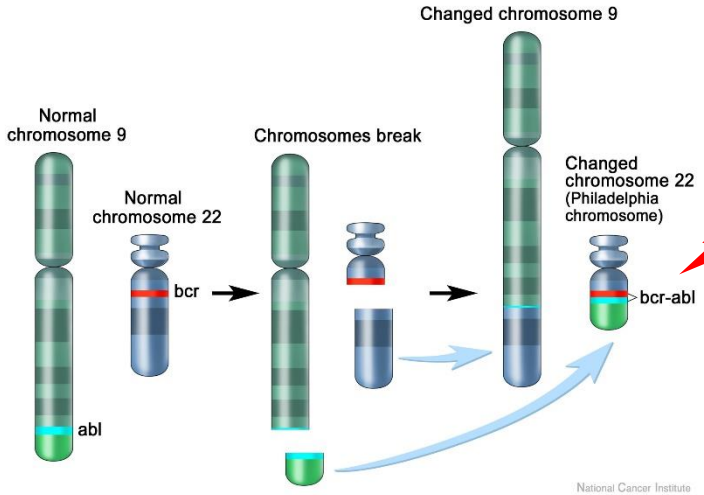
- Bepalen van risicogroep
- Therapie op maat

- Chemotherapie
- Stamceltransplantatie: kleine subgroep

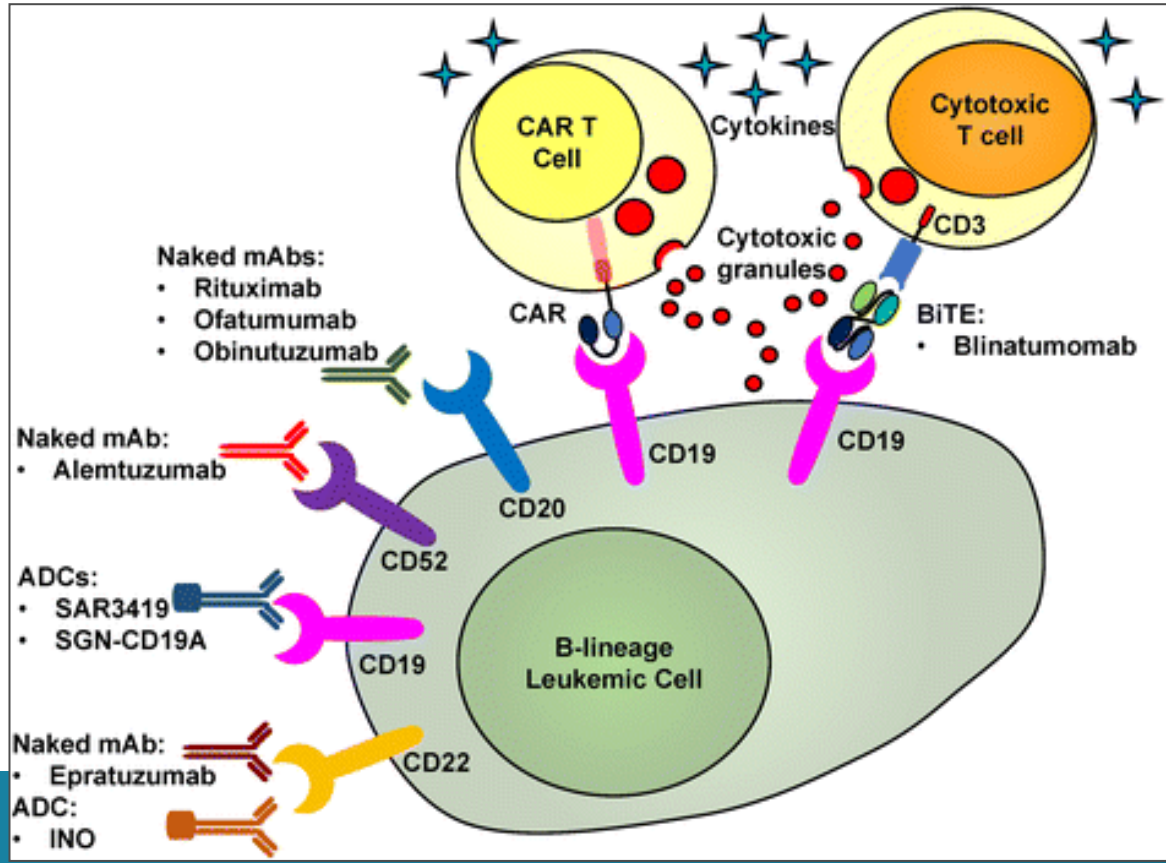
ALLTogether1 protocol overview



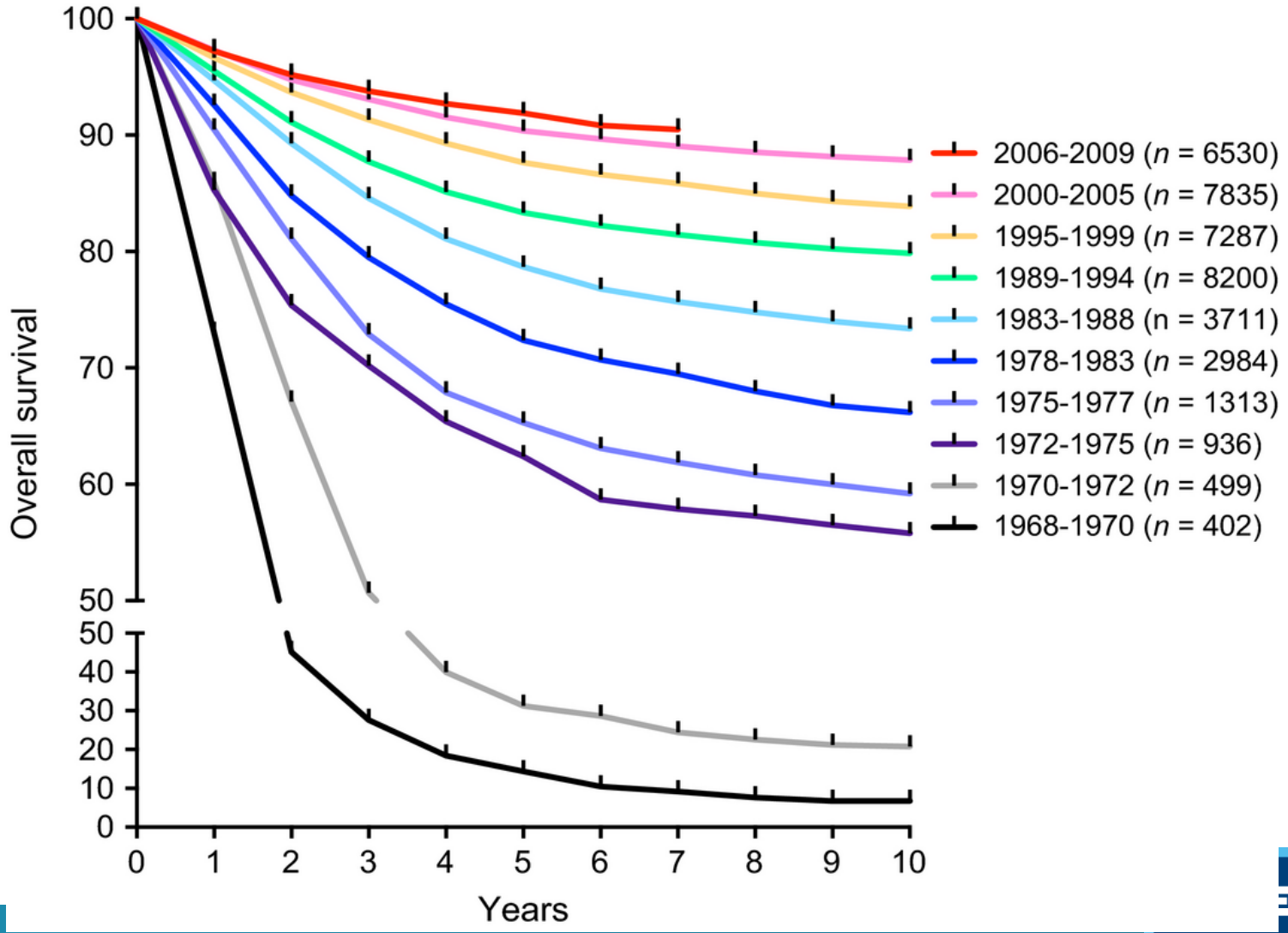
New drugs



imatinib



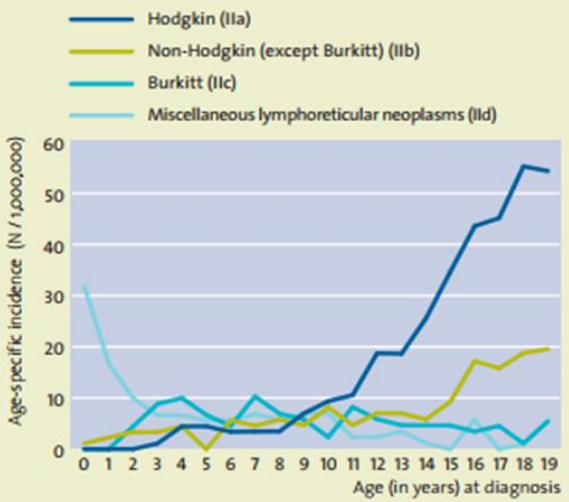
Improved overall survival of ALL



Lymfomen

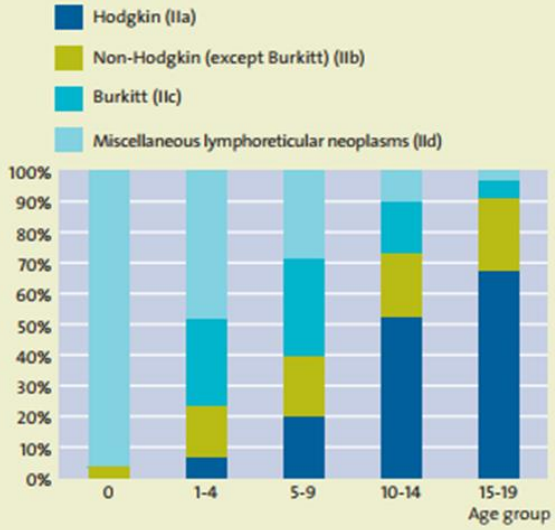
- Non Hodgkin lymfoom
  - Lymfoblastisch lymfoom
  - Burkitt lymfoom
  - Diffuus large B-cell lymfoom
  - Anaplastisch large cell lymfoom
- Hodgkin lymfoom

Figure 25 Lymphomas and reticuloendothelial neoplasms: Age-specific incidence rates, Belgium 2010-2016



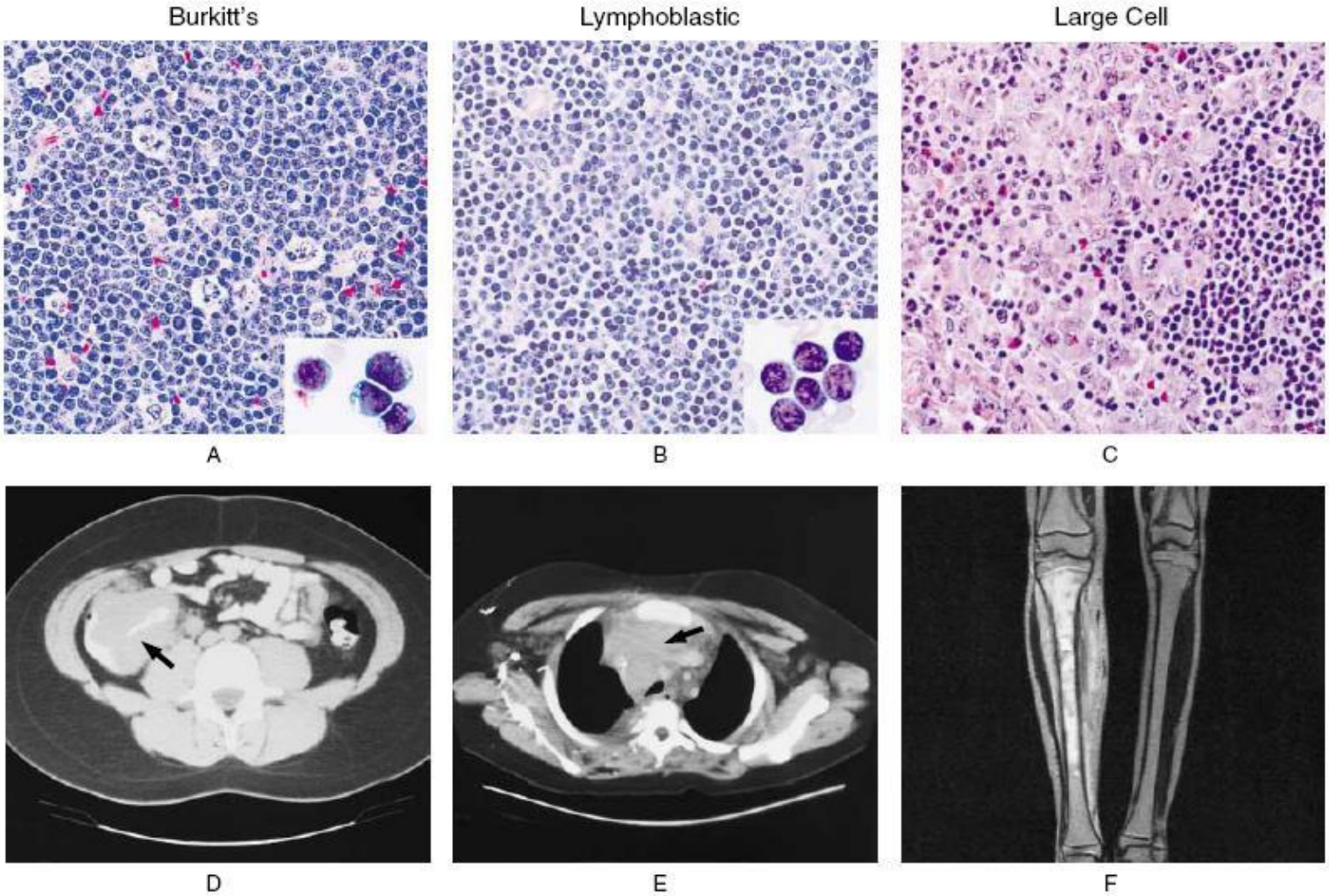
Source: Belgian Cancer Registry

Figure 26 Lymphomas and reticuloendothelial neoplasms by age group, Belgium 2010-2016



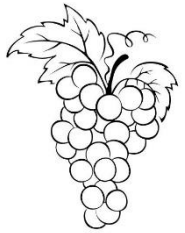
Source: Belgian Cancer Registry

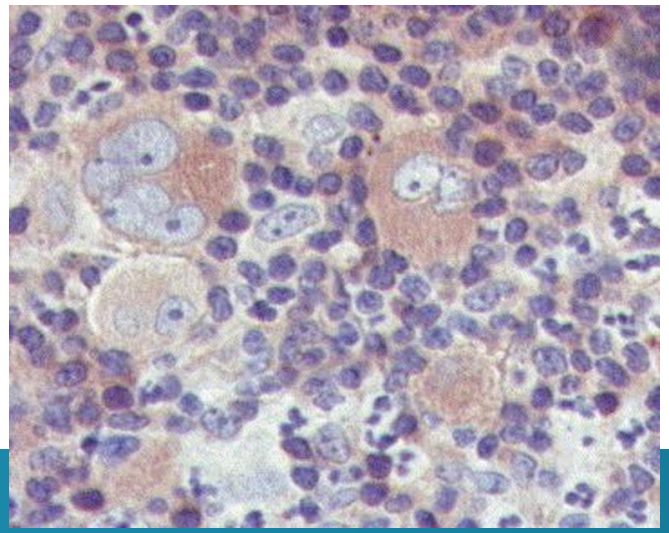
Non Hodgkin lymfomen

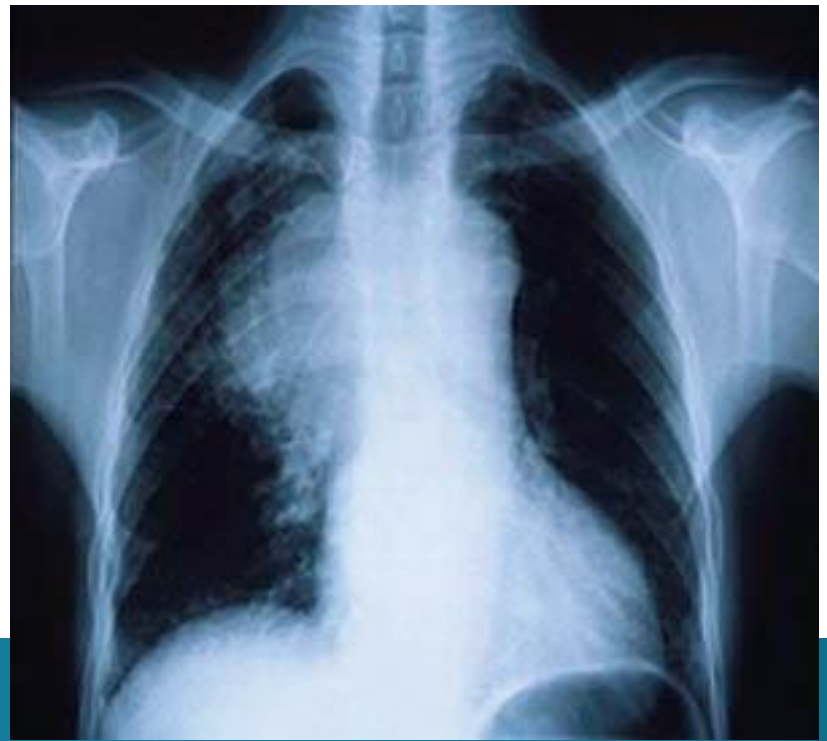


Symptomen bij Hodgkin

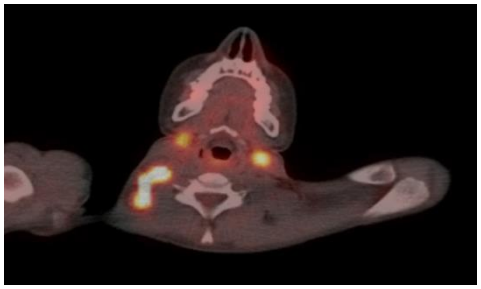
- Adenopathieën: pijnloos, rubberachtig, druiventros
- Mediastinale massa 50-60%
- B-symptomen
  - koorts
  - gewichtsverlies > 10 %
  - nachtzweten
- Jeuk
- Vermoeidheid
- Anorexie

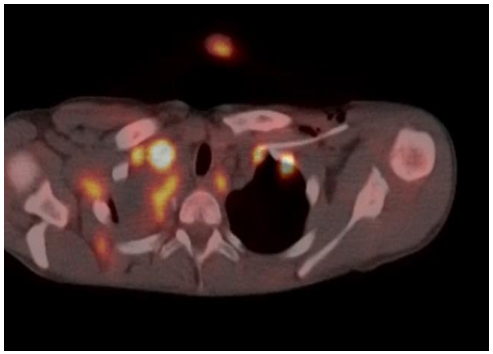


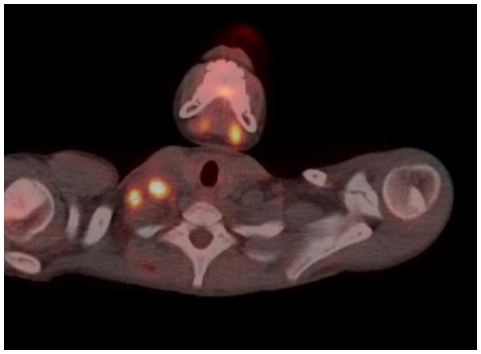


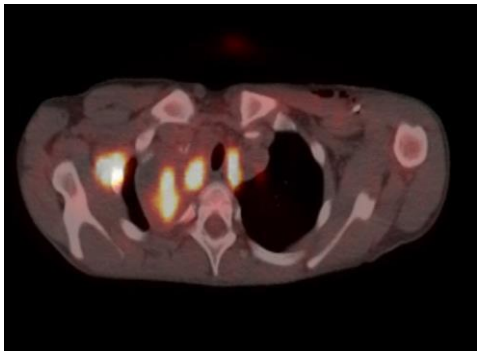


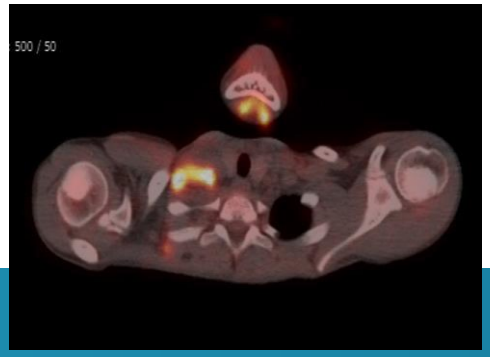
Staging PET-CT

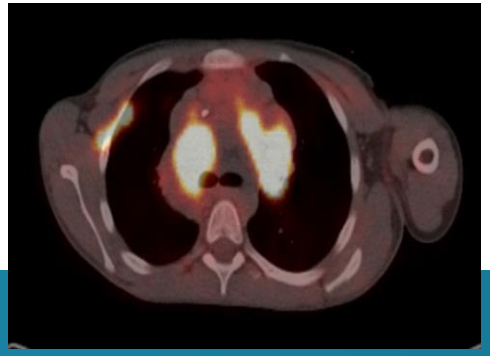


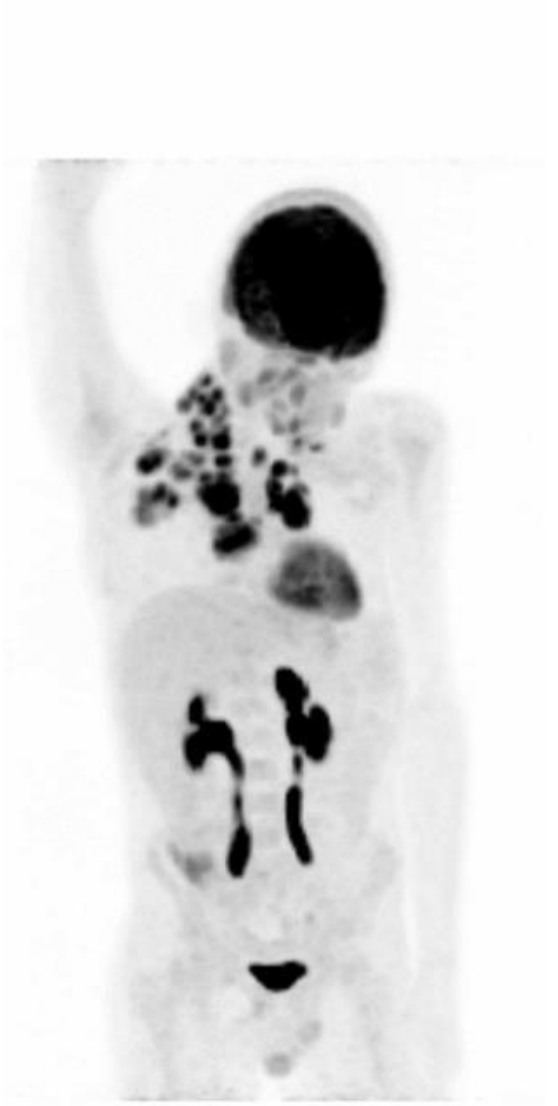












Behandeling Hodgkin

- Chemotherapie
- Radiotherapie enkel nog bij minder goede respons, in functie van PET respons na 2 cycli chemotherapie

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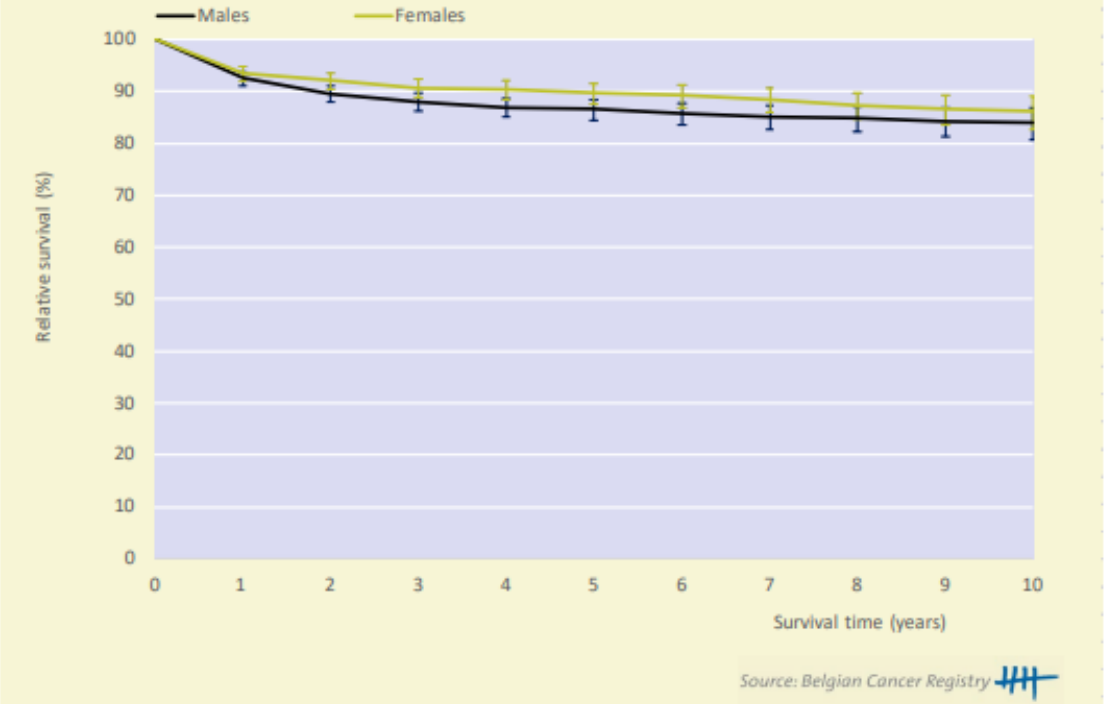
Prognose & overleving

Uitstekend!

Opvolgen van lange termijn problemen

Figure 8 Hodgkin lymphomas: Relative survival* by sex, Belgium 2009-2018



* The relative survival values are represented with 95% Confidence Intervals

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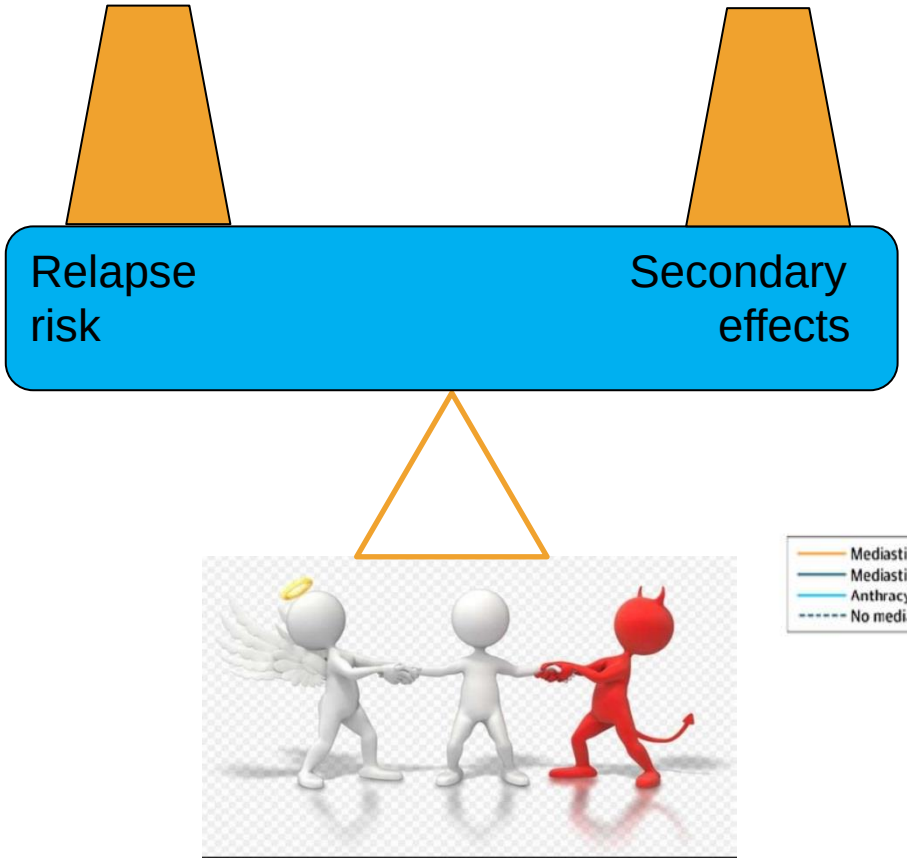
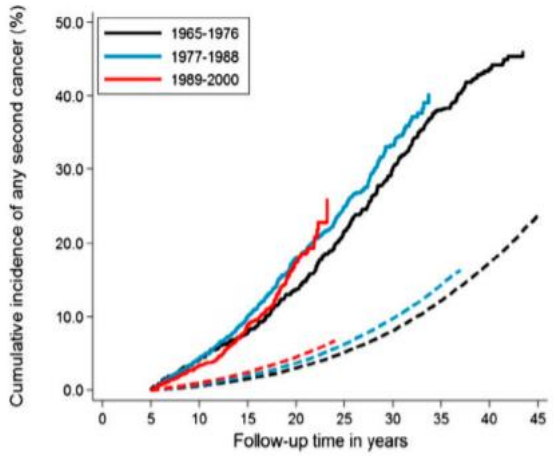
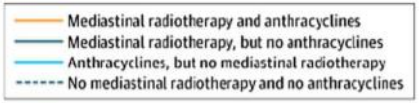
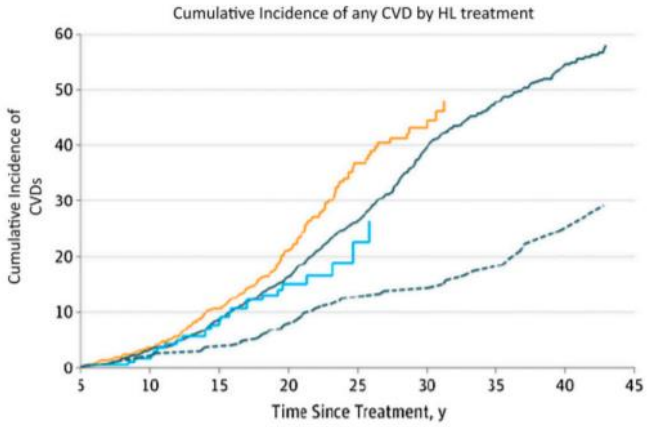
Therapie Hodgkin lymfoom





Cumulative incidence 40 years after HL: **43.6%**





Harel S, et al. Haematologica 2011;96:1692-9
Van leeuwen FE, Ng AK. Hematology Am Soc Hematol Educ Program 2016;2016:323-30

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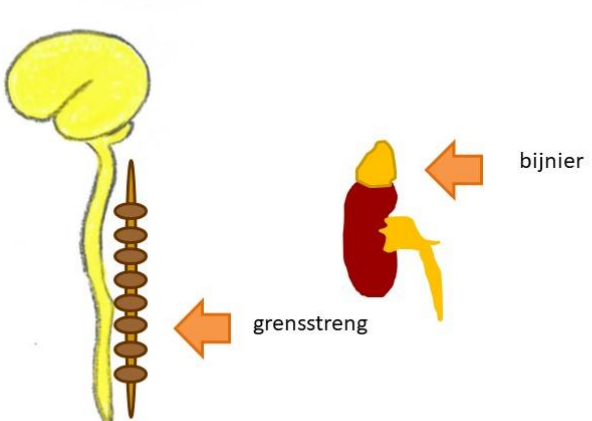
Neuroblastoom

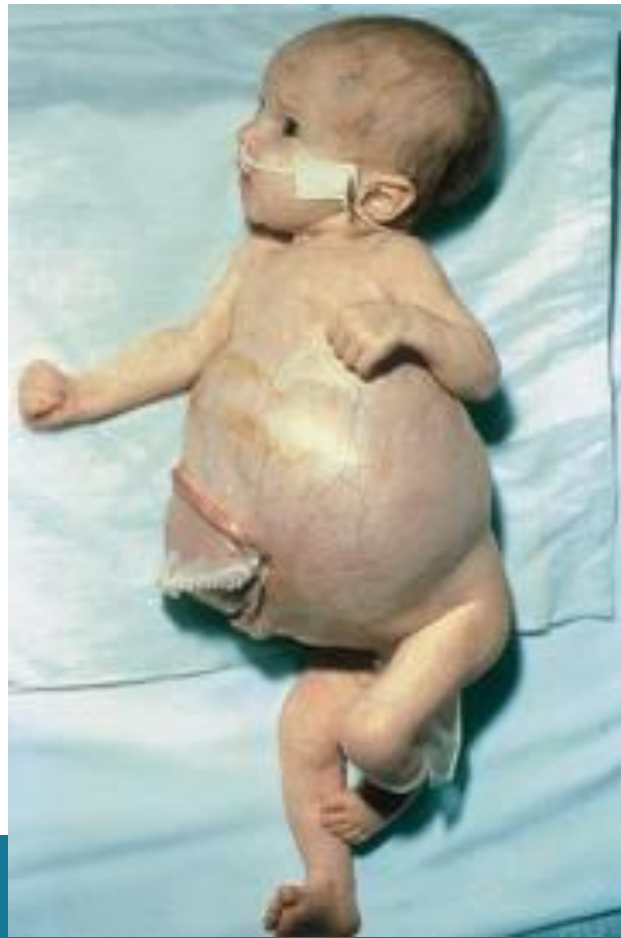
- 15 % van alle tumoren voor de leeftijd van 4 jaar
- Embryonale tumor
- Uitgaande van cellen van de neurale lijst die later de sympathische ganglia en bijniermerg gaan bevolken
- Zowel heel kwaadaardig gedrag als spontane regressie/differentiatie in goedaardige tumoren beschreven

Sympatische zenuwstelsel



Symptomen en Kliniek

- Jong kind
- Ziek: pijn, vermageren, koorts
- Tumorlocalisatie: bijnier, sympatische keten: opgezette buik, grote lever
- Orbitale en peri-orbitale infiltratie, brilhematoom



Therapie

- Chemotherapie: intensief
- Chirurgie
- Radiotherapie
- Autologe stamceltransplantatie
- Vitamine A zuur
- Monoclonale antistoffen

Prognose

- Leeftijd <1 jaar: uitstekend
- Biologische markers: N-MYC amplificatie
- Stadium afhankelijk
- Ouder dan 1 jaar en stadium 4: EFS < 55%
- Prognose: goed $\rightarrow$ zeer slecht

Wilms' tumor

- Niertumor van jonge kind
- 6 % van de tumoren bij de kinderen
- Typische kindertumor: ontstaat uit "embryonaal nierweefsel"

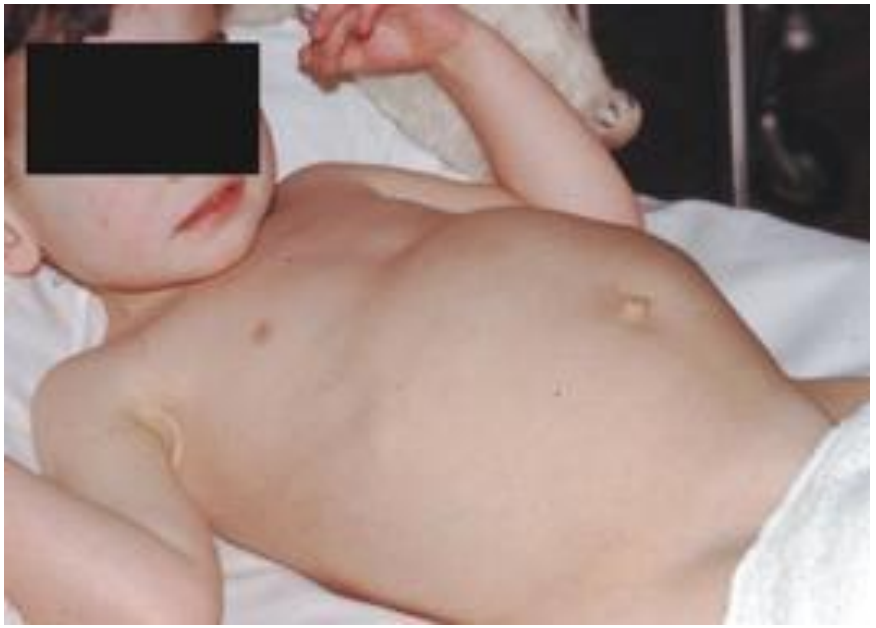
  → nefrogene resten

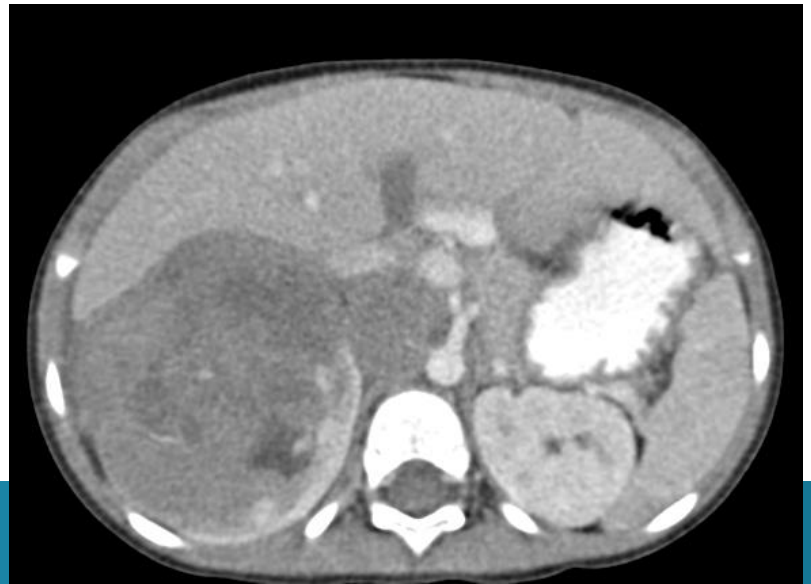
  → congenitaal mesoblastisch nefroma
- Zeer goede prognose

Kliniek

Abdominale massa:

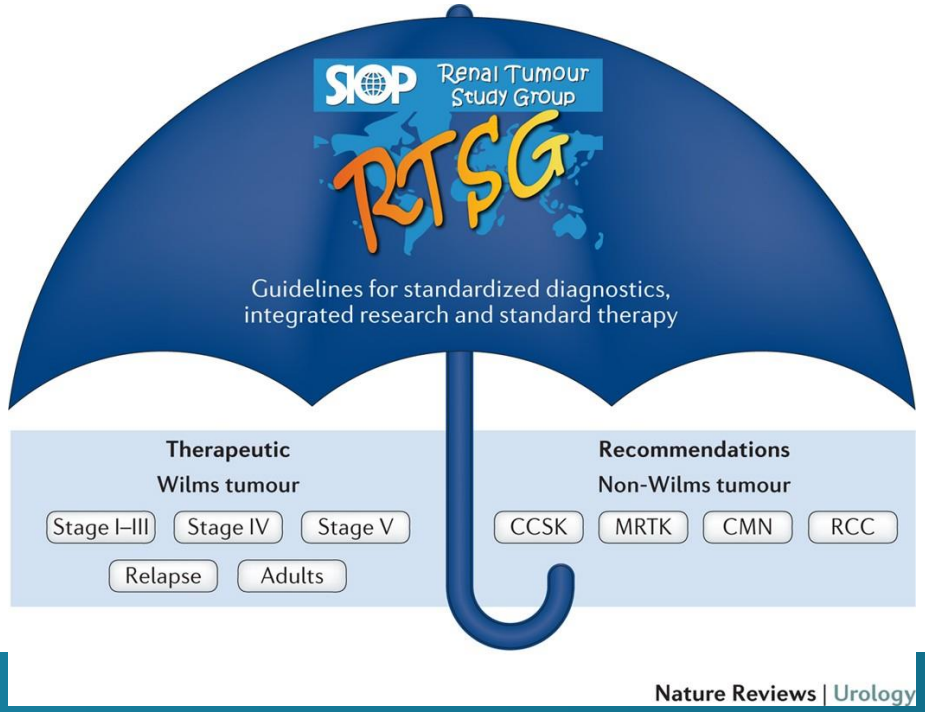
- toevallige vondst
- pijnloos
- snelgroeiend
- voelbaar,
  soms zichtbaar in de flank
- soms bloed in urine





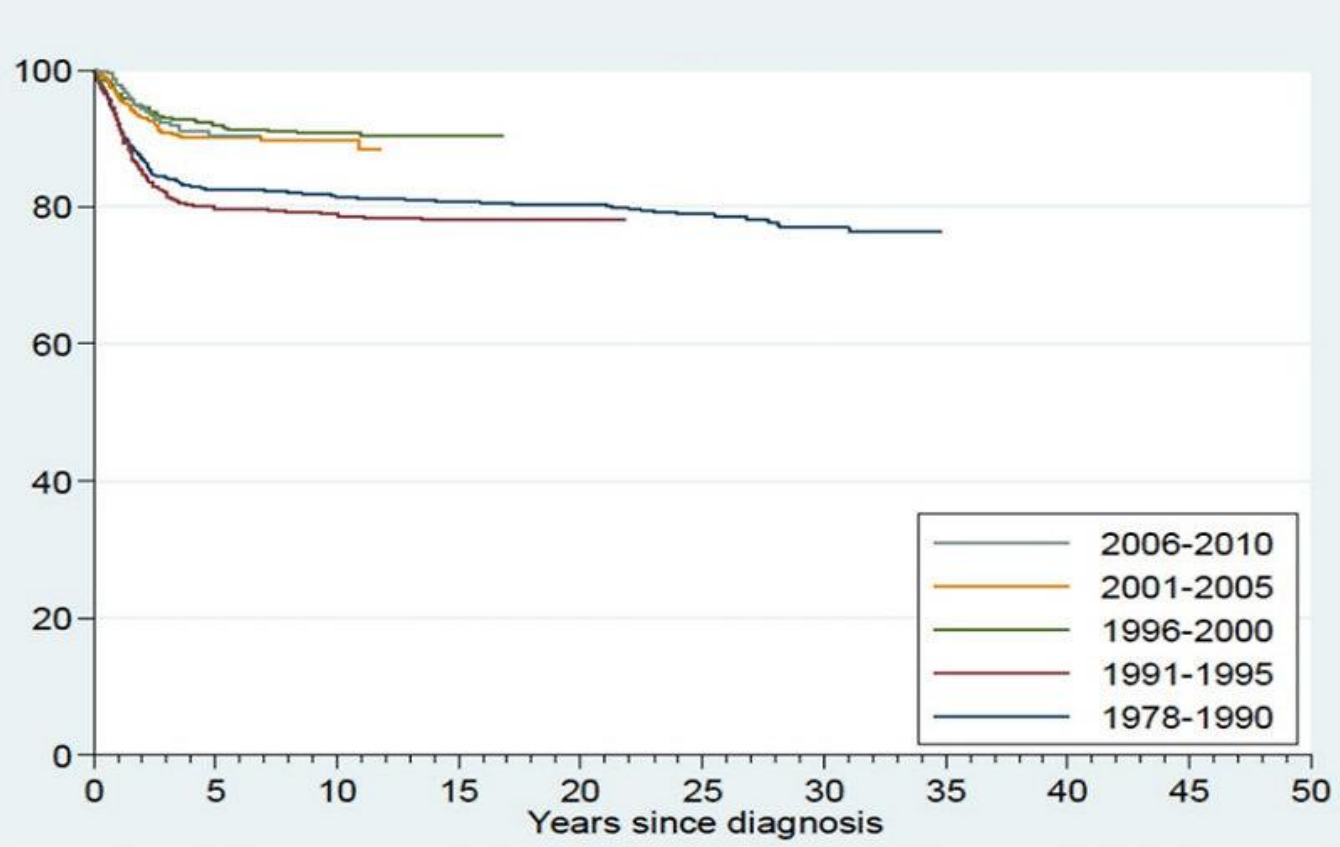
Therapie

- Pre-operatieve chemotherapie om chirurgie te vergemakkelijken: kleinere tumor
- Nefrectomie
- Postoperatieve chemotherapie
- (Radiotherapie)



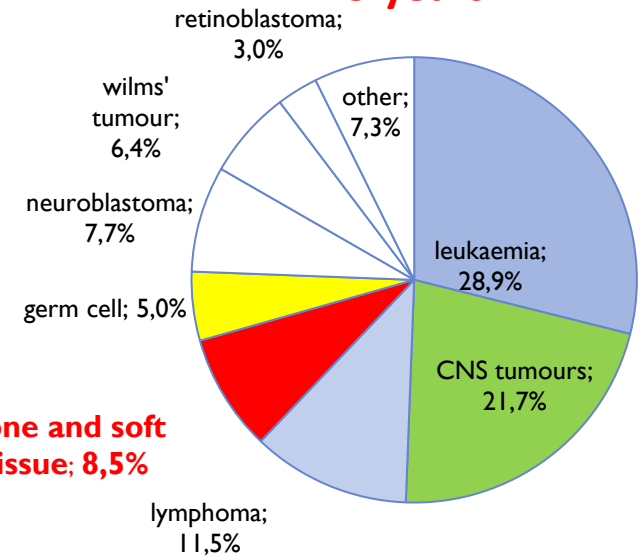
Prognose

- Zeer goed
- 80 – 95% definitieve genezing



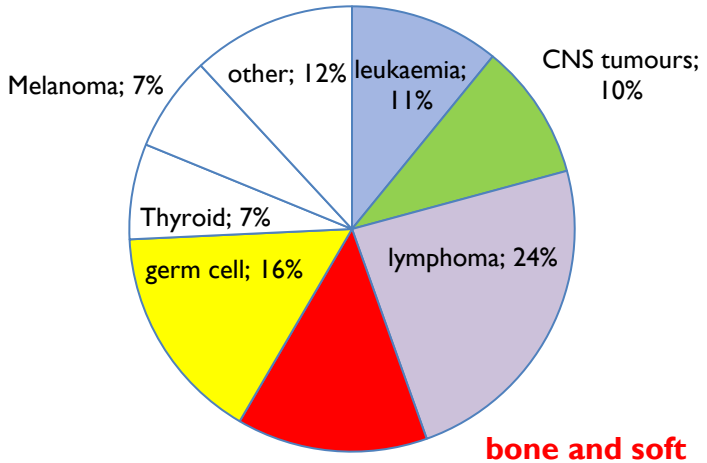
Weke delen sarcomas

< 15 years



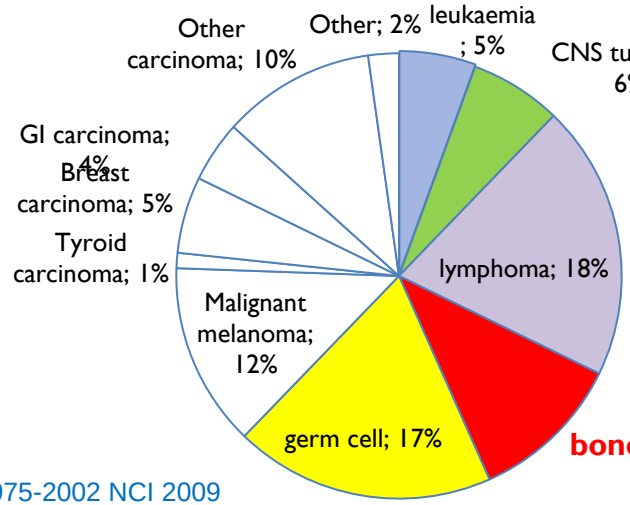
bone and soft tissue; 8,5%

15 – 19 years



bone and soft tissue; 14%

20 – 29 years



bone and soft tissue; 10%

Ries L et al. SEER Cancer Statistic Review,1975-2002 NCI 2009

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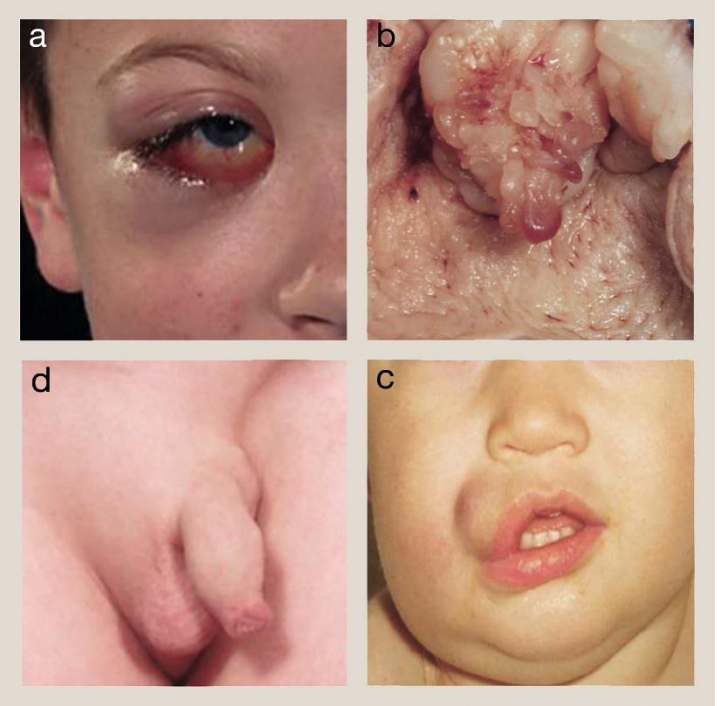
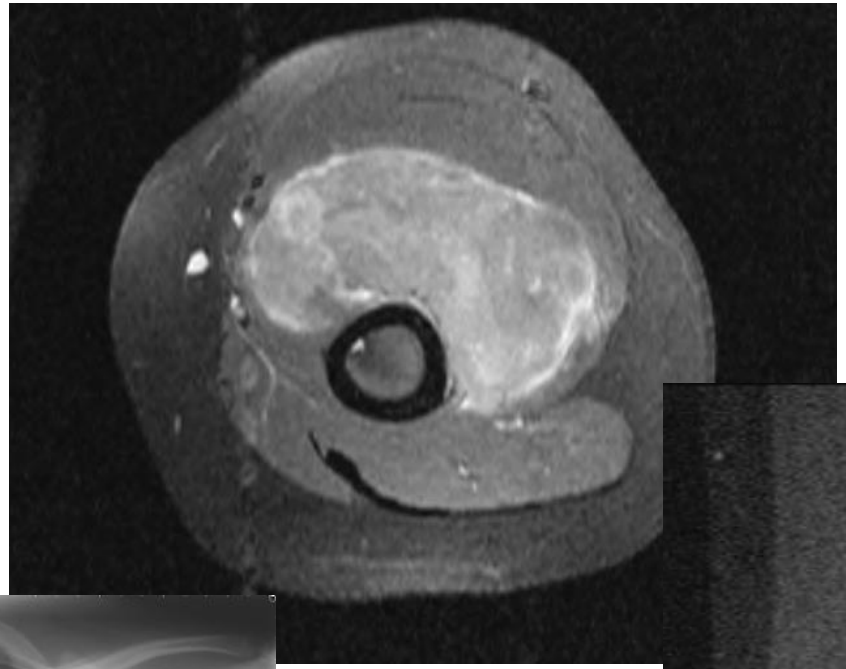
Rhabdomyosarcoma

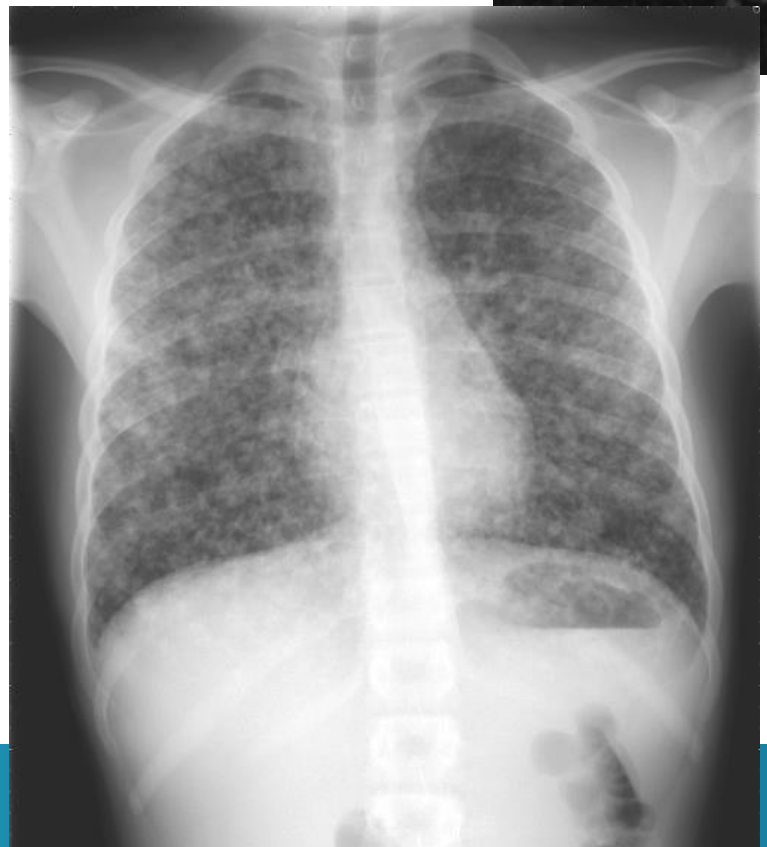
- Mesenchymale oorsprong
- 2 subtypes - embryonale
  - alveolaire
- Localisatie: - hoofd en nek
  - orbitaal
  - genito-urinaire tract
  - ledematen
  - romp

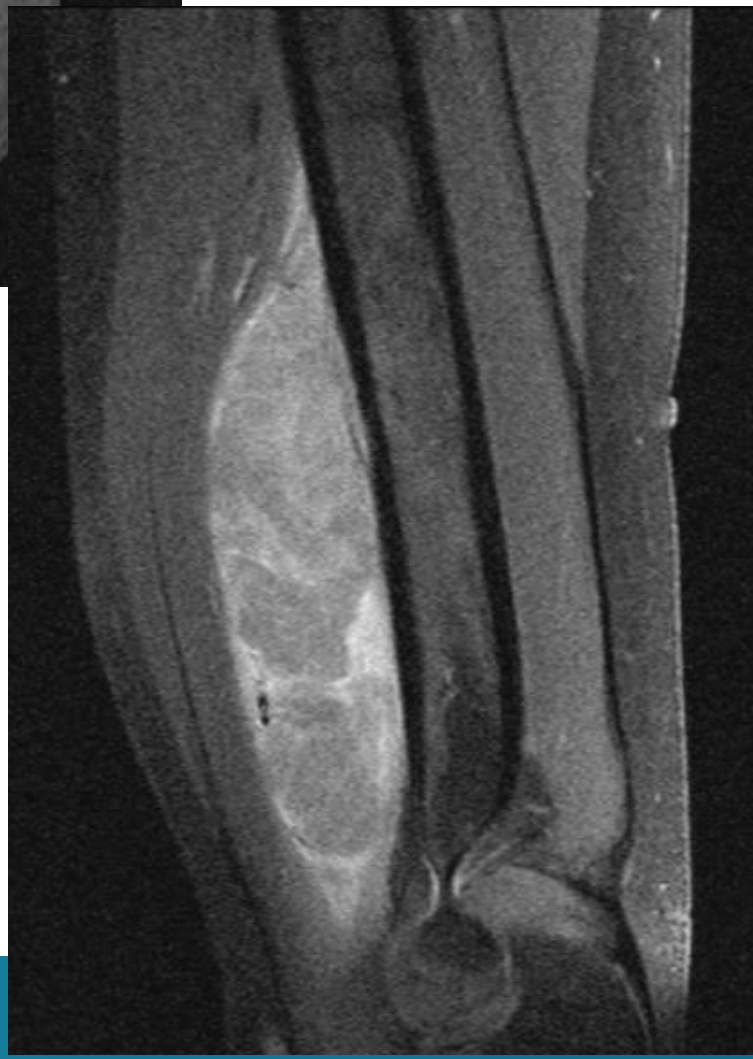


Ewing sarcoma

- Neuronale oorsprong
- Bot-weke weefsels
- Voorkeursleeftijd: 10 $\rightarrow$ 30 jaar
- Symptomen localisatie afhankelijk:
  - pijn
  - zwelling
  - uitvalsverschijnselen
  - “pneumonie”
- Laattijdige diagnose
- Systeemaandoening: micrometastasen: -long
  -bot
  -beenmerg

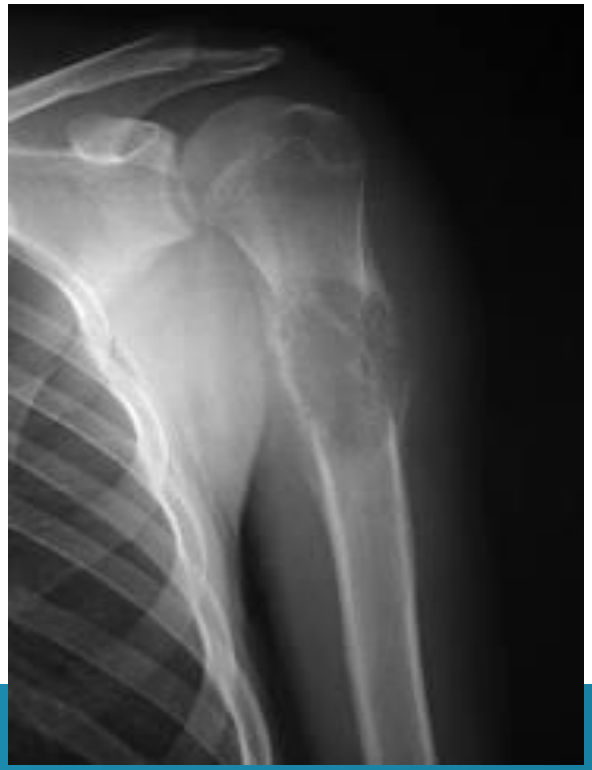


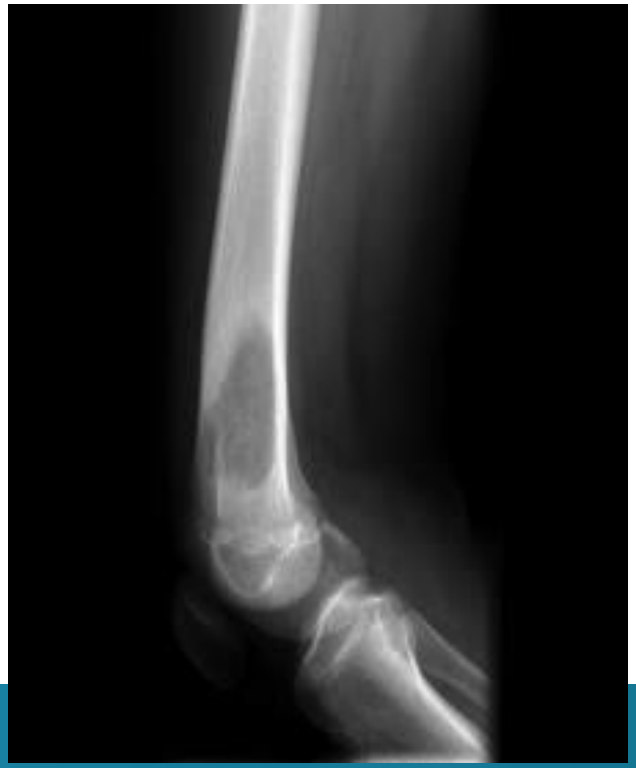




Bottumoren

- Ewingsarcoom
- Osteosarcoom
- Voorkeursleeftijd: 10 $\rightarrow$ 30 jaar





Kiemceltumoren: karakteristieken

Characteristic	Children Age 0 to 14 years		AYAs Age 15 to 39 years		Adults Age 40 years or older	
						
Location						
Histology	Teratoma/YST	Teratoma/YST	Teratoma, mixed GCT	Teratoma, dysgerminoma, mixed GCT	Seminoma	Uncommon
Cytogenetics	Loss: 1p, 4, 6q Gain: 1q	Loss: 1p, 4, 6q Gain: 1q	i12p Loss: 1p, 11,13,18 Gain: 7, 8, 21	i12p	i12p	i12p

Biologie prepubertair en postpubertair is totaal verschillend

AYAs: minder extragonadale lokalisatie
gemengde kiemceltumor
vaker gemetastaseerd

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Published in: Adriana Fonseca; A. Lindsay Frazier; Furqan Shaikh; *Journal of Oncology Practice* 2019 15433-441.
DOI: 10.1200/JOP.19.00190
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Hersentumoren

- 2 leeftijdspieken : < 10 jaar en > 60 jaar
- heel veel verschillende soorten:

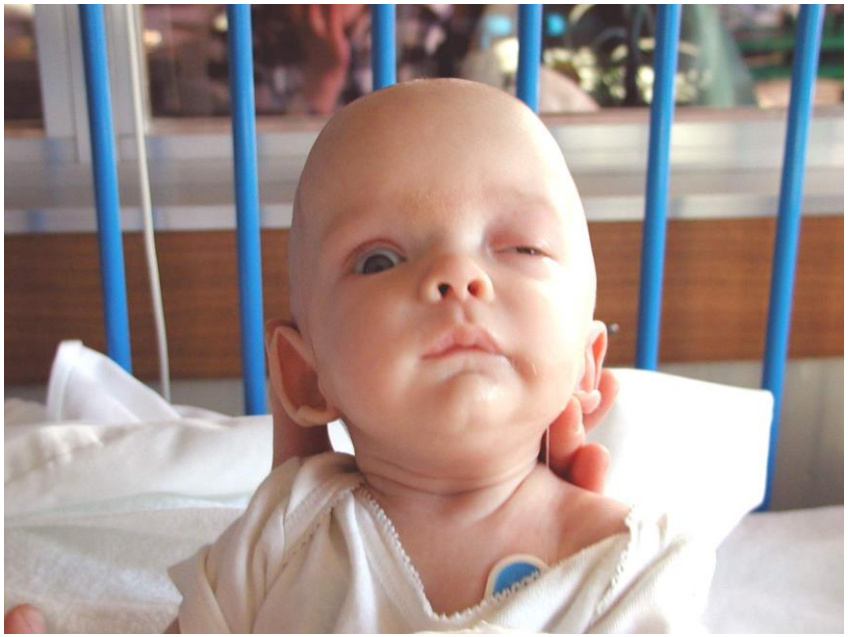
- Gliomen :
  - Goedaardige : 30-40 %
  - Hooggradige : 10-15 %
- Medulloblastomen : 10-20 %
- Ependymomen : 5-10 %
- Craniopharyngiomen : 6-9 %

Symptomen

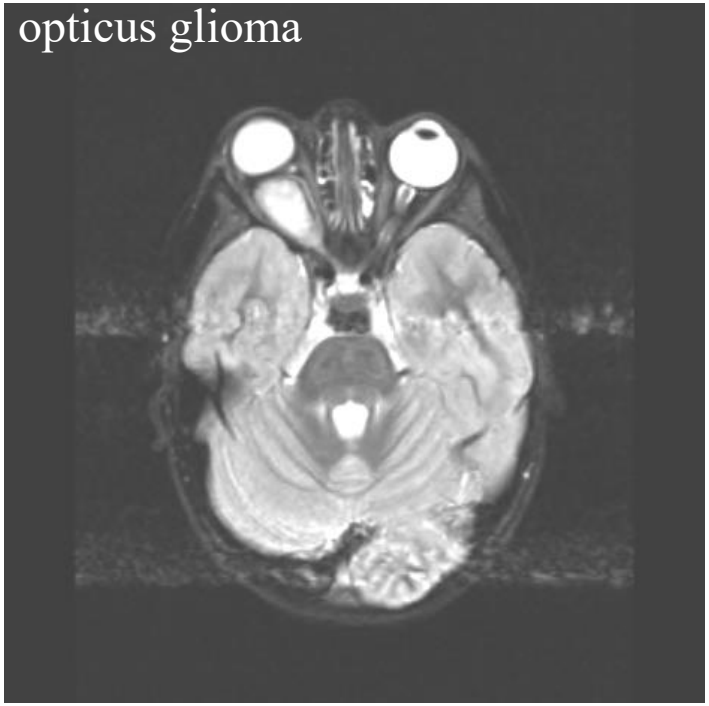
- Vaak heel aspecifiek !
- Tgv druk op hersenen zelf of ↑ ICP
- Kleine kinderen :
  - Irritabiliteit, anorexia, ontwikkelingsvertraging...
- Grotere kinderen :
  - Triade : ochtendmisselijkheid, hoofdpijn, lethargie
  - ↓ schoolprestaties, karakterveranderingen, epilepsie...

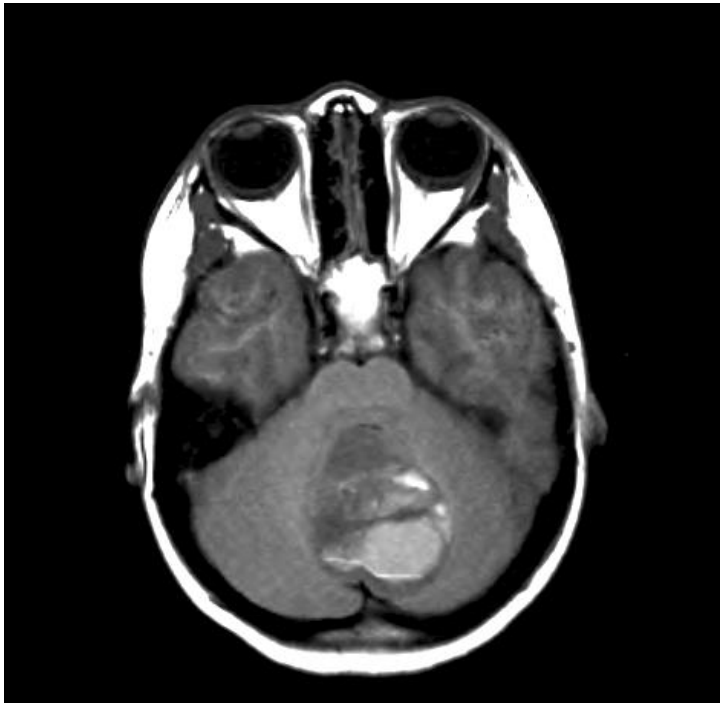
Klinische tekens

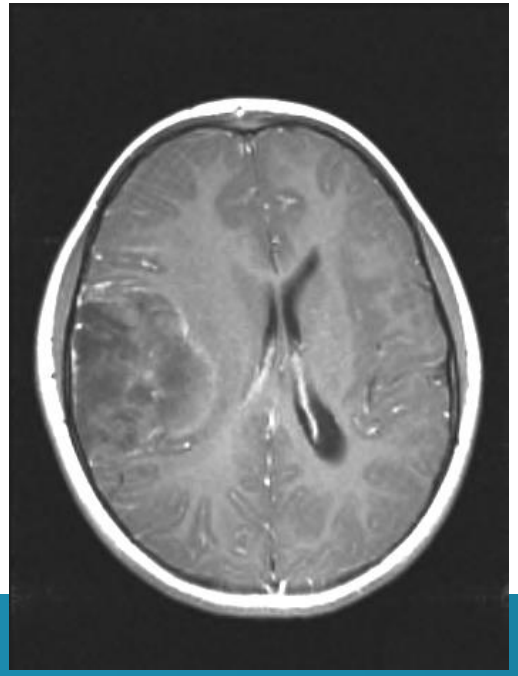
- Toenemende schedelomtrek
- Papiloedeem
- Sunset fenomeen
- Evenwichtsstoornissen
- Visusstoornissen

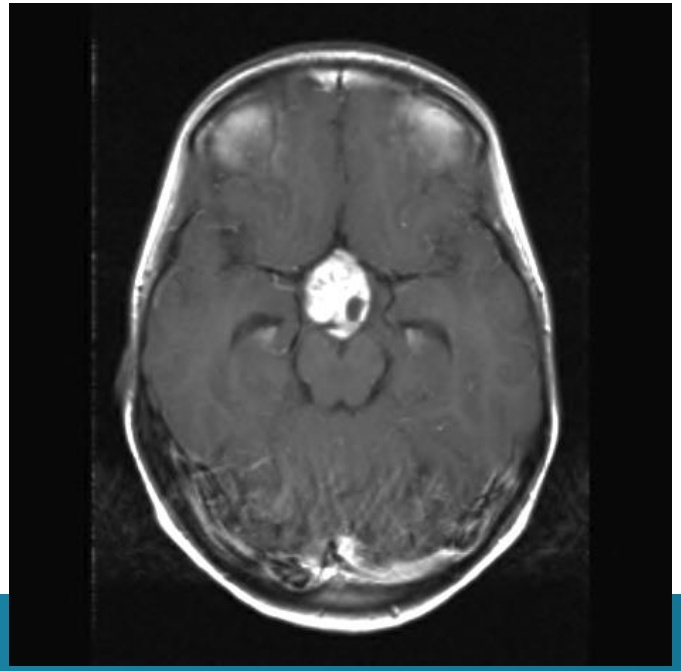


opticus glioma









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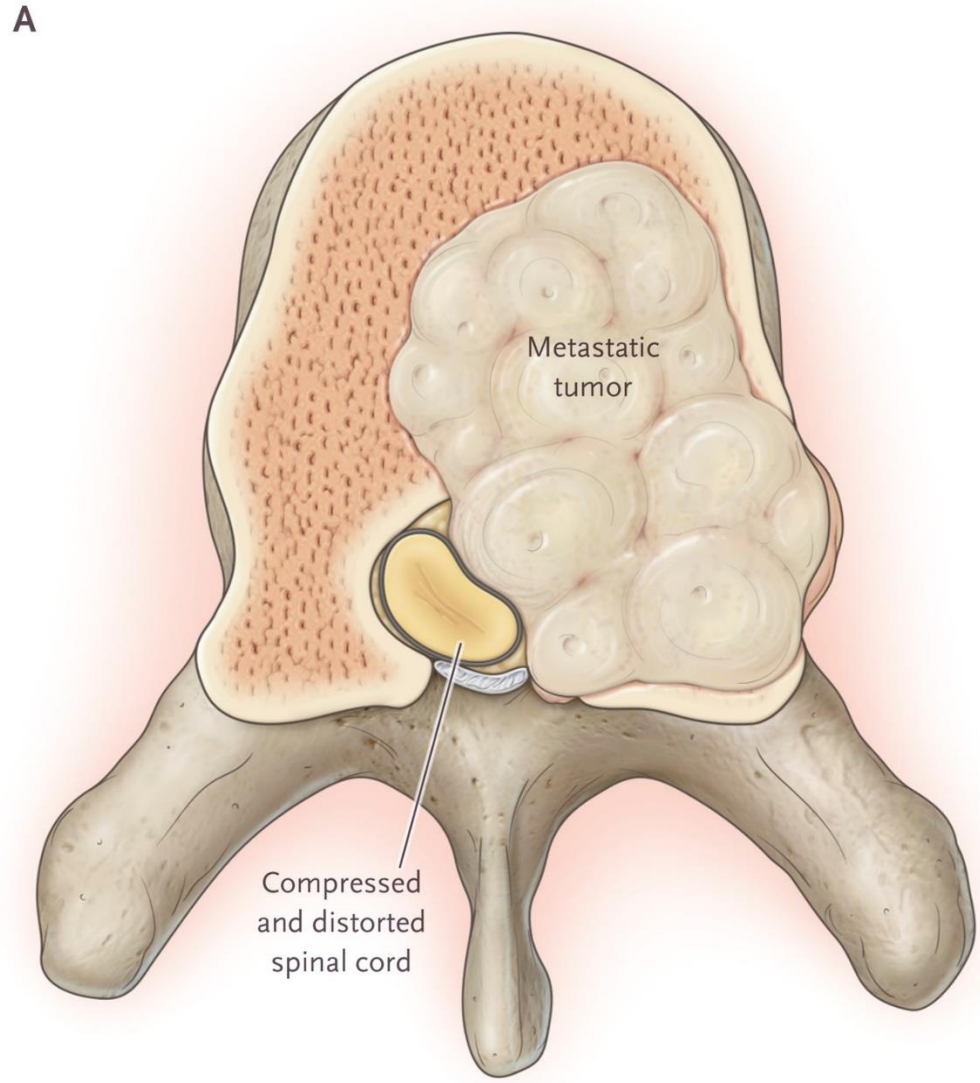

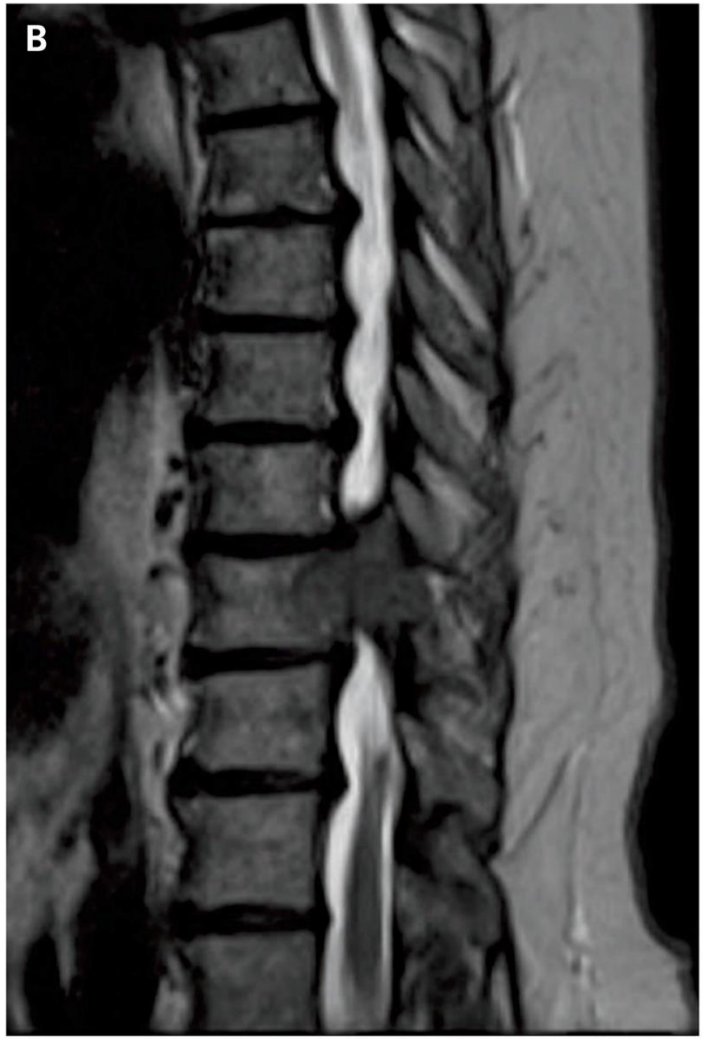

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Therapie

- Gliomen :
  - goedaardige : neurochirurgie, chemo
  - hooggradige : neurochirurgie, zeer intensieve chemotherapie, RT
- Craniopharyngiomen :
  - neurochirurgie ± RT
- Ependymomen :
  - neurochirurgie : totale resectie ! eventueel 2de OK
  - chemotherapie, RT : om totale resectie mogelijk te maken

Hersentumoren

- Doel van invoeren van chemotherapie :
  - overleving verbeteren
  - neveneffecten verminderen door
    - vervangen RT door chemotherapie
    - uitstellen RT tot na bepaalde leeftijd (3 jr, 5 jr)
    - dosis RT verlagen
    - protontherapie

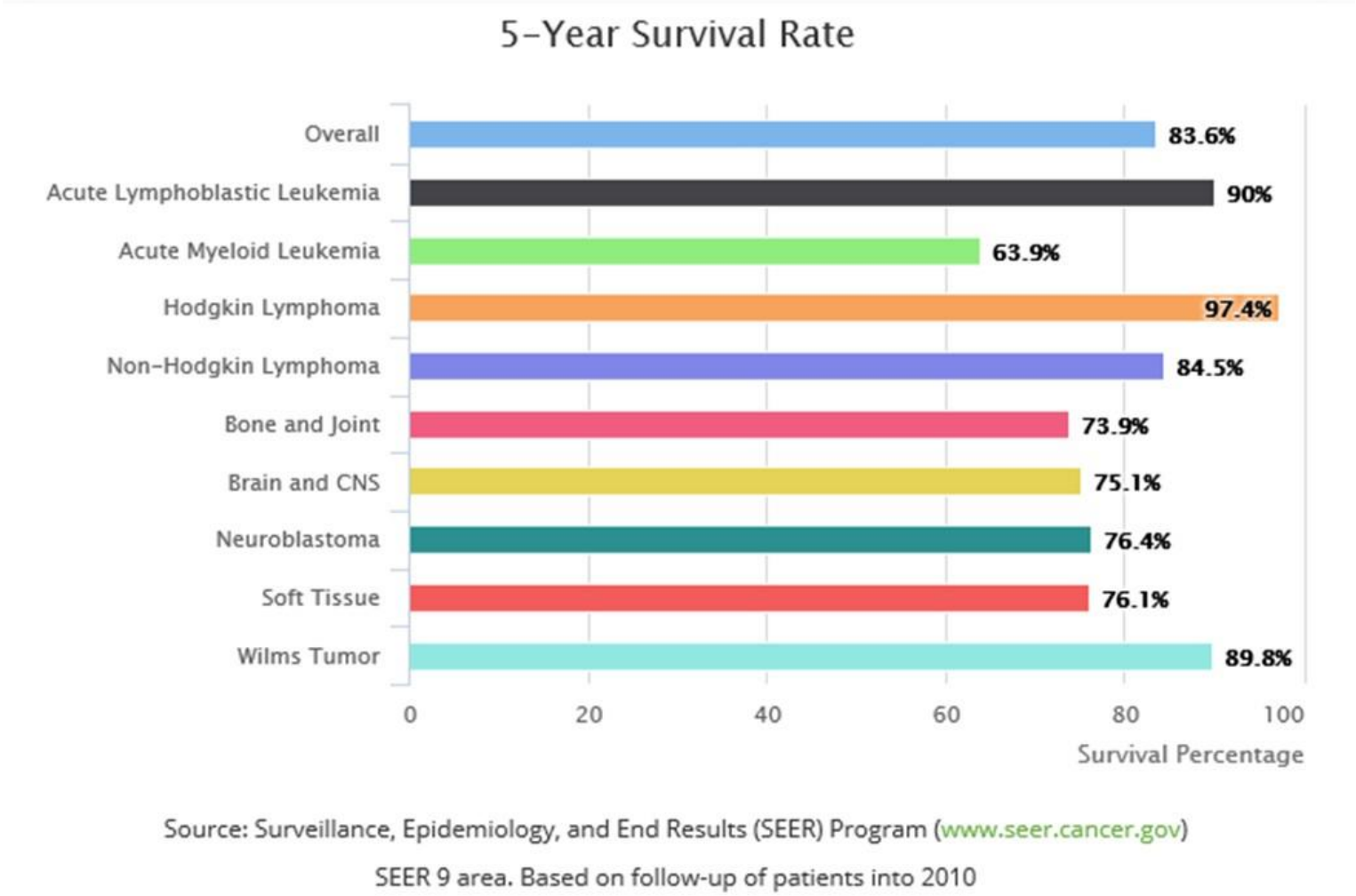
Globale overleving kinderkanker

- Kinderen hebben een betere prognose dan volwassenen
- Tumortype
- Therapie
- Klinische studies

Klinische trials in kinderoncologie

- Investigator-driven clinical trials IDCTs
- Bepalen van prognostische factoren
- Identificeren van subgroepen in functie van prognose en outcome
- Therapie stratificatie
  - Intensificatie voor high risk patiënten
  - Reductie van therapie – toxiciteit in laag risico patiënten

Overleving kinderkanker



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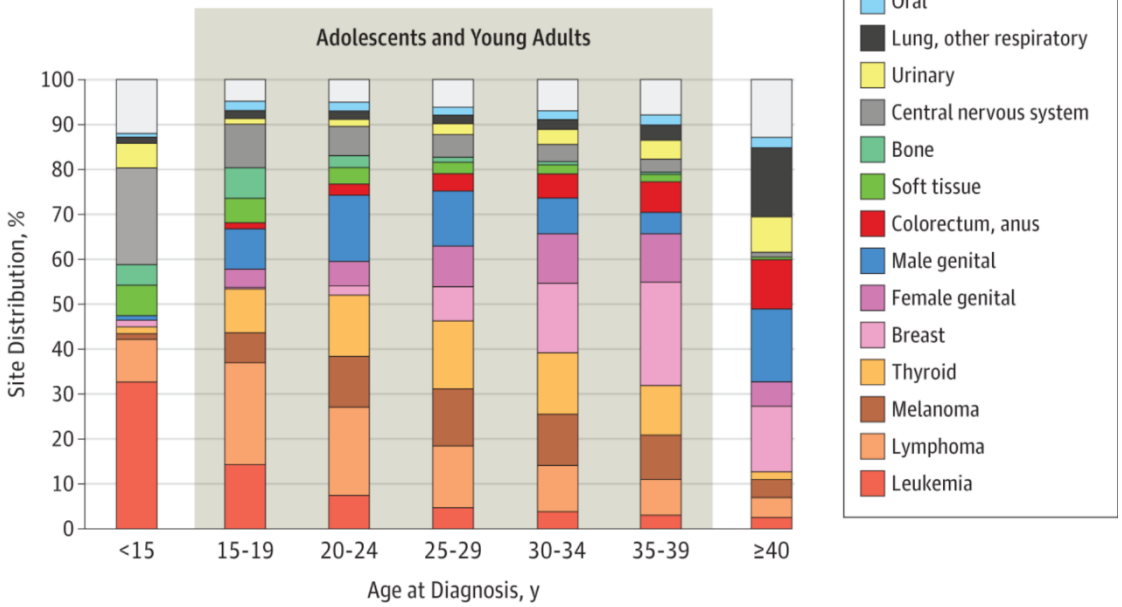
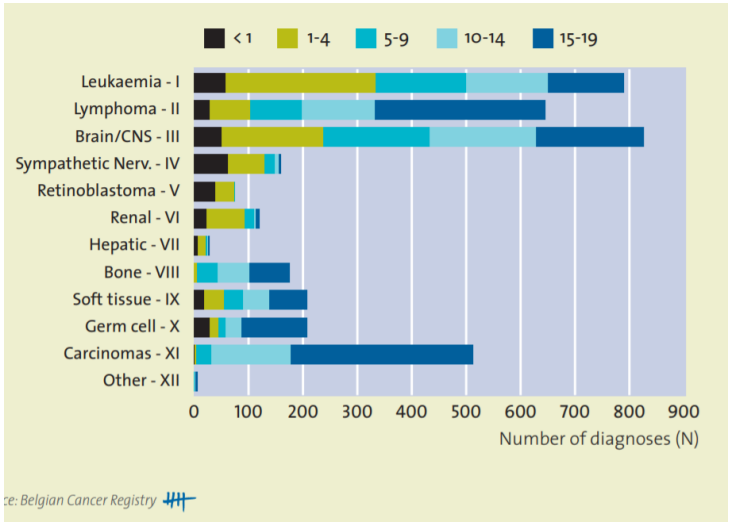
Verdeling kanker op basis van leeftijd





http://kankerregister.org/media/docs/publications/SKR_CancerChildrenandAdolescents_2004_2016_HR12092019.pdf

Barr RD, et al. JAMA Pediatr 2016;170:495-501

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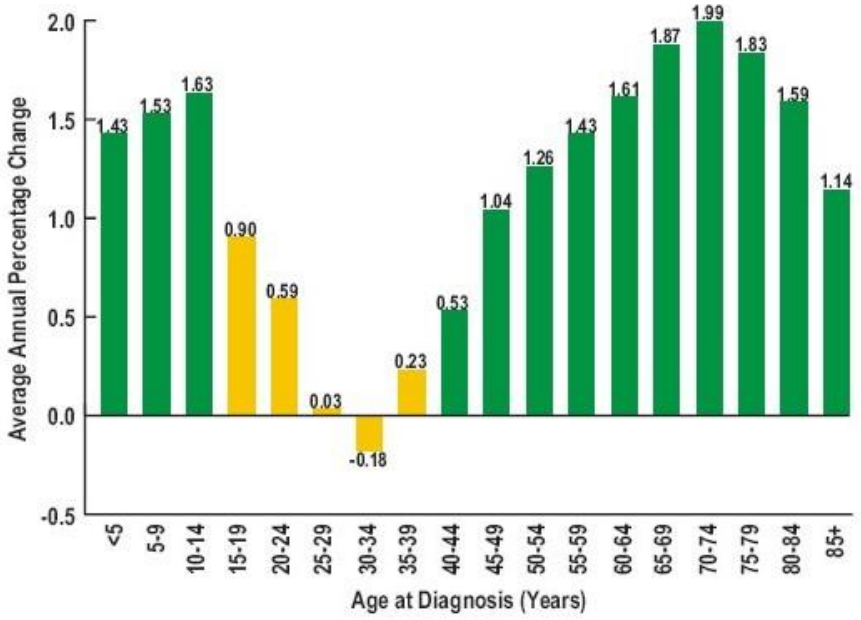
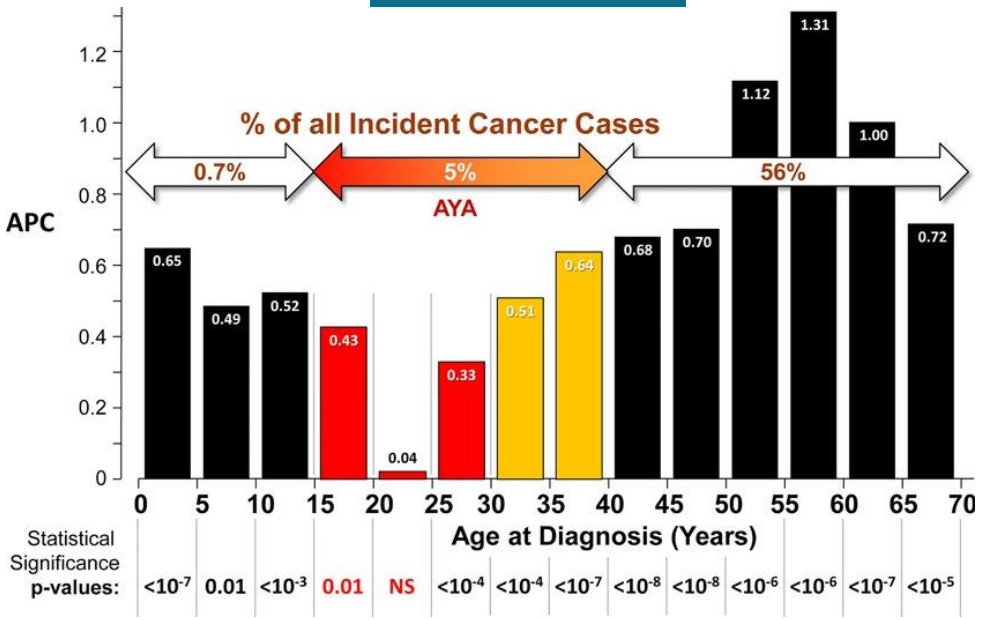
Survival gap in AYAs



1975-1997

1990-2010



Redenen?

Seer.cancer.gov

Bleyer A, et al. Pediatr Blood Cancer 2017;64

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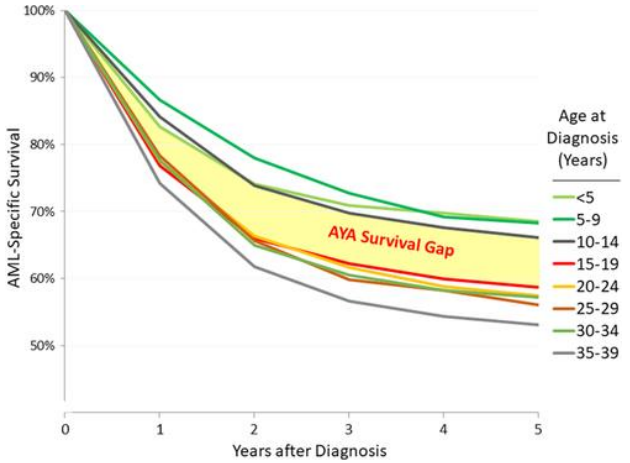
Survival gap

- Vertraging in diagnose en behandeling
- Tolerantie voor en trouw aan therapie
- Lage inclusie in klinische studies
- Minder verwijzingen naar expertcentra
- Verschillen in tumor biologie
- Laattijdige nevenwerkingen
- Genetische predispositie
  - Li-Fraumeni syndrome
  - Ataxia telangiectasia
  - Turner syndrome
  - Beckwitt-Wiedemann
  - Down syndrome
  - Neurofibromatosis NF1
  - Fanconi



Creutzig U, et al. Pediatr Blood Cancer 2018;65:e27089

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Why this lack in survival progress?

- Tumortypes waarbij jonge kinderen een betere overleving hebben dan AYA
- Tumortypes waarbij oudere populatie betere overleving heeft dan AYA
- Biologisch gedrag van de tumor varieert met de leeftijd
- Therapie tolerantie verandert met de leeftijd, comorbiditeit neemt toe
- Therapie regime is verschillend

International evolution

- Engagement of national governments
- Deployment of multidisciplinary teams
- Collaboration between pediatric and adult oncologists
- Strong voice of AYAs in program development

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AYA conventie

- Expertise in AYA cancers
- AYA MOC
- Fertility preservation
- Access to clinical trials
- Counseling
- Support services
- AYA coordinator

➔Start 1/12/2023 in 6 centra in België
verbonden aan kinderoncologie dienst

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Survivors of childhood cancer

35.000 childhood cancer diagnoses annually in Europe

80% long term survival

Nearly 500.000 childhood cancer survivors, increasing every year

75 % of survivors experience one or more late effects

Follow-up care is needed to prevent, detect and treat late effects!

Lange termijn effecten

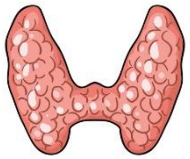
- Orgaanschade
- Verminderde vruchtbaarheid
- Intellectuele en gedragsproblemen
- Secundaire tumoren
- Sociale problematiek

Orgaanschade



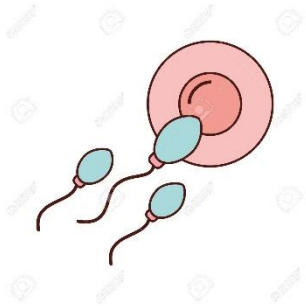







- cardiomyopathie
- ritmestoornissen
- osteonecrose/osteoporose
- longfibrose
- hormonale stoornissen
- neurocognitief verlies
- nierlijden
- hypertensie
- gehoorsdaling
- tinnitus
- cataract
- schildklierpathologie

Verminderde vruchtbaarheid

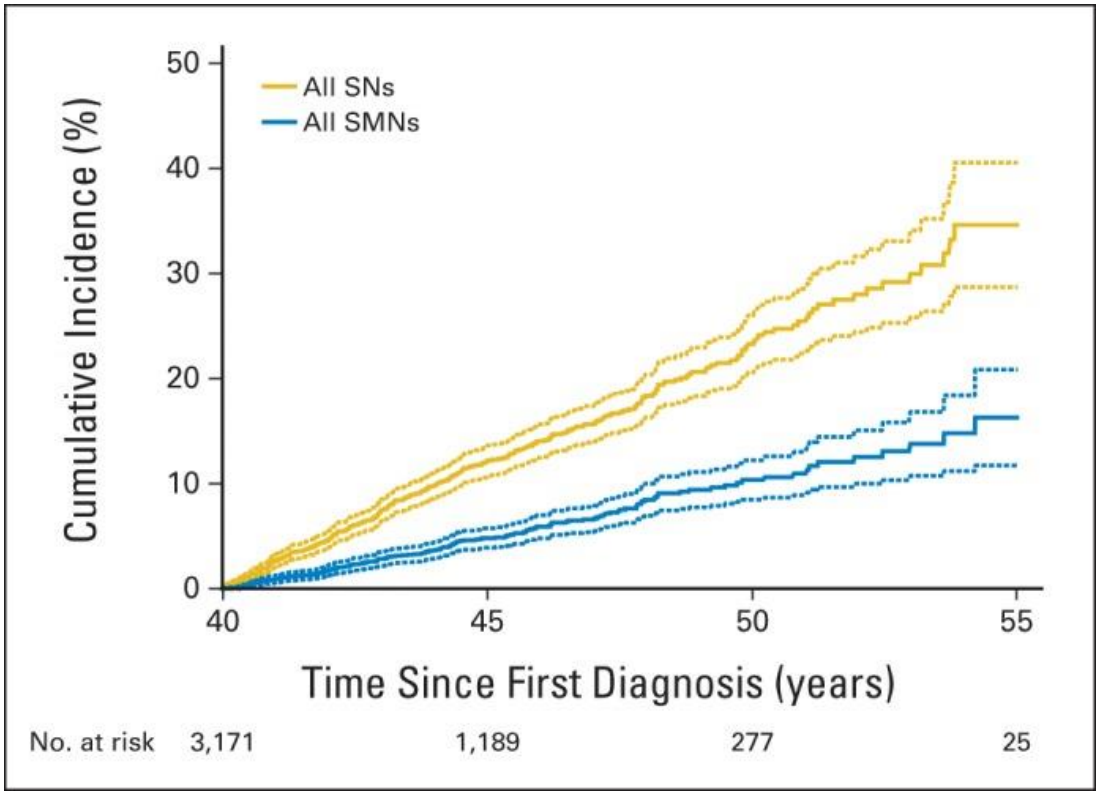


- Operatie met wegname van eierstok of teelbal
- Bestraling van eierstok, teelbal
- Minder hormoonproduktie door bestraling of chemotherapie
- Vroegtijdige menopauze

Zwangerschap en offspring

- Geen verhoogd risico op aangeboren afwijkingen bij de baby's van de survivors
- Groter risico op zwangerschapsproblemen na abdominale bestraling en TBI
  - miskraam
  - vroegtijdige arbeid
  - laag geboorte gewicht

Second tumours



Meest frekwente types

- Botkanker (SIR: 19.1)
- Borstkanker (SIR: 16.2)
- Schildklierkanker (SIR: 11.2)

Risicofactoren

- Vrouw zijn
- Jongere leeftijd bij diagnose
- Radiotherapie, alkylerende agentia
- Eerste kanker Hodgkin, sarcomen
- Genetische predispositie

J Clin Oncol. 2015 Nov 1; 33(31): 3568–3575.

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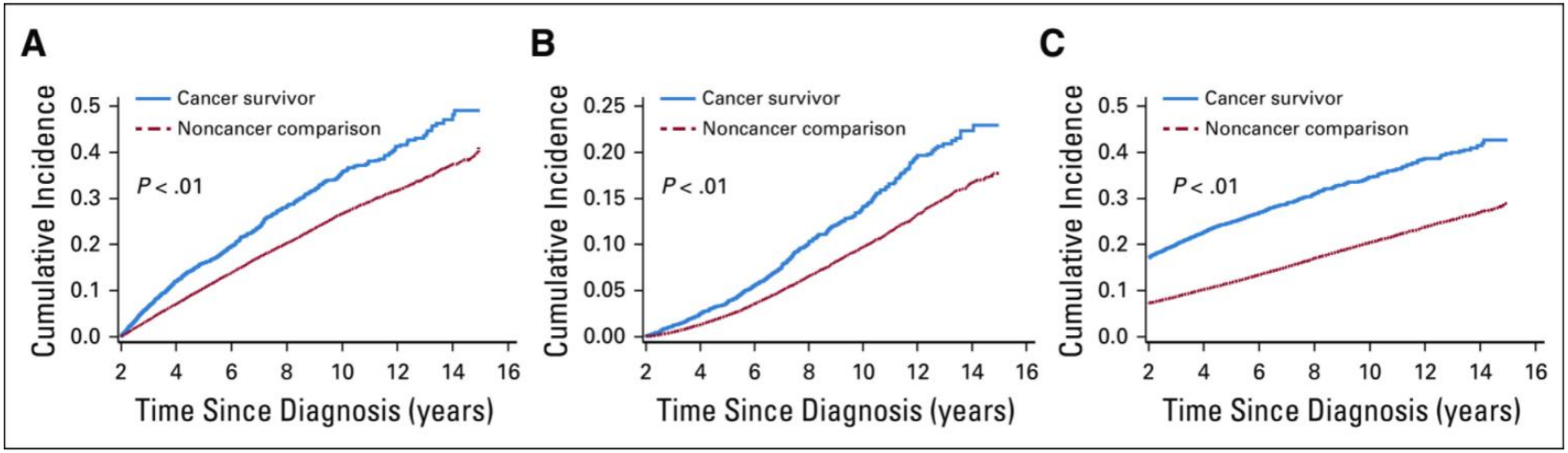
Late effecten & comorbiditeit



Incidence of (A) any comorbidity, (B) ≥ 2 new comorbidities, and (C) ≥ 2 comorbidities by cancer survivor status.

40% van AYA survivors vertonen meerdere (≥ 2) comorbiditeiten 10 jaar na diagnose, vergeleken met leeftijdsgenoten slechts 20%

Chao C et al, J Clin Oncol. 2020 Sep 20; 38(27): 3161–3174.

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Lange termijn kliniek

Survivorship paspoort

- Diagnose en staging
- Samenvatting van de behandeling
  - Chemotherapie: cumulatieve dosis van de verschillende cytostatica
  - Radiotherapie: dosis en veld
  - Chirurgie
- Guidelines voor follow-up gekoppeld aan de toegediende therapie
- Familiale anamnese/predispositie
- Levensstijl

PanCare SurPass

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Take home message

Kinderoncologie 2023 = Therapie optimalisatie

- Risico stratificatie
- Chemotherapie -> outcome & QoL
- Radiotherapie: age adapted, protontherapy
- Nieuwe molecules
- Therapie op maat

SIOP Europe
the European Society for Paediatric Oncology

Beating childhood cancer. Cure more and cure better.
Towards zero deaths & zero late effects.

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