UMC Utrecht

International Waldentrom's Patient Meeting
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# Disease morbidities 1; Polyneuropathy, Bing Neel, Amyloid

Monique Minnema, internist-hematologist

# Waldenstrom Macroglobulinemia

## Cancer cells :

- B lymfocytes
- Plasmacells
- Represented as % in reports

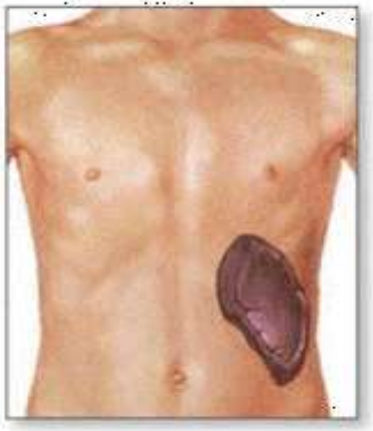
## Blood;

- “wrong protein ” = M protein/paraprotein

- Represented in gr/L

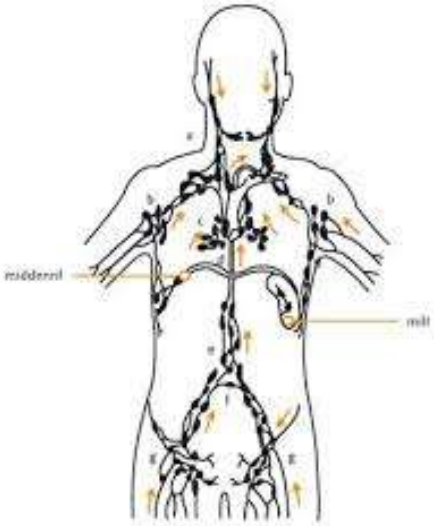
Healthy bone marrow is ”factory” of blood cells

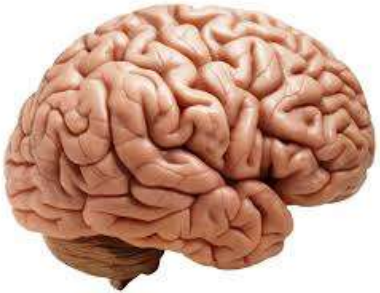
# Besides bone marrow the cancer cell can be present in other places of the body



Spleen, 15-30%

Lymphe nodes ;
15-30%





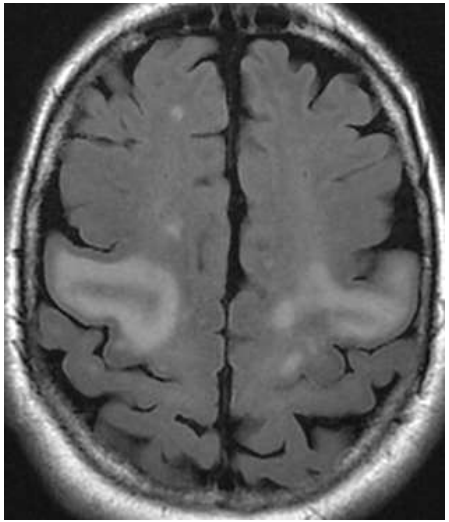
Brain + Spinal fluid
≈ 1%; **Bing Neel Syndrome**

# Bing Neel syndrome

- Complaint difficult to recognise and very diverse
  - Mood disorder, psychic differences
  - Diminished strength arm or leg
  - Cranial nerve loss
  - Neuropathy
  - Balance disorder
  - Dizziness
  - Pain neck, back, legs
  - Memory loss

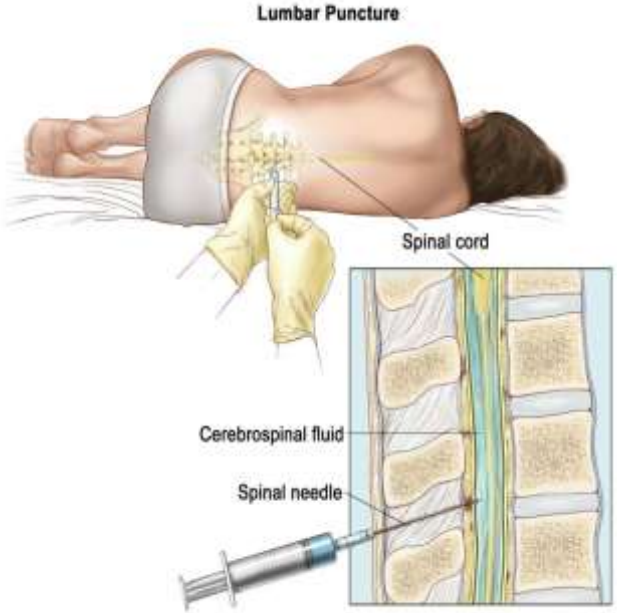
- Bing Neel Syndrome can arise while bone marrow disease and M proteine is stable.

# Bing Neel Syndrome ; Diagnosis



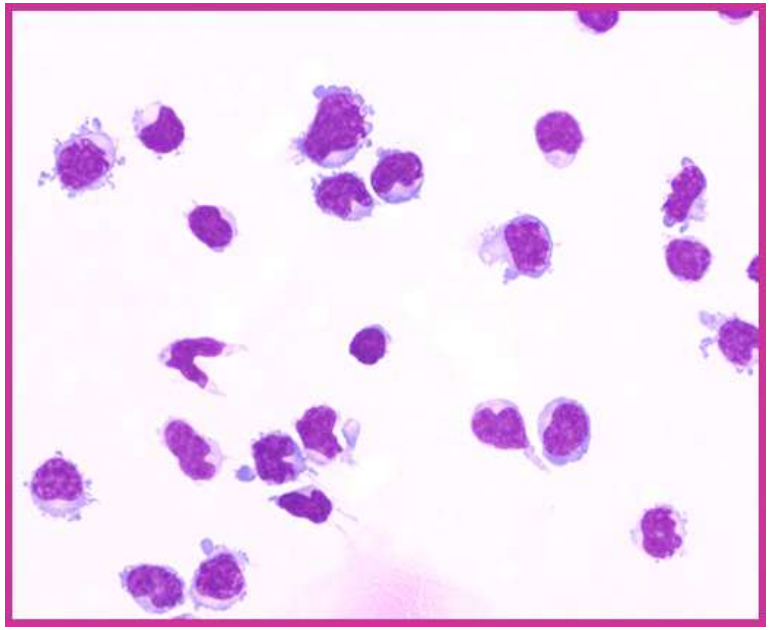
MRI scan of brain and spine

Operation for brain biopsy




Lumbar puncture

# Bing Neel Syndrome; Spinal fluid



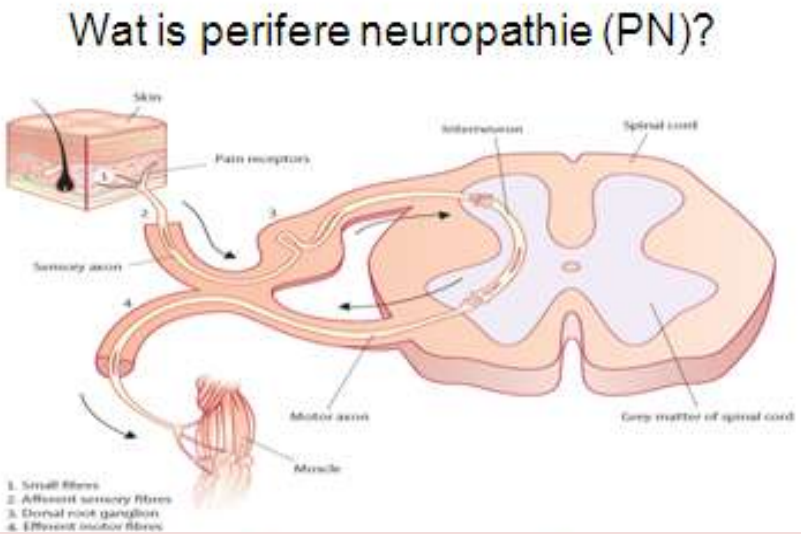
- Presence of too many lymphocytes?
- Different lymphocytes in morphology?
- Clonal cells ?
  - Flow cytometry
  - Molecular *MYD88*$^{L265P}$ mutation present ?

# Bing Neel Syndrome

- Can be treated, several possibities
- Recovery of complaints is possible

- **Milestones in IWWM9?**
  - First international guideline published
  - Recognition of BNS improved
  - Discussion of several treatment options
  - Possibility for clinical study created

# What is Polyneuropathy?




Peripheral neuropathy = nerve damage which manifestes peripherally (toes, fingers)
PN can be sensory, motorial and autonomous
PN can induce pain

**Sensory Neuropathy**

-tingling
-change in temperature
-pain
-lack of coordination
-feeling of tight sock/glove

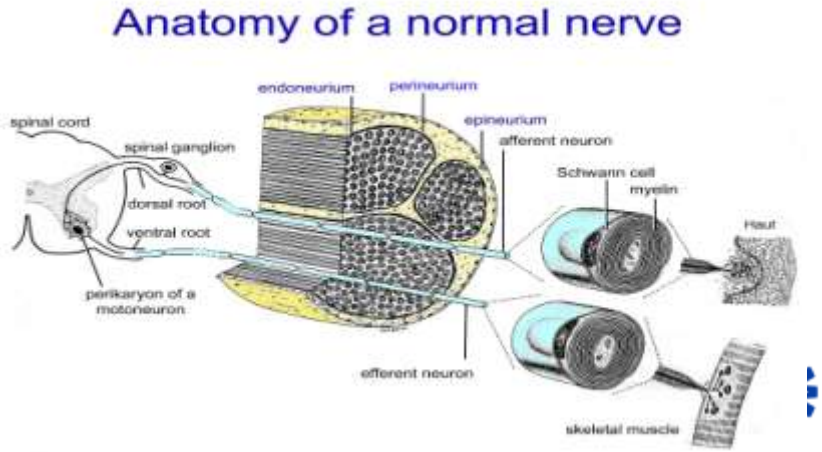
**Motorial Neuropathy**

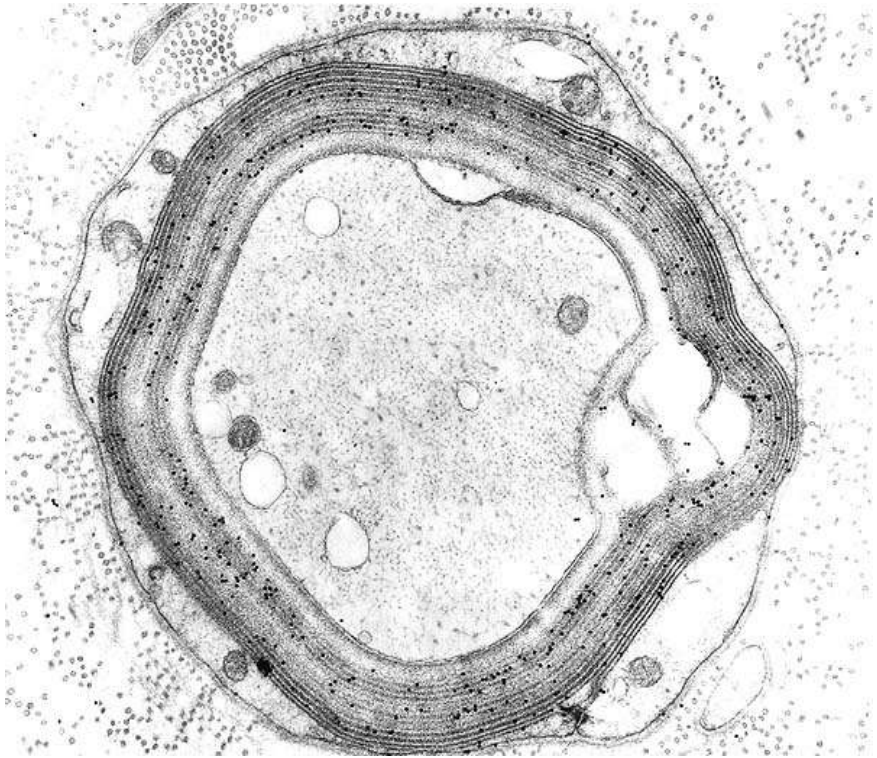
-weak muscles, paralyis
-painfull cramps

# Neuropathy in Waldenström's

- IgM paraprotein reacts with part of nerve cell, such as myelin (anti-MAG antibody); Inflammation and complaints
- 25-30% has neuropathy at diagnosis
- IgM related disease ; MGUS with neuropathy

- Other causes ;
  - Amyloidosis
  - Cryoglobulinaemia
  - POEMS syndrome





anti-MAG antibodies in myelin leaflet ; complaints!

Not everybody has anti MAG antibodies

# CIPN: Chemotherapy induced neuropathy

- Bortezomib
- Vincristin
- Anti-CD20 antibodies can sometimes increase PN
- Waldenström patients more sensitive to CIPN

# Treatment of Waldenström related PN

- Treatment of the disease itself
  - Do not use therapy with increased risk of CIPN
- Chance on positive result; 50%
- Nerve cells divide very slowly
- Pain medication

- IgM MGUS related neuropathy; monotherapy Rituximab/anti CD20 therapy

# Treatment of CIPN

- Not possible
- Complaints can be reversible after stopping therapy
- Important to stop in time with anti WM therapy
- Pain medication in PN:
  - Amytriptylline
  - Neurontin
  - Lyrica
- Be cautious: Vitamin B6 can induce PN! (> 200 mg/daily)

# Polyneuropathy; IMMW9

- Multidisciplinary guideline prepared for evaluation and treatment of the different types of PN, related to IgM diseases and Waldenstrom

- New medication (ie BTK inhibitors, oral proteasome inhibitors)
  - effect on PN improvement unknown
  - Do not induce CIPN

# Amyloidosis;
## disease caused by protein accumulation as insoluble fibres

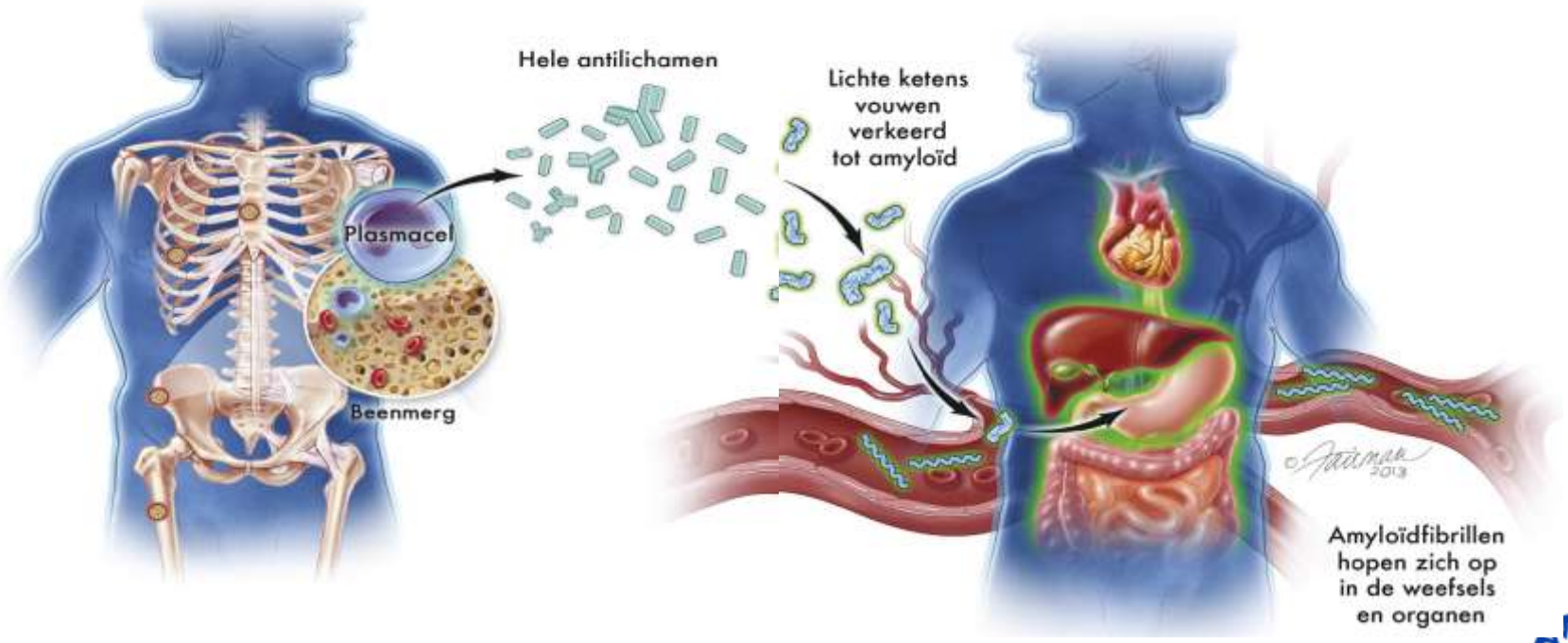
- Amyloid is formed from abnormal M protein
- Insoluble fibres in organs, detoriation of organs; complaints start.
- 6% of AL amyloidosis caused by IgM M proteins due to Waldenström or IgM-MGUS

- 94% caused by MGUS/Multiple Myeloma (IgG of IgA M-protein)

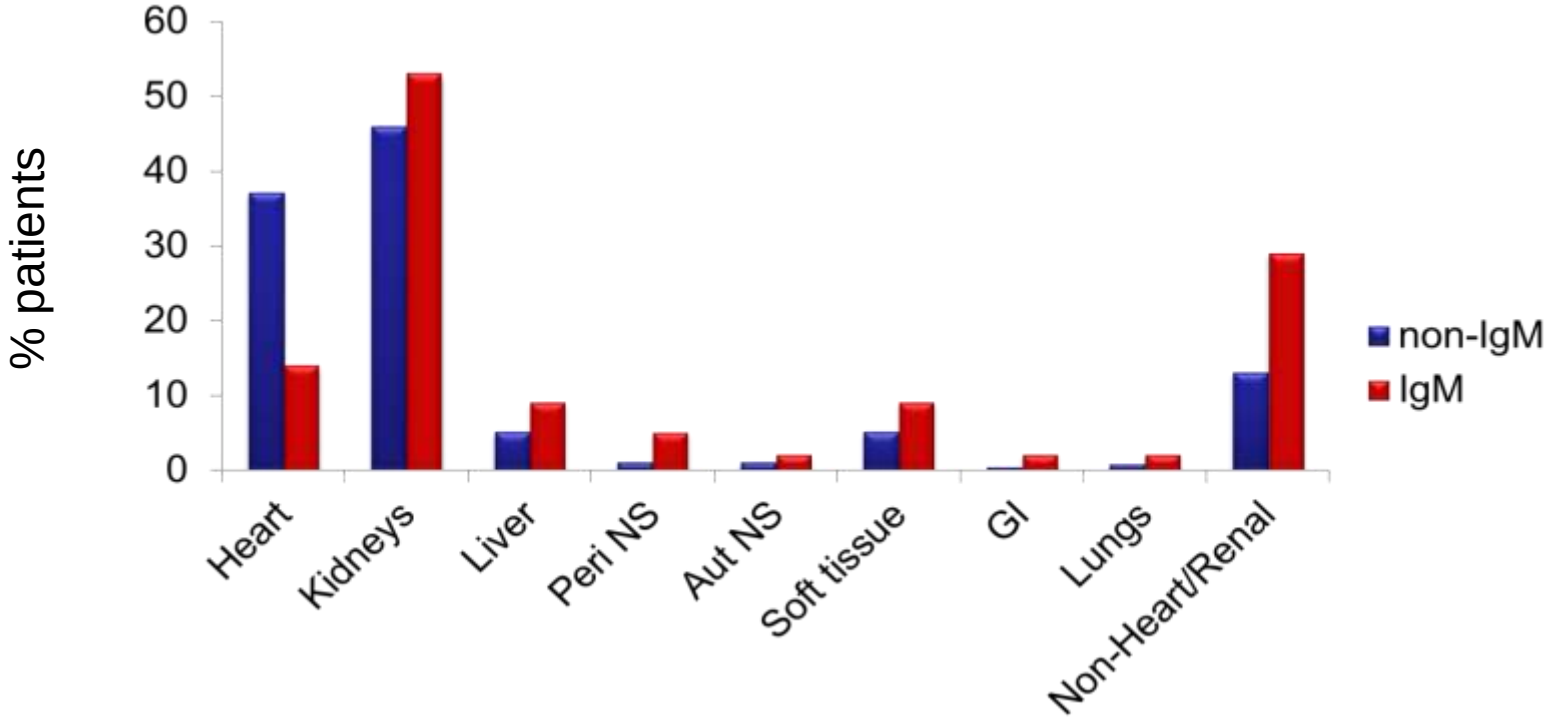
# Symptoms

- Polyneuropathy
- Fatigue
- Worse kidney function
- Proteinurie
- Thickening Cardiac wall
- Enlarged lymphenodes
- Bleeding
- Enlarged liver
- Diarrhea

# How are amyloid fibres formed



# Dominant organ at diagnosis AL amyloidosis



# “underlying” disease

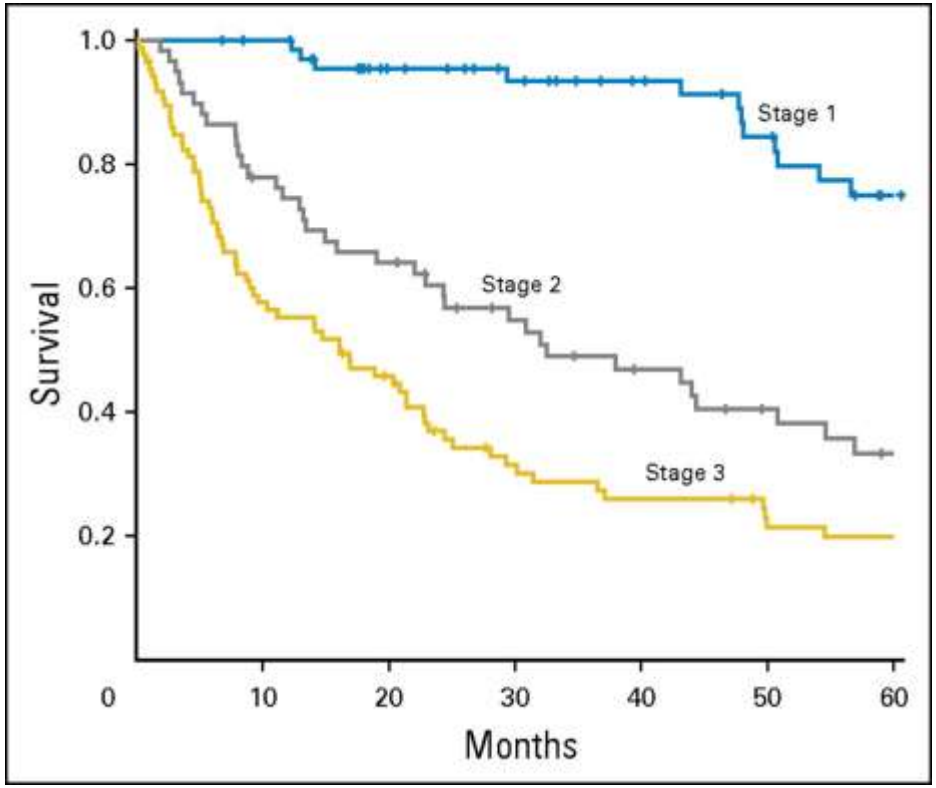
## Non-IgM

- Plasma cell dyscrasia
- Median ~ 7-9% plasma cell infiltration
- 15% have Multiple Myeloma

## IgM

- Lymphoproliferative disease – 52%
- ‘Plasma cell’ – 6%
- Normal bone marrow – 14%
- Unknown – 28%
- Lymphoproliferative disease
  - ✓ Waldenstrom – 74%
  - ✓ NHL-ns – 25%
  - ✓ Follicular, CLL – 1%

# New staging system for IgM AL amyloidosis




Factors:

- NT-proBNP >332
- Trop-T >0.03 ug/L
- Liver involvement
- Neuropathy ; autonomous

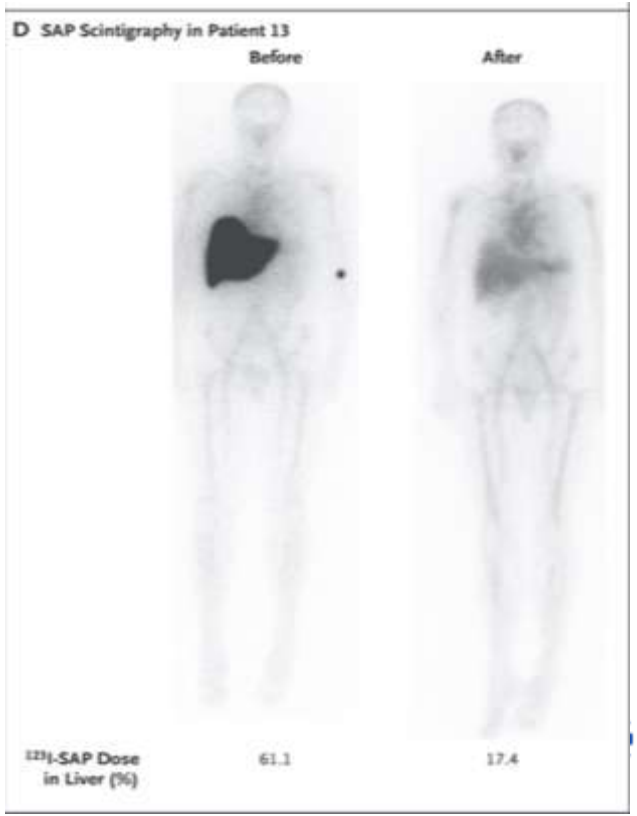
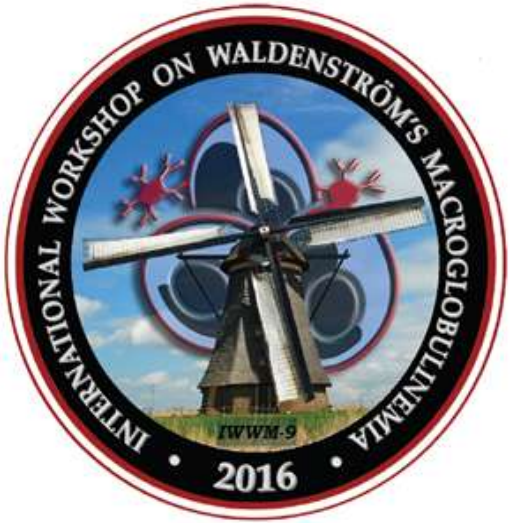
Stage I – 0 (90 m)
Stage II– 1 (32m)
Stage III - 2 or more (16m)

*Sachchithanantham S . J Clin Oncol. 2016 Jun 10;34(17):2037-45.*

# Treatment

- Goal ; M protein as low as possible
  - CR / VGPR
- Vulnarable patients
  - Bortezomib
  - Fludarabine
  - Autologous stem cell transplantion

- New ; anti amyloid antibodies



# Waldenström workshop