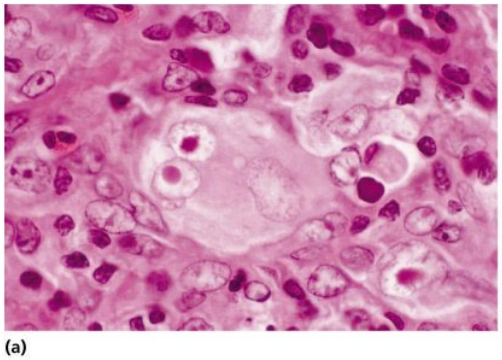
Lymphomas and Myeloma
淋巴瘤及骨髓瘤

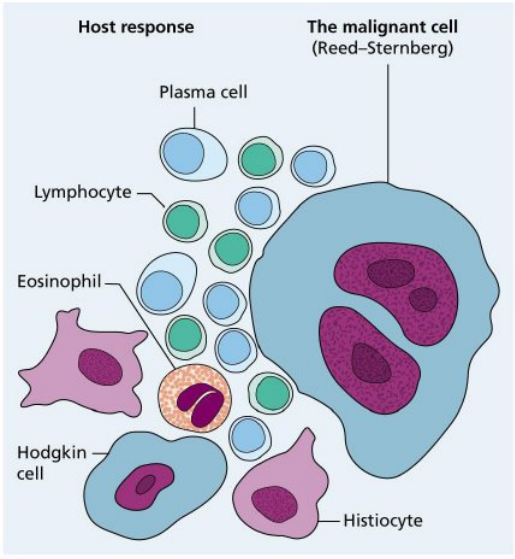
Lymphomas (淋巴瘤)

- A group of diseases caused by malignant lymphocytes that accumulate in lymph nodes
- Occasionally, they may spill over into blood ("leukaemic phase") or infiltrate organs outside the lymphoid tissue
- Tissue diagnosis (excisional biopsy) is the most important diagnostic test (fine needle aspiration is not adequate because architecture is important)
- Major subdivisions: Hodgkin vs. non-Hodgkin

Hodgkin Lymphoma (HL)
何傑金氏淋巴瘤

- The distinctive multinucleate polyploid Reed-Sternberg (RS) cell is central to the diagnosis
- Subtypes:
  - **Classical (95%)**
    - **Nodular sclerosis**
    - **Lymphocyte rich**
    - **Mixed cellularity**
    - **Lymphocyte depleted**
  - **Nodular lymphocyte-predominant**





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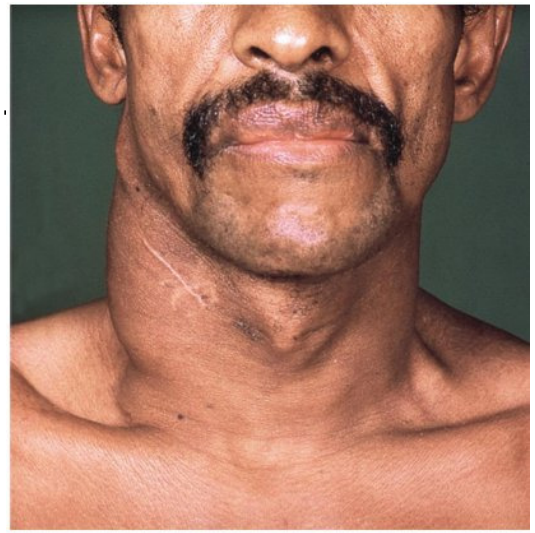
HL: Clinical Features

- Enlarged lymph nodes
  - Painless, non-tender, asymmetrical, firm, discrete, rubbery enlarged superficial LNs
  - Cervical 頸部 (60-70%), axillary 腋下 (10-15%), inguinal 腹股溝 (6-12%)
- Splenomegaly 脾大 (50% of patients), hepatomegaly 肝腫大
- Mediastinal (縱隔) involvement
- Skin (10%) and other organ involvemen
- Constitutional symptoms
  - **B symptoms**
    - Unexplained fever > 38 °C
    - Night sweats, or
    - Loss of >10% of body weight within 6 months
  - Alcohol induced pain in disease area



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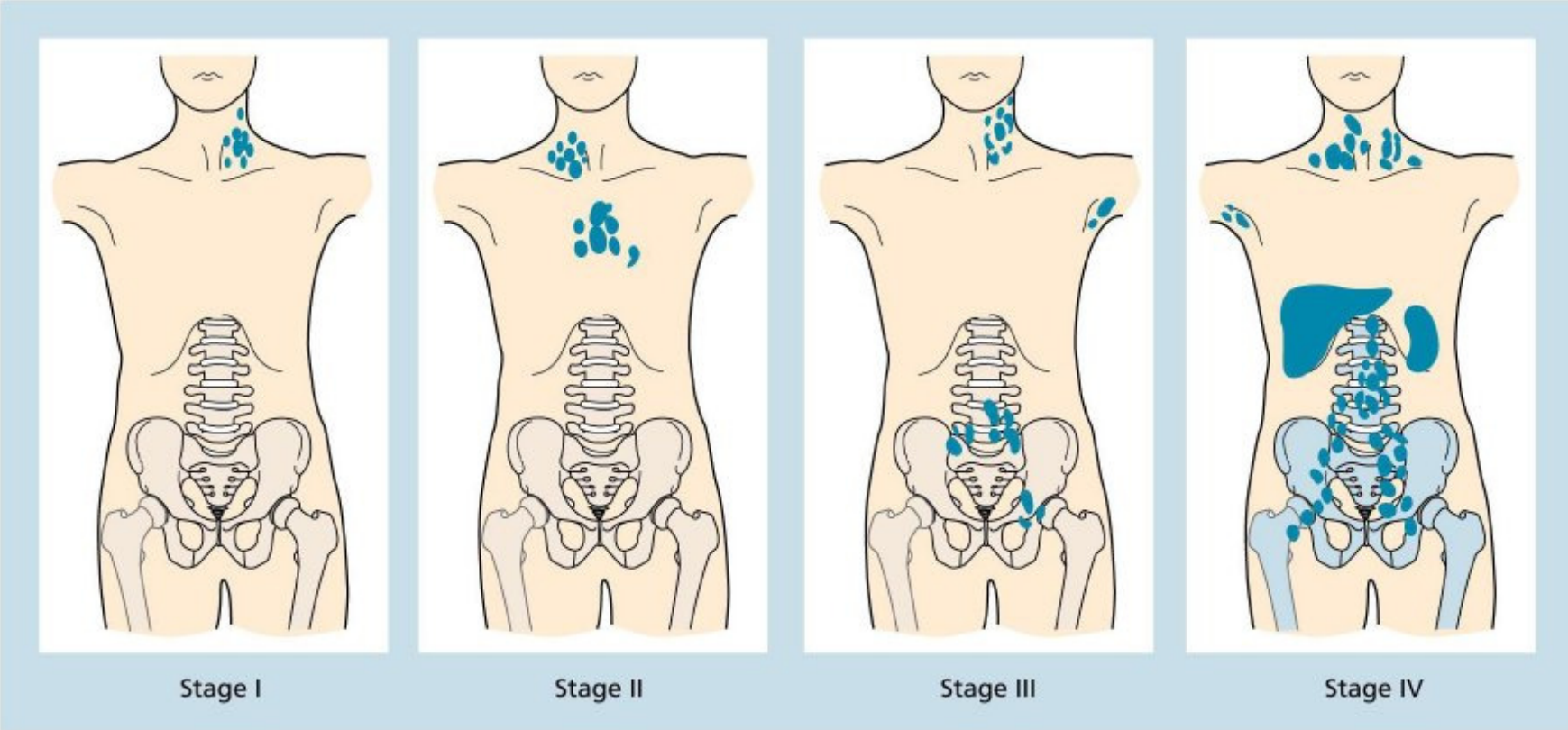
HL: Laboratory Findings

- Normochromic normocytic anaemia (血色及紅細胞正常的貧血)
- Neutrophilia 中性白細胞增多 (1/3 of patients), eosinophilia 嗜酸性細胞增多
- Lymphopenia 淋巴細胞減少 in advanced disease
- ↑ Erythocyte sedimentation rate 血沉降率 (ESR) and C-reactive protein C-反應蛋白 (CRP)
- ↑ Serum lactate dehydrogenase 乳酸脫氫酶 (LDH)

Techniques for Staging (疾病分期) of Lymphoma

- Chest X-ray
- Computed tomography (CT) of neck, thorax, abdomen and pelvis
- Positron emission tomography 正電子釋放斷層掃描 (PET) or PET/CT
- Magnetic resonance imaging 磁力共振掃描 (MRI)
- Bone scan
- Bone marrow examination

HL: Staging



(A) or (B) indicating the absence of presence of B symptoms

HL: Treatment

Radiotherapy (RT)

•patients with stage I and IIA disease may be cured by RT alone

•also a role in the treatment of bulky tumour masses

Chemotherapy

•used for stage III and IV disease

•in stage I and II patients who have bulky disease, type B symptoms or have relapsed following initial RT

•e.g. adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) for 6 cycles or 4 after achievement of complete remission

HL: Treatment

Combination therapy (RT + chemotherapy)

•allows shorter courses of chemotherapy + reduced levels of RT to reduce side effects

Treatment of Relapsed (復發) Cases

•An alternative combination of chemotherapy +/- RT

•If disease remains chemosensitive (化學敏感的) + younger age (e.g. < 65 years) and no significant comorbidities (共患疾病), high-dose chemotherapy and autologous stem cell transplantation (自體幹細胞移植)

•Allogeneic stem cell transplantation (異體幹細胞移植)

HL: Prognosis (預後)

- Prognosis is excellent and > 85% of patients can expect to be cured.
- Late side effects of treatment are a concern:
  - secondary cancers, e.g. lung and breast (RT)
  - myelodysplastic syndrome (骨髓異常增生綜合症, MDS) or acute myeloid leukaemia (急性髓性白血病, AML) after chemotherapy
  - Sterility (不育)
  - Intestinal complications
  - Cardiac or pulmonary complications

Non-Hodgkin Lymphoma (NHL)
非何傑金氏淋巴瘤

- A large group of clonal lymphoid tumours
- About 85% are B-cells and 15% are T or natural killer (NK) cells
- Increasing frequency over the past 50 years
- Aetiology (病因) is largely unknown
- Characterized by an irregular pattern of spread and a significant proportion of patients develop extranodal (結外組織) disease

WHO Classification of Lymphoid Neoplasms

Mature B-cell neoplasms	Mature T-cell and NK-cell neoplasms
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	T-cell prolymphocytic leukaemia
B-cell prolymphocytic leukaemia	T-cell large granular lymphocytic leukaemia
Splenic marginal zone lymphoma	Adult T-cell lymphoma/leukaemia
Hairy cell leukaemia	Extranodal NK/T-cell lymphoma, nasal type
Lymphoplasmacytic lymphoma – Waldenstrom macroglobulinaemia	Enteropathy-associated T-cell lymphoma
Heavy chain diseases	Mycosis fungoides
Plasma cell myeloma	Sezary syndrome
Plasmacytoma	Peripheral T-cell lymphoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Angioimmunoblastic T-cell lymphoma
Follicular lymphoma	Anaplastic large cell lymphoma, *ALK* positive
Mantle cell lymphoma	
Diffuse large B-cell lymphoma	
Burkitt lymphoma	

Low- vs High-grade NHL

- Vary from highly proliferative and potentially rapidly fatal diseases to indolent (懶惰) and well-tolerated malignancies
- Commonly subdivided into
  - Low-grade (低度的)
    - Indolent, respond well to chemotherapy but difficult to cure
  - High-grade (高度的)
    - Aggressive and need urgent treatment but more often curable

Low- vs High-grade B-cell NHL

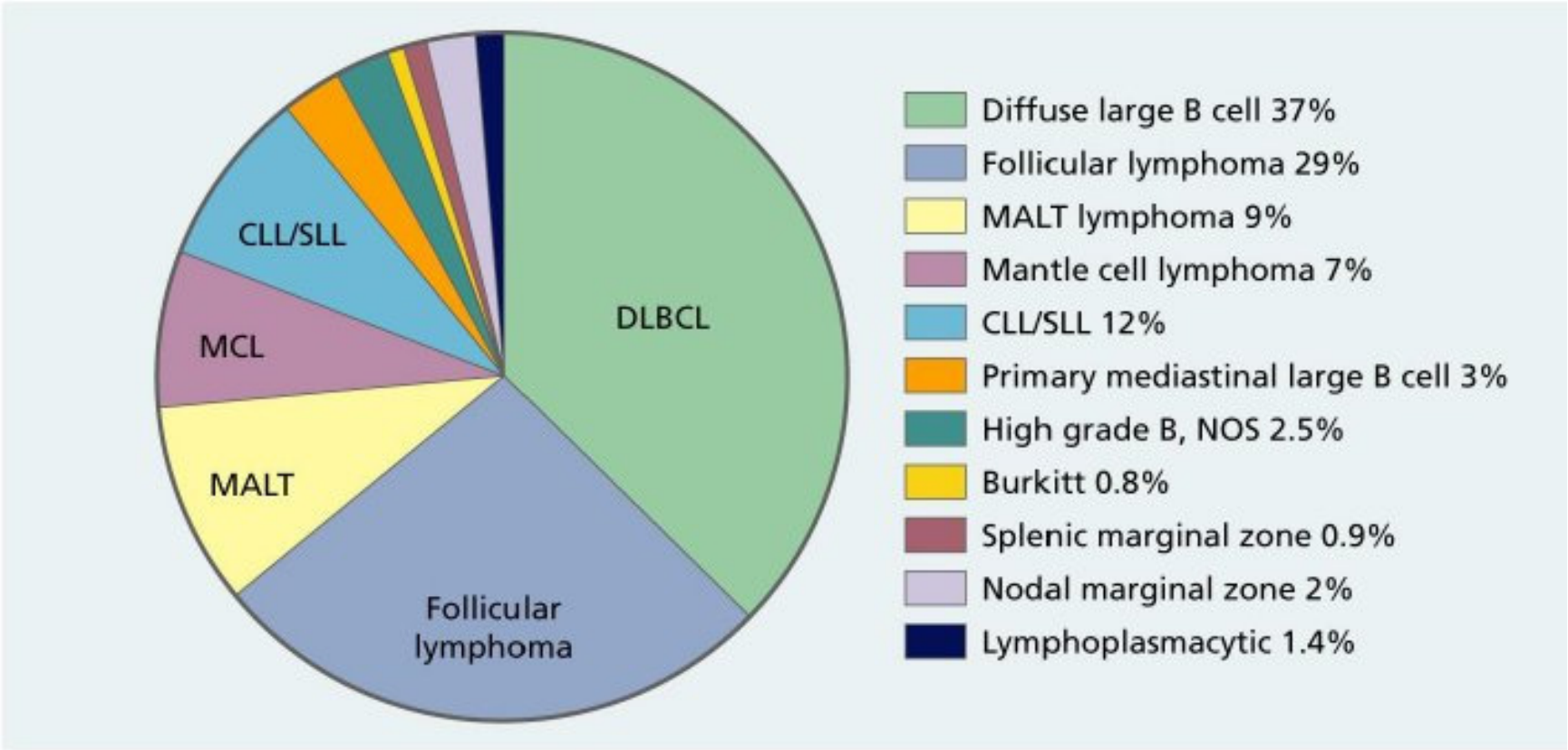
Low grade

- Small lymphocytic lymphoma (SLL)
- Lymphoplasmacytoid lymphoma
- Marginal zone lymphoma
- Follicular lymphoma
- Mantle cell lymphoma

High grade

- Diffuse large B-cell lymphoma (DLBCL)
- Burkitt lymphoma
- Primary central nervous system lymphoma
- Lymphoblastic lymphomas

Relative Frequency of B-cell NHLs

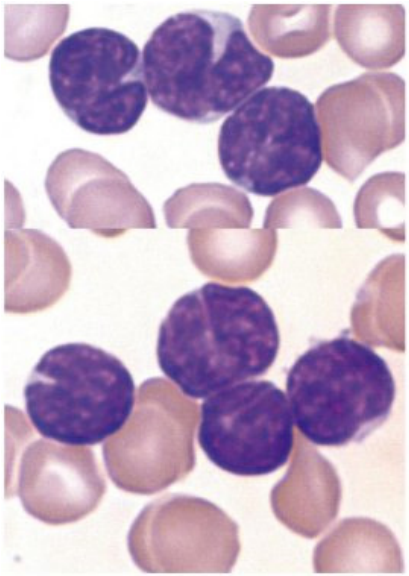


NHL: Clinical Features

- Lymph node enlargement
  - Asymmetric painless enlargement of lymph nodes in one or more peripheral LN regions
- Constitutional symptoms
  - Fever, night sweating, weight loss
  - Usually associated with disseminated (彌漫性) disease
- Oropharyngeal involvement (Waldeyer's ring)
- Anaemic and bleeding symptoms, infections
- Other organs involvement (e.g. hepatomegaly, splenomegaly, skin, brain)

Laboratory Findings

- Complete blood picture
  - Anaemia, thrombocytopenia, neutropenia In advanced disease with marrow involvement or splenomegaly
  - Lymphoma cells may be found in peripheral blood



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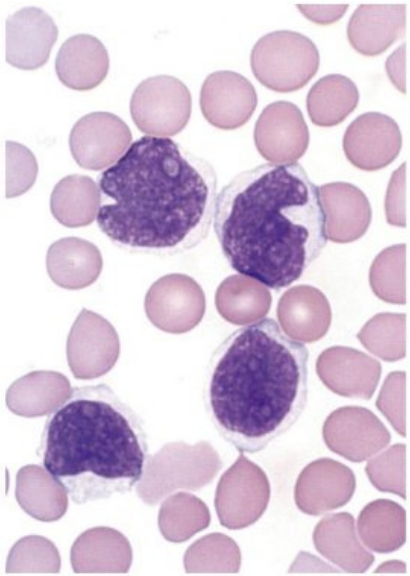

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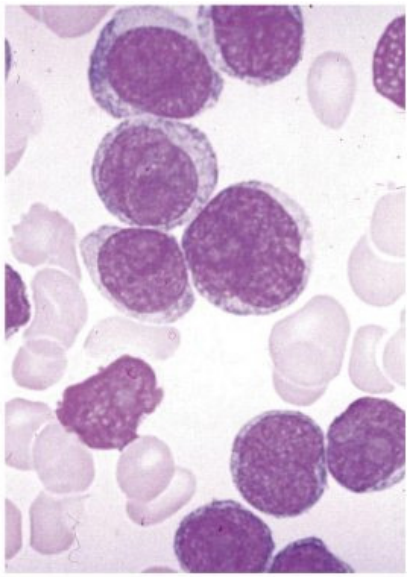

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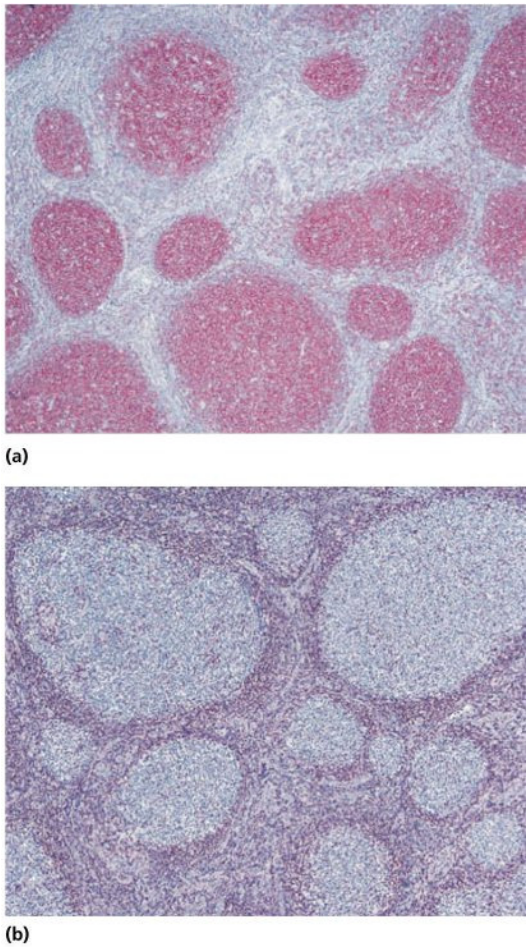
Laboratory Findings

- Bone marrow biopsy
  - may show lymphoma infiltration
- Serum lactate dehydrogenase (LDH)
  - Raised in more rapidly proliferating and extensive disease
- Immunoglobulin electrophoresis
  - May reveal a paraprotein (副蛋白質)

Follicular Lymphoma 濾泡性淋巴瘤

- About 25% of NHL
- Median age of onset: 60 years
- Associated with the t(14;18) translocation in majority of cases
  - Leads to constitutive expression of the BCL-2 gene with increased survival of cells
- A benign course for many years
- Median survival from diagnosis ~ 10 years
- Transformation to aggressive lymphoma may occur



(a)

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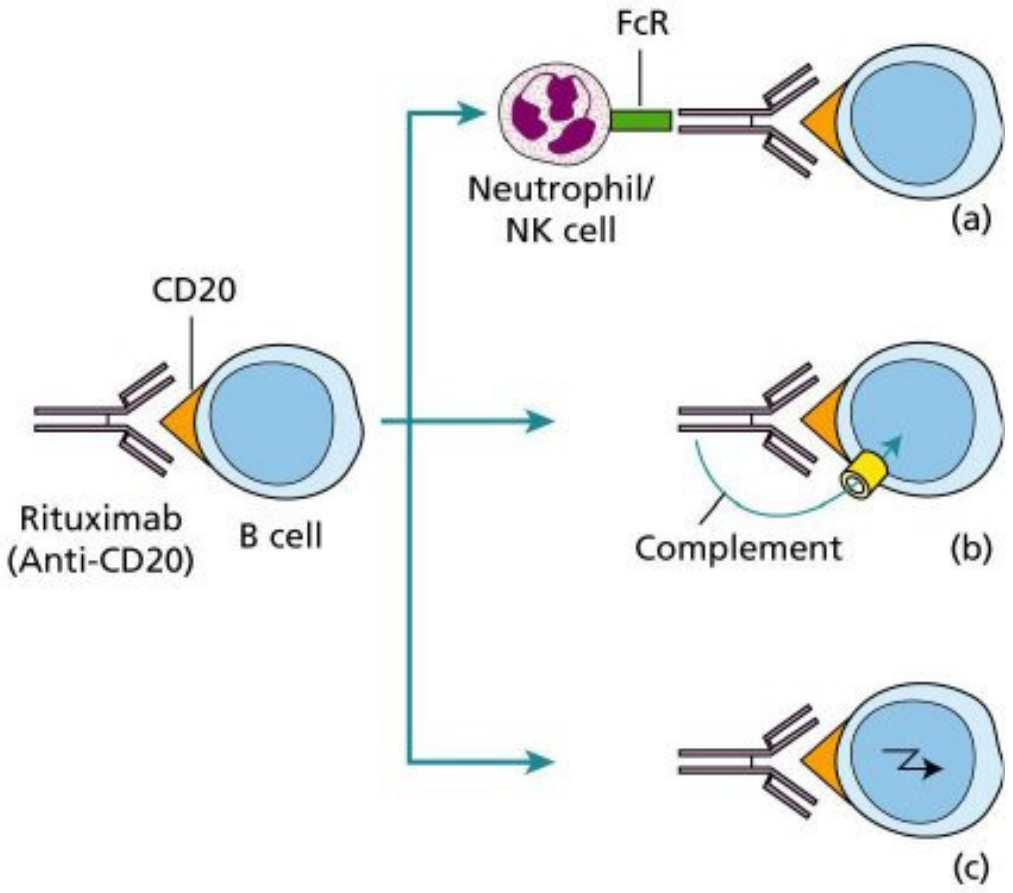
Follicular Lymphoma: Treatment

- Localized disease (stage I) may be cured with radiotherapy
- Disseminated disease (stage II-IV) are generally not treated in the absence of symptoms (watch and wait)
- Treatment:
  - Rituximab (anti-CD20 monoclonal antibodies) + cyclophosphamide, vincristine, prednisolone (R-CVP)
  - Rituximab + bendamustine
  - Rituximab + chlorambucil

Rituximab (Anti-CD20 Monoclonal Antibodies)

Targeted therapy

標靶治療



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Follicular Lymphoma: Treatment

- Initial treatment can provide responses in up to 90% of patients and usually achieve a remission of several years
- Chemotherapy is **not** curative
- Disease relapse for stage II-IV disease is almost inevitable
- Over time the disease becomes increasingly difficult to control

Follicular Lymphoma: Treatment

Relapsed cases

- More intensive chemotherapy or radiolabelled antibody therapy may be considered
- Autologous stem cell transplantation
- Allogeneic stem cell transplantation
  - Potential curative treatment

Diffuse Large B-cell Lymphoma

- A heterogeneous group of disorders
- Classic “high-grade” lymphoma
- Present with rapidly progressive lymphadenopathy associated with a fast rate of cellular proliferation
- Progressive infiltration may affect the bone marrow, gastrointestinal tract, brain, spinal cord and other organs

Diffuse Large B-cell Lymphoma

International Prognostic Index (IPI) for high-grade lymphoma

	Good	Bad
Age	< 60 years	> 60 years
Performance status	0 or 1	> 2
Stage	I or II	III or IV
Number of extranodal sites	0 or 1	> 2
Serum LDH	Normal	Raised

Diffuse Large B-cell Lymphoma

Initial Treatment

- Rituximab in combination with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone) x 6-8 cycles
- Combined RT and chemotherapy (e.g. 3 cycles) may be optimal for localized disease
- Prophylactic therapy to CNS, e.g. intrathecal (椎管內) or high-dose systemic methotrexate (甲氨蝶呤) for high risk disease

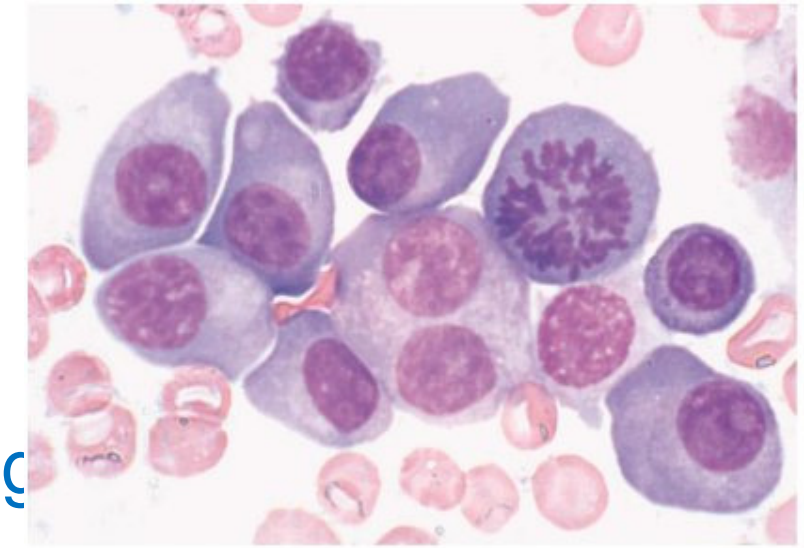
Diffuse Large B-cell Lymphoma

Treatment of relapsed cases

- More intensive chemotherapy can be effective
  - Etoposide, cytosine arabinoside, methylprednisolone, cisplatin (ESHAP)
  - Rituximab, ifosfamide, carboplatin, etoposide (R-ICE)
- Autologous stem cell transplantation for patients who responded to chemotherapy
- Overall long term survival is about 65%

Multiple Myeloma (MM)
多發性骨髓瘤

- A neoplastic disease characterized by
  - plasma cell (漿細胞) accumulation in the bone marrow
  - presence of monoclonal protein in the serum and/or urine

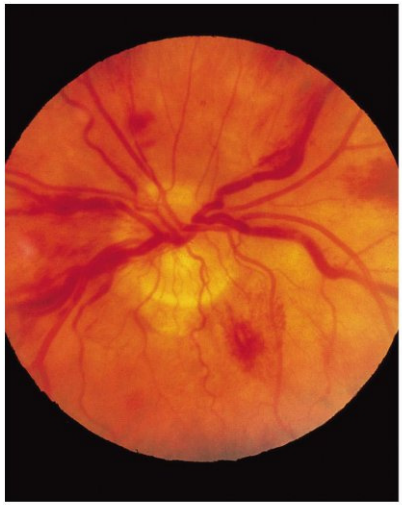


- Symptomatic
  - related tissue damage

- Asymptomatic (smouldering
  - no organ or tissue damage

MM: Clinical Features

- Bone pain (especially back pain)
  - vertebral collapse and pathological fractures
- Symptoms of anaemia
- Recurrent infections
- Symptoms of renal failure and/or hypercalcaemia
- Abnormal bleeding tendency
- Amyloidosis (澱粉樣變)
- Hyperviscosity (粘滯性過高) syndrome
  - haemorrhages, visual failure, CNS symptoms, heart failure



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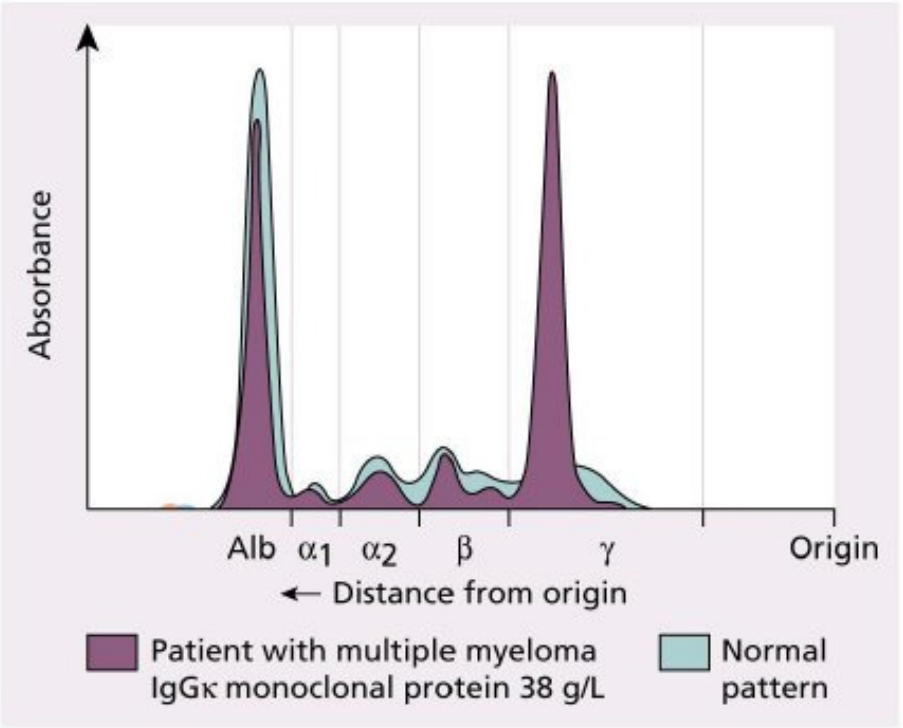
MM: Investigations

- Complete blood picture and blood film exam
- Renal function test
- Liver function test
- Bone profile (calcium, phosphate)
- Serum protein electrophoresis (蛋白電泳)
- Immunoglobulin pattern
- Serum free light chain
- Urine Bence Jones protein
- Serum β2-microglobulin (β2-微球蛋白)
- Bone marrow examination
- Skeletal survey
- Other imaging: CT, MRI

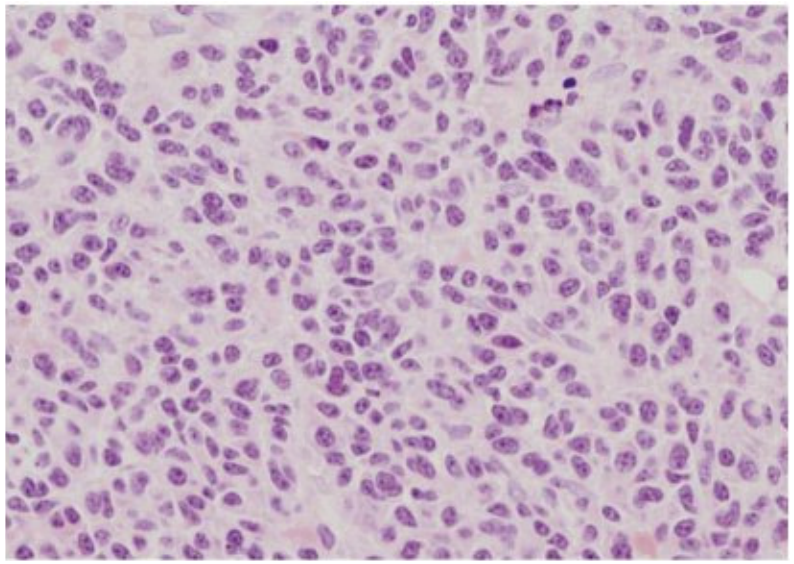
MM: Laboratory Findings

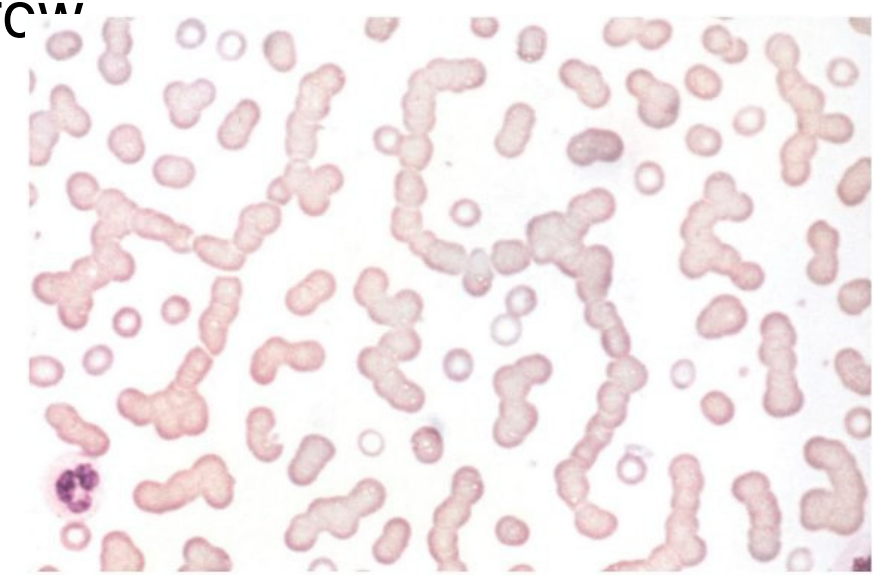
- Presence of a paraprotein
- ↑ serum immunoglobulin-free light chains
- Normal serum immunoglobulin levels are reduced
- Bence-Jones protein (free light chain) in urine
- Normochromic normocytic anaemia, thrombocytopenia, neutropenia



Laboratory Findings

- High erythrocyte sediment rate (ESR)
- ↑ plasma cells in bone marrow
- High plasma calcium
- ↑ plasma creatinine level
- Low serum albumin





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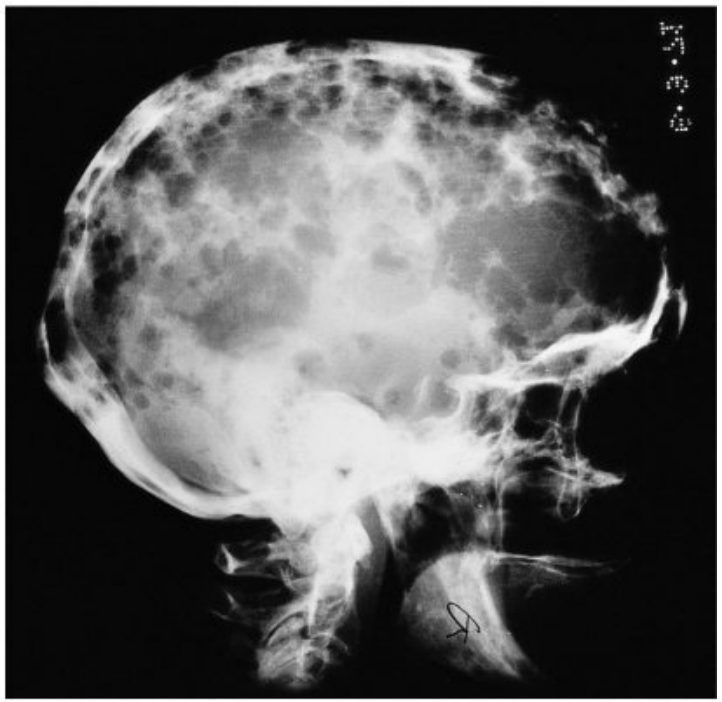
Radiological Examination

- Osteolytic (溶骨的) bone lesions



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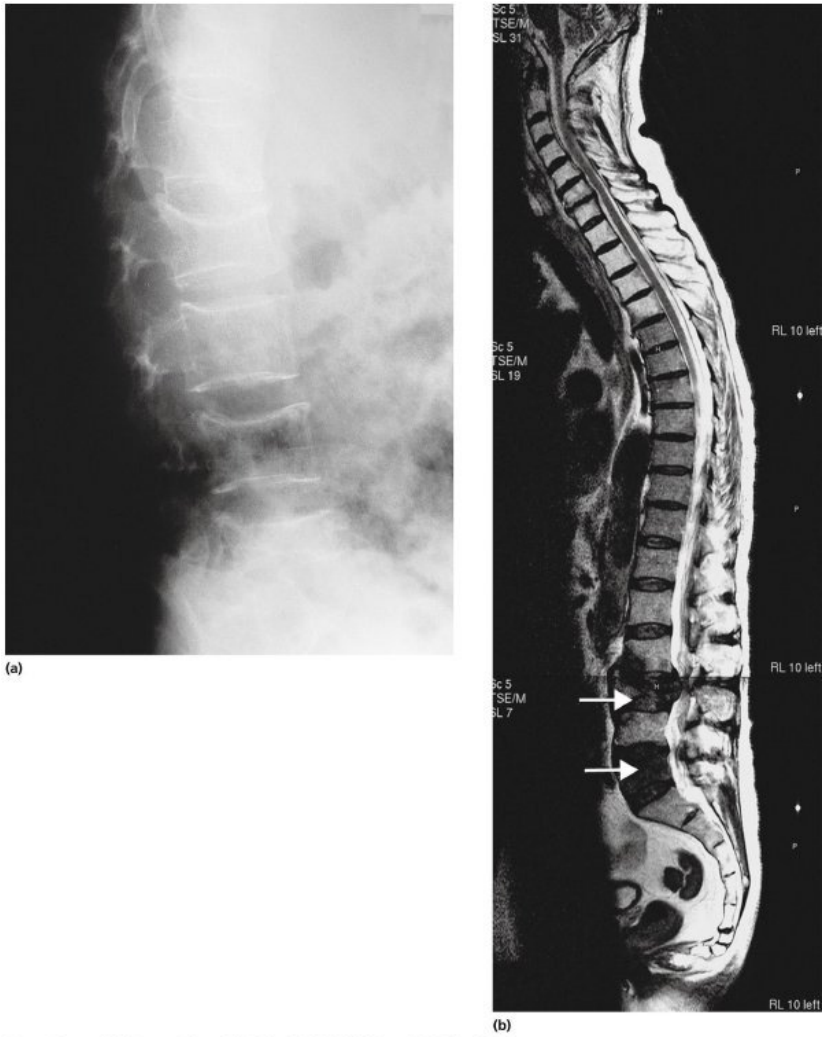

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MM: Diagnosis

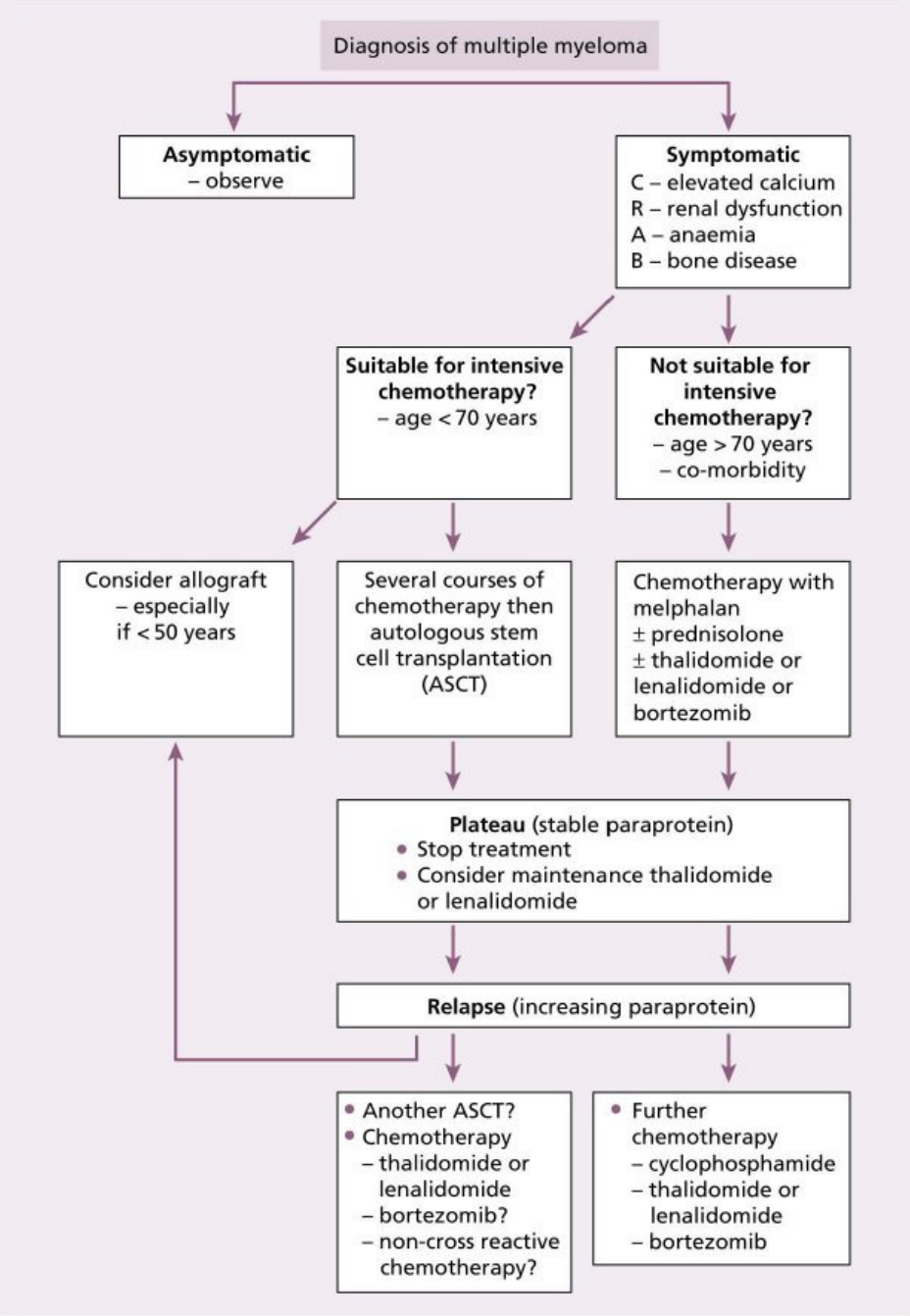
Symptomatic myeloma is diagnosed if:

1. Monoclonal protein in serum and/or urine
2. Increased clonal plasma cells in the bone marrow and
3. Related organ tissue impairment **(CRAB)**
   - hyper**C**alcaemia
   - **R**enal impairment
   - **A**naemia
   - **B**one disease

MM: Treatment

Intensive therapy (age < 65 years and no significant comorbidity)

- 4-6 courses of chemotherapy (e.g. cyclophosphamide, thalidomide, dexamethasone, CTD) to reduce tumour burden
- Autologous stem cell collection
- High dose chemotherapy followed by autologous stem cell transplantation



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MM: Treatment

- **Non-intensive therapy** (for elderly and/or with significant comorbidity)
  - Oral alkylator (melphalan or cyclophosphamide) + thalidomide + prednisolone (e.g. MPT)
  - Repeated courses till a “plateau phase” is reached in which the paraprotein level stop falling
  - Then stop treatment and observe
  - Further treatment (e.g. using newer agents such as bortezomib) when patient develops relapse

MM: Supportive Care

- Renal failure
  - Rehydrate and treat the cause (e.g. hypercalcaemia)
- Bone disease and hypercalcaemia
  - Bisphosphonates, e.g. pamidronate, zoledronic acid
- Compression paraplegia (下身癱瘓麻痺)
  - Surgery or radiotherapy
- Infection
  - Antibiotics, prophylactic immunoglobulin infusion

MM: Prognosis

- Median survival with non-intensive chemotherapy is 3-4 years
- Improved by approximately 1-2 years with high dose chemotherapy and autologous stem cell transplantation
- Survival is improving with the development of various new agents

Monoclonal gammopathy of undetermined significance (MGUS)

- Detection of a serum paraprotein without evidence of multiple myeloma
- Increasingly common with age
  - 1% in persons > 50 years
  - 3% in persons > 70 years
- No clinical complications and the proportion of plasma cells < 10% (normal or slightly raised)
- No treatment is needed
- Progress to myeloma or lymphoma ~ 1% per year