# Primary and Secondary Bone Lymphomas

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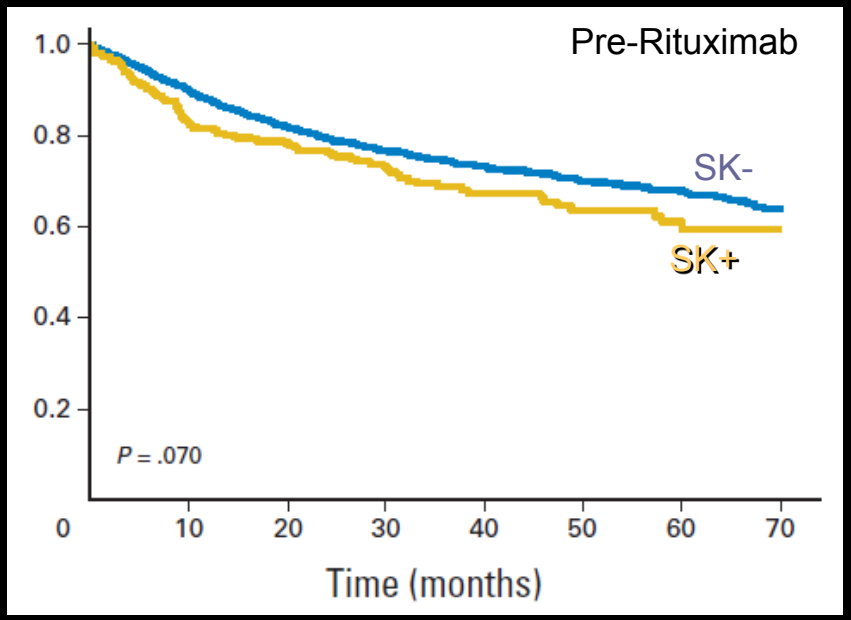
# Bone Lymphomas: Definition

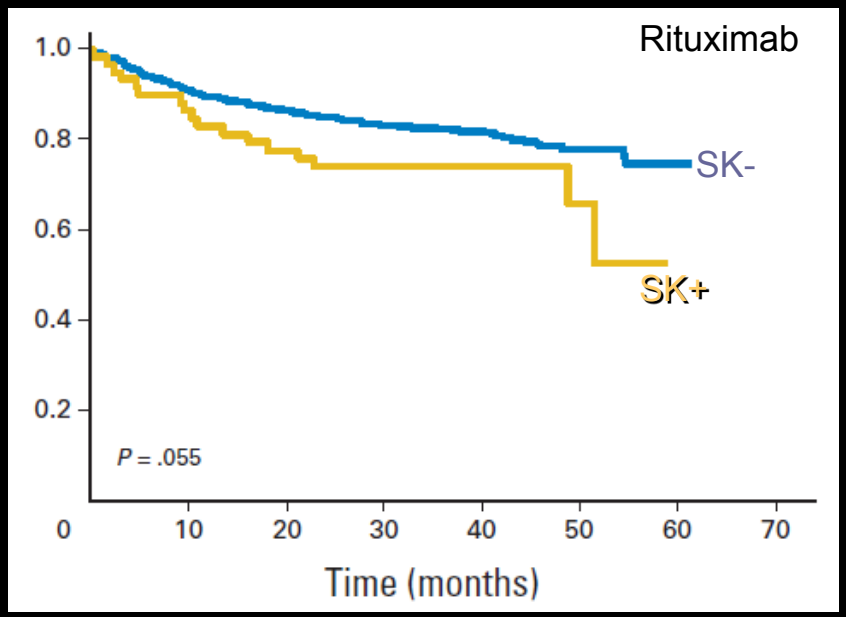
- ✓ Criteria used to define bone lymphomas changed several times.
- ✓ Cases with a solitary bony lesion should be considered as a PBL (consensus).
- ✓ Multifocal osseous disease or cases with soft tissue, visceral ± LN infiltration?
- ✓ In the previous version of the WHO classification of tumours of soft tissue and bone, PBL was defined by a single or multiple skeletal lesions without LN or visceral involvement.
- ✓ The last versions of the WHO Classification does not provide definition criteria.
- ✓ Only cases with a clear bone origin should be considered as PBL:
    - a single bony lesion ± regional lymph nodes
    - multiple bony lesions without lymph nodal or visceral disease (‘‘multifocal osseous lymphoma’’ or ‘‘polyostotic lymphoma’’).
    - Disseminated lymphomas with skeletal involvement= ‘‘secondary bone lymphoma’’. It counts as a systemic extra-nodal site (stage IV).

# PBL Definition: Difficult Cases

- ✓ A lymphoma that has arisen in soft tissues, LN or other organs and infiltrates an adjacent bone secondarily should not be considered to be a PBL.
- ✓ It may be very difficult to separate these two situations, specially in nasal-paranasal bones (mucosal vs. osseous lymphomas) or spine (i.e., bone or nearby soft tissues).
- ✓ In many cases, a subjective judgement will be required about whether a case should be categorized as PBL or lymphoma secondarily affecting the bone.

# DLBCL: Skeletal Involvement (3.840)

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# Patient Characteristics

| | Limited stage DLBCL ($n = 161$) | MB-DLBCL ($n = 37$) | Stage IV DLBCL ($n = 63$) |
|---|---|---|---|
| Males | 51% | 59% | 40% |
| Median age; years (range) | 55 (18–99) | 53 (17–75) | 62 (28–83) |
| *Clinical presentation (%)* | | | |
| ECOG-PS > 1 | 15% | 38% | 62% |
| High LDH serum level | 34% | 30% | 65% |
| B symptoms | 9% | 24% | 30% |
| Pain | 82% | 92% | 90% |
| Swelling | 40% | 45% | 34% |
| Bulky disease | 23% | 15% | 32% |
| Fracture | 15% | 25% | 29% |
| *Sites of involvement (%)* | | | |
| Skull | 15% | 32% | 19% |
| Spinal cord | 17% | 65% | 51% |
| Pelvis | 17% | 32% | 33% |
| Humerus | 7% | 13% | 17% |
| Forearm | 7% | 16% | 8% |
| Femur | 20% | 38% | 24% |
| Forefoot | 13% | 19% | 14% |
| Lymph nodes | – | – | 28% |
| Cerebrospinal fluid | – | 3% | 1% |
| Bone marrow | – | – | 35% |
| Other | 4% | – | – |

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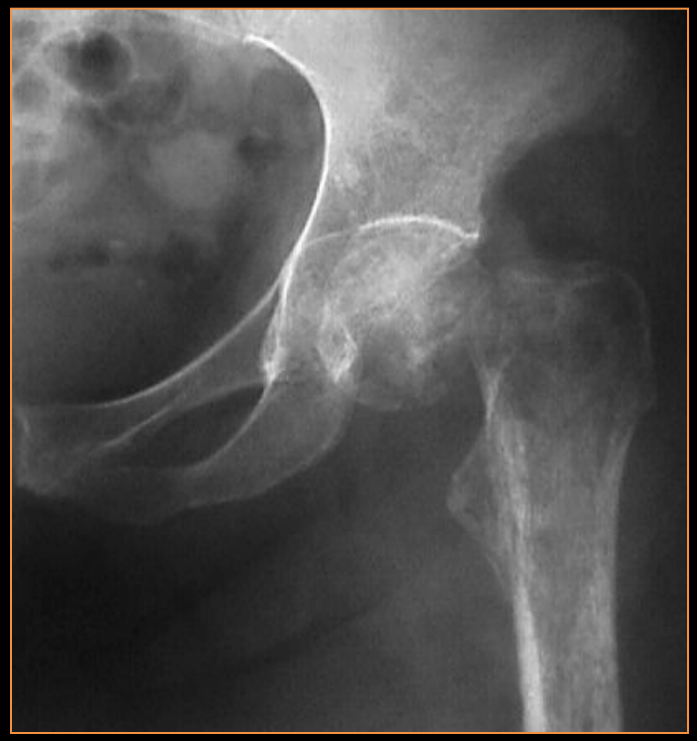
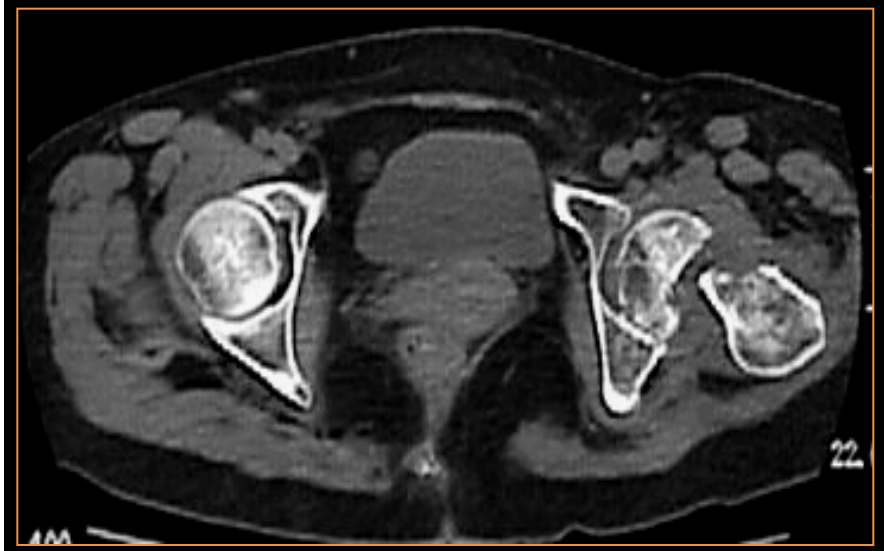
# Radiographic Findings: Rx



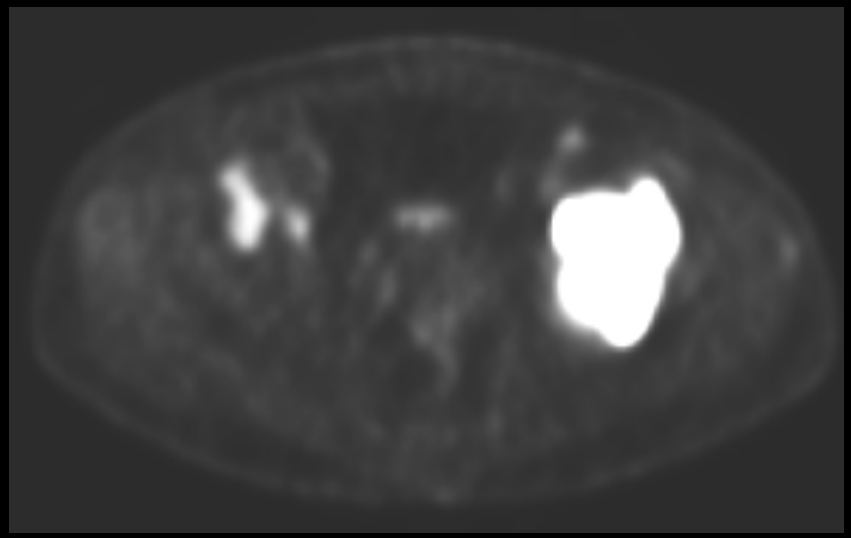
- Usually non-specific, with important limitations to distinguish lymphomas from other tumours Ewing's s, osteosarcoma and chondrosarcoma.
- Lesions are mostly lytic, but half of the pts have also osteoblastic lesions or both.
- Cortex shows a mixture of permeative, moth-eaten or destructive patterns.
- The periosteum often shows reactive changes, and osteosarcoma-like features (onionskin layering, breach of the periosteum or sunburst appearance.

# Radiographic Findings: CT scan



- CT scan is the primary modality for staging, restaging, and follow-up.
- CT demonstrates extraosseous extension, cortical breakthrough, distinguish osteolysis, osteosclerosis and bone sequestra.
- MRI reveals the extent of disease in more detail, identifying cortical changes, intratumoural fibrosis and infiltration of trabecular bone and bone marrow.
- Abnormal signal intensity areas are visible on both T1 and T2 w images with minimal contrast enhancement, hypointense in T1-w and hyperintense in T2-w.
- Restricted diffusion with low apparent diffusion co-efficiency value on DWI (OR definiton).

# Functional Imaging



- $^{18}$FDG-PET: increased uptake on bone and soft tissue lesions, with a higher specificity and sensitivity than conventional bone scintigraphy.
- $^{18}$FDG-PET-CT simultaneously provides functional and anatomical information, with a higher sensitivity and specificity than standard CT scan in lymphoma pts.
- The addition of $^{18}$FDG-PET to CT scan results in upstaging in 42% of lymphoma patients.
- PET-CT is recommended by the Lugano Classification as a standard tool for initial evaluation, staging and response assessment of FDG-avid lymphomas.

# Diagnosis

- Biopsy is mandatory to confirm lymphomatous nature and to define histotype.
- Excision biopsy should be avoided; biopsies should be limited in size to reduce the risk of pathological fracture.
- Some bony sites (a.e., skull base) are difficult to biopsy, with the risk of false negative results & delayed diagnosis.
- In cases with stage-IIE disease, lymphadenectomy is advisable because it is associated with a lower risk of orthopaedic sequelae and facilitates pathologist's diagnostic performance.

# Diagnosis

Pathological classification with relative frequencies in the largest series of PBL.

| Histology | Zinzani [59] | Beal [1] | Ramadan [29] | Alencar [91] | Cai [72] |
|---|---|---|---|---|---|
| Diffuse large B-cell | 44 (84%) | 66 (80%) | 103 (79%) | 44 (83%) | 91 (78%) |
| Diffuse mixed | – | 4 (5%) | – | – | – |
| Follicular | 2 (4%) | 3 (4%) | 7 (5%) | 3 (5.7%) | 7 (6%) |
| Peripheral T-cell | – | – | 2 (1.5%) | 2 (3.8%) | – |
| Extra-nodal marginal zone | – | – | 4 (3%) | 1 (1.9%) | – |
| Mantle cell | – | – | 1 (1%) | 1 (1.9%) | – |
| Small lymphocytic | 2 (4%) | 3 (4%) | 2 (1.5%) | 1 (1.9%) | – |
| Transformed MALT | – | – | – | 1 (1.9%) | – |
| Burkitt's/Burkitt like | 2 (4%) | 1 (1%) | 2 (1.5%) | – | – |
| Anaplastic large T-cell | 2 (4%) | – | 4 (3%) | – | 6 (5%) |
| Lymphoma NOS | – | 2 (2%) | – | – | – |
| Plasmocitoid | – | 1 (1%) | – | – | – |
| Immunoblastic | – | 1 (1%) | – | – | – |
| Lymphoblastic | – | 1 (1%) | 2 (1.5%) | – | – |
| Unclassifiable low grade | – | – | 1 (1%) | – | – |
| Other | – | – | – | – | 12 (11%) |

**Evidence of GC derivation in 50% of cases.**
**Positive for B-cell markers: CD45, CD20, CD21, CD45, CD79a**
**Immunoreactivity for CD75 and CD10 is variable.**
**T-cell markers are usually negative.**
**BCL-2 and BCL-6 immunoreactivity in 35% and 69% of cases, respectively.**

# Diagnosis

Cytogenetic and molecular feature related to DLBCL.

A monoclonal pattern in 54% of cases. IgH gene rearrangement in 72%

BCL-2 translocation in 5% of cases.

BCL2 protein expression (55–70%) (gene amplification?).

c-MYC translocations in 9% of cases.

BCL6, PAX5, ALK, and CCND1 rearrangements 0% (specific).

Increased expressions of osteoclast-activating factors, such as MIP-1$\alpha$, MIP-1$\beta$ and RANKL, suggest a potential causative role in osteolysis and hypercalcemia.

# Indolent PBL

| | Limited disease* ($n = 11$) | Stage IV disease ($n = 15$) |
|---|---|---|
| Median age; years (range) | 63 (27–77) | 57 (40–80) |
| Males | 5 (46%) | 10 (67%) |
| Histological type | | |
| Small lymphocytic lymphoma | 5 (46%) | 5 (33%) |
| Follicular lymphoma | 3 (27%) | 7 (47%) |
| Lymphoplasmacytic lymphoma | 3 (27%) | 3 (20%) |
| Clinical presentation | | |
| Fever | 1 (9%) | 3 (20%) |
| Swelling | 0 (0%) | 1 (7%) |
| Weight loss | 0 (0%) | 1 (7%) |
| Pain | 10 (91%) | 13 (87%) |
| Tumefaction | 2 (18%) | 5 (33%) |
| Fracture | 1 (9%) | 1 (7%) |
| Sites of involvement | | |
| Skull | 2 (18%) | 4 (27%) |
| Column | 3 (27%) | 6 (40%) |
| Pelvis | 2 (18%) | 7 (47%) |
| Humerus | 0 (0%) | 2 (14%) |
| Femur | 2 (18%) | 5 (33%) |
| Upper limbs | 0 (0%) | 1 (7%) |
| Lower limbs | 2 (18%) | 1 (7%) |
| Lymph nodes | 1 (9%) | 4 (27%) |
| Cerebrospinal fluid | - | 1 (7%) |
| Extranodal sites | - | 5 (33%) |
| Bone marrow | - | 4 (27%) |
| Treatment | | |
| Radiotherapy alone | 4 (36%) | 0 (0%) |
| Chemotherapy + radiotherapy | 4 (36%) | 10 (66%) |
| Chemotherapy alone | 3 (27%) | 5 (33%) |

| Subgroups | $n$ | 5-year PFS | $p$-Value | 5-year OS | $p$-Value |
|---|---|---|---|---|---|
| Age | | | | | |
| ≤ 60 years | 13 | 42 ± 13% | | 56 ± 13% | |
| > 60 years | 13 | 52 ± 13% | 0.46 | 53 ± 13% | 0.10 |
| ECOG PS | | | | | |
| 0–1 | 15 | 57 ± 13% | | 73 ± 11% | |
| 2–4 | 9 | 30 ± 14% | 0.02 | 36 ± 15% | 0.03† |
| Stage | | | | | |
| I–II | 11 | 64 ± 13% | | 78 ± 11% | |
| III–IV | 15 | 24 ± 13% | 0.07 | 32 ± 12% | 0.01† |
| Surgical resection | | | | | |
| No | 20 | 43 ± 10% | | 50 ± 11% | |
| Yes | 6 | 53 ± 16% | 0.15 | 67 ± 16% | 0.19 |
| Radiotherapy | | | | | |
| No | 8 | 13 ± 12% | | 26 ± 16% | |
| Yes | 18 | 55 ± 13% | 0.06 | 64 ± 11% | 0.13 |
| Histological type | | | | | |
| SLL | 10 | 56 ± 17% | | 67 ± 16% | |
| FL | 10 | 25 ± 15% | 0.05* | 23 ± 14% | 0.02* |
| Lpc | 6 | 33 ± 19% | | 50 ± 20% | |

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# Staging

Staging procedures in patients with bone lymphoma.

| *Test/procedure* |
|---|
| Demographics and medical history* |
| Physical examination |
| Blood tests# |
| Chest X-ray |
| Contrasted CT scan of the neck, chest, abdomen, and pelvis |
| MRI of bony lesions |
| $^{18}$FDG-PET |
| Bone marrow biopsy |
| *In case of suspicion of involvement of particular organs* |
| Cerebrospinal fluid (CSF) examination§ |
| Gadolinium-enhanced brain MRI§ |
| Gastrointestinal tract endoscopy |
| Blood smears |

IELSG staging system for DLBCL of the bone.

| IELSG stage | Lymphoma extension | Ann Arbor stage |
|---|---|---|
| IE | Single bony lesion | IE |
| IIE | Single bony lesion with involvement of regional lymph nodes | IIE |
| IVE | Multifocal disease in a single bone or lesions in multiple bones in a disease exclusively limited to the skeleton (without lymph nodal or visceral disease) – called also "multifocal osteolymphoma" or "polyostotic lymphoma" | IV |
| IV | Disseminated lymphoma with at least one bony lesion | IV |

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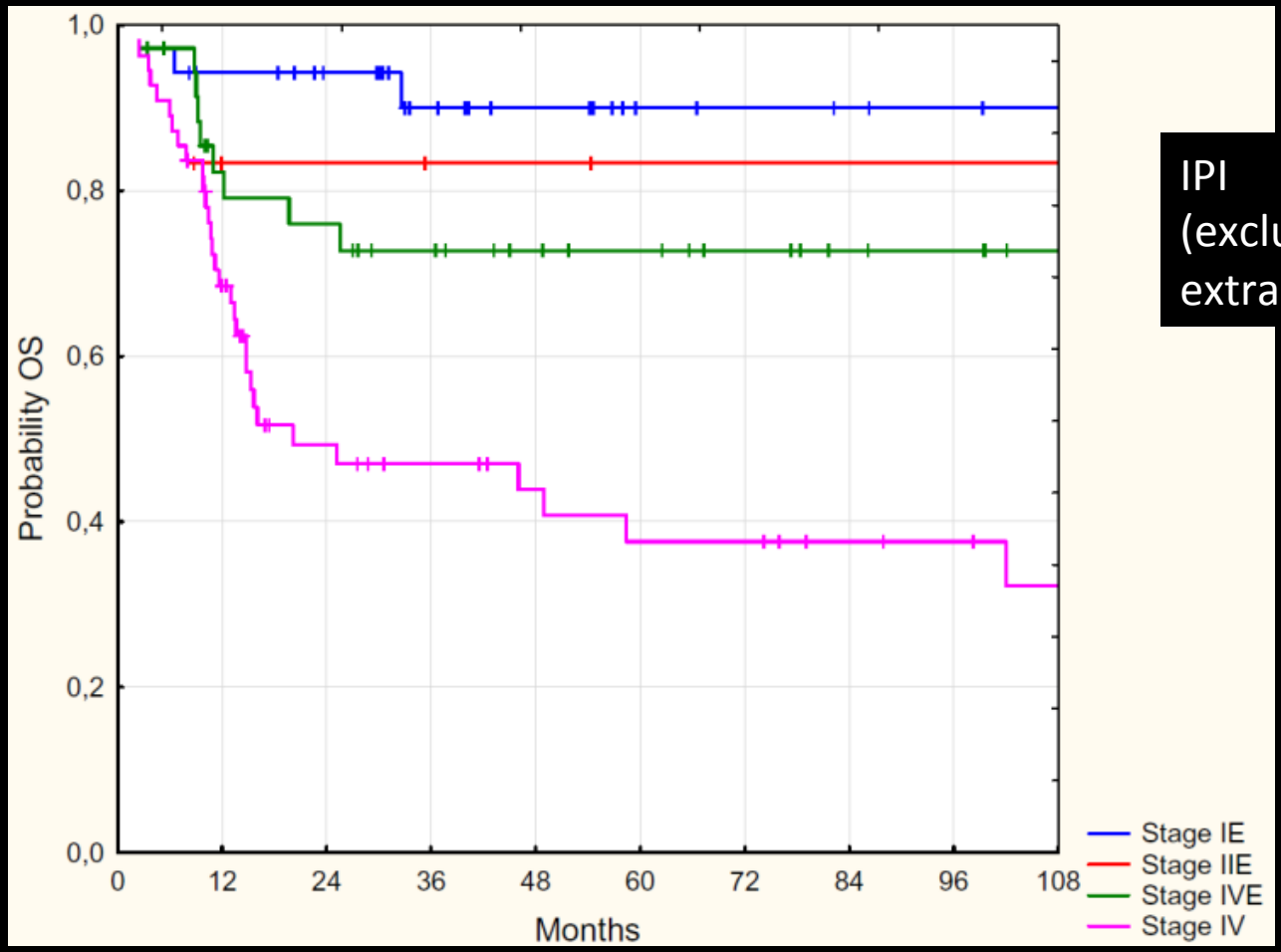
# IELSG Staging System

CHOP or similars




IPI
(excluding stage and extranodal sites)

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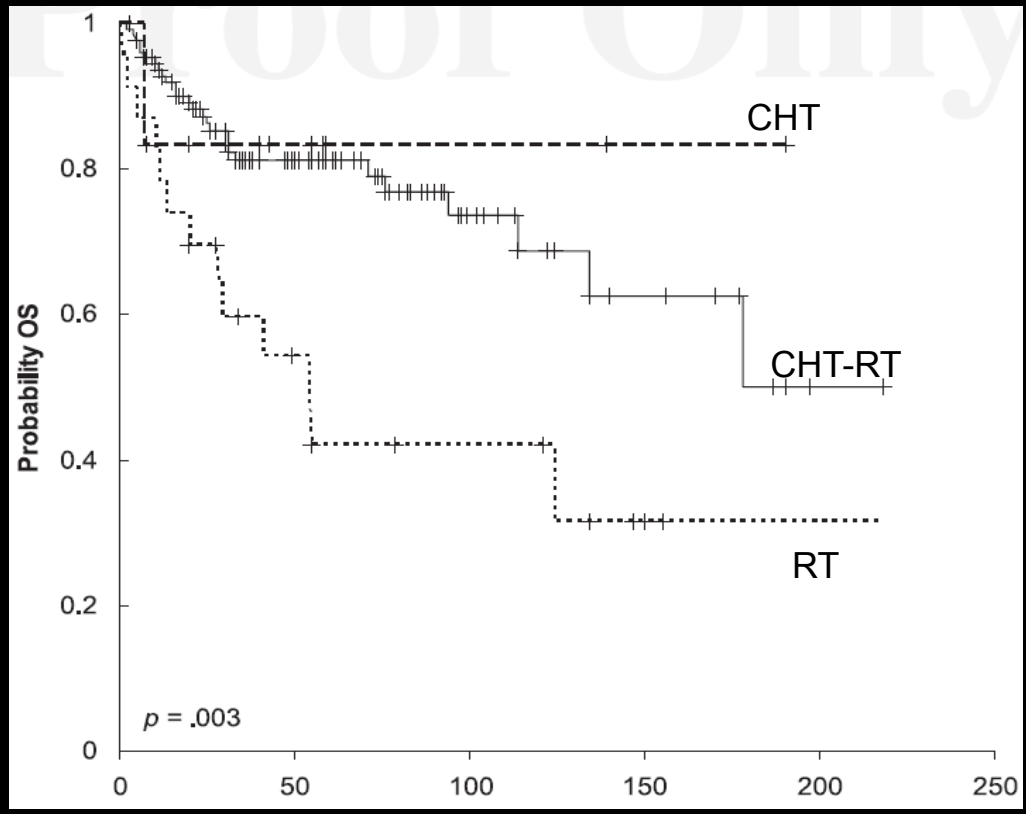
# Limited-stage DLBCL of the Bone

| Parameter | Value |
|---|---|
| Patients, *n* (%) | 161 (100) |
| Median age (yr) (range) | 55 (18–99) |
| Age >60 years old, *n* (%) | 62 (39) |
| Male gender, *n* (%) | 90 (51) |
| Male/female ratio | 1:2 |
| Stage IIE, *n* (%) | 20 (13) |
| B symptoms, *n* (%) | 14 (9) |
| High LDH serum level, *n* (%)[a] | 54/158 (34) |
| IPI risk group (score), *n* (%) | |
| Low (0–1) | 113 (70) |
| Low intermediate (2) | 36 (22) |
| High intermediate (3) | 7 (4) |
| Unknown | 5 (3) |
| Site, *n* (%) | |
| Femur | 33 (20) |
| Spine | 27 (17) |
| Pelvis | 27 (17) |
| Skull | 25 (15) |
| Lower limb, excluding femur | 21 (13) |
| Upper limb, excluding humerus | 11 (7) |
| Humerus | 11 (7) |
| Others | 6 (4) |
| Geographical region, *n* (%) | |
| North America | 25 (16) |
| South America | 13 (8) |
| Europe | 70 (43) |
| Asia | 13 (8) |
| Oceania | 40 (25) |

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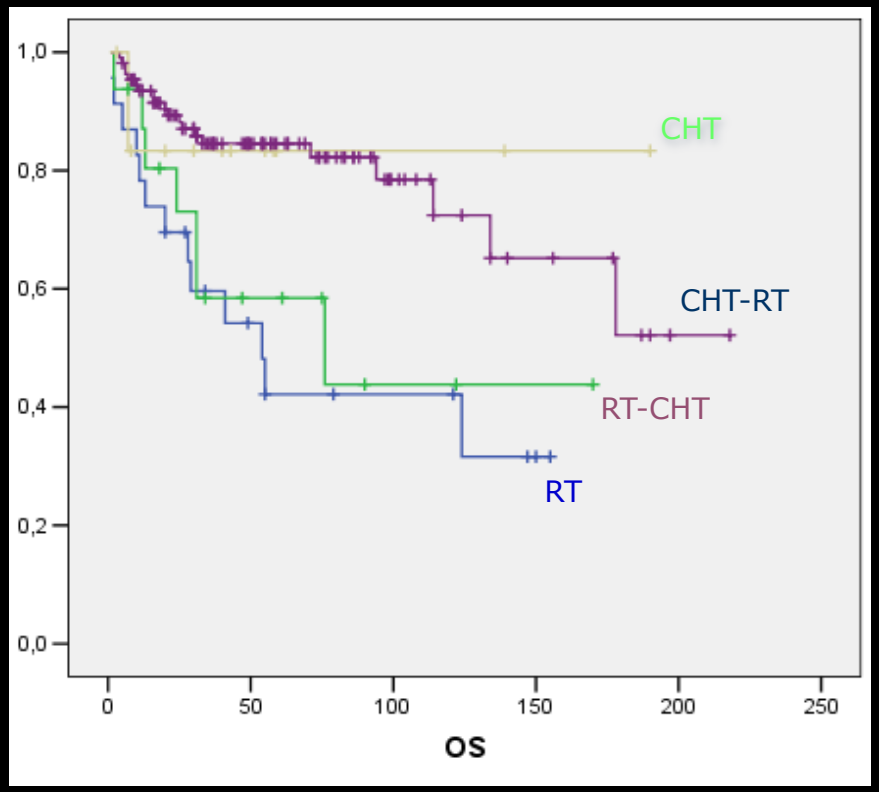
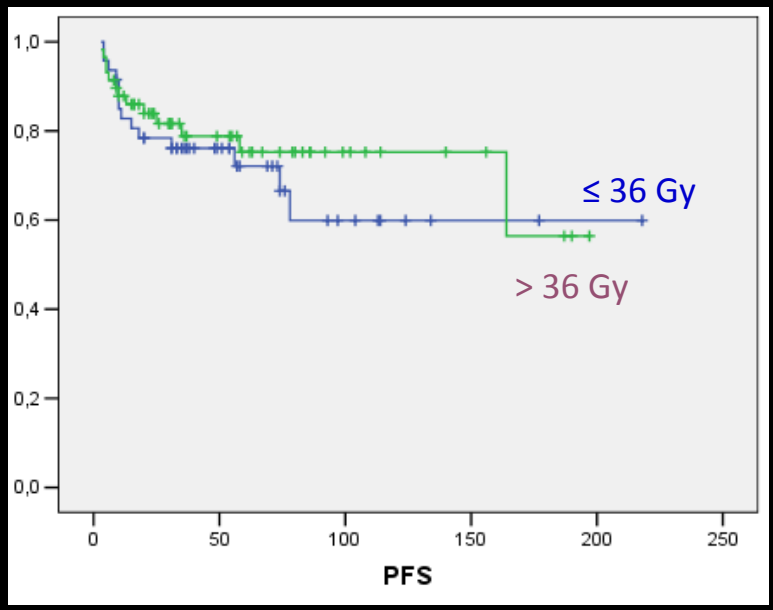
# Treatment of PBL




| Variable | Subgroup | Odds ratio | 95% CI | *p* |
|---|---|---|---|---|
| Age | Continuous | 1.04 | 1.02–1.07 | .0001 |
| ECOG-PS | 0–1 | 1.88 | 0.98–3.61 | .057 |
| | 2–4 | | | |
| Stage | I | 1.27 | 0.44–3.67 | .65 |
| | II | | | |
| LDH | Normal | 0.92 | 0.44–1.93 | .83 |
| | High | | | |
| B symptoms | No | 1.25 | 0.37–4.27 | .71 |
| | Yes | | | |
| Fracture | No | 0.87 | 0.41–1.85 | .71 |
| | Yes | | | |
| Primary chemotherapy | No | 0.42 | 0.22–0.81 | .009 |
| | Yes | | | |

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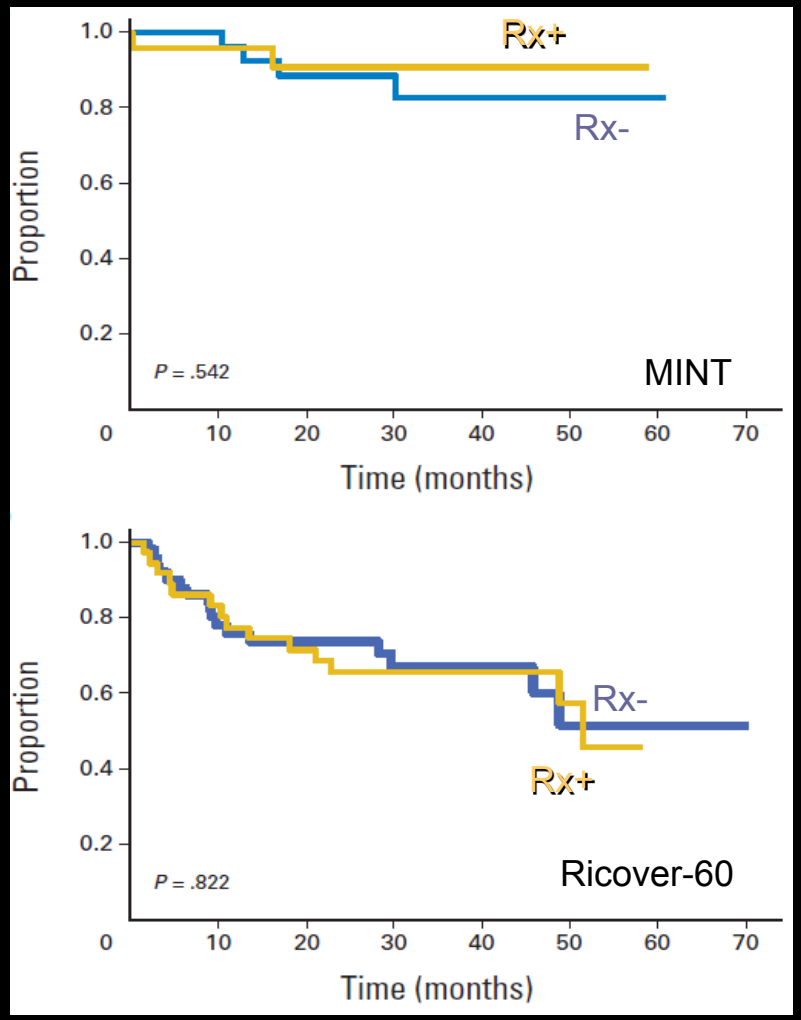
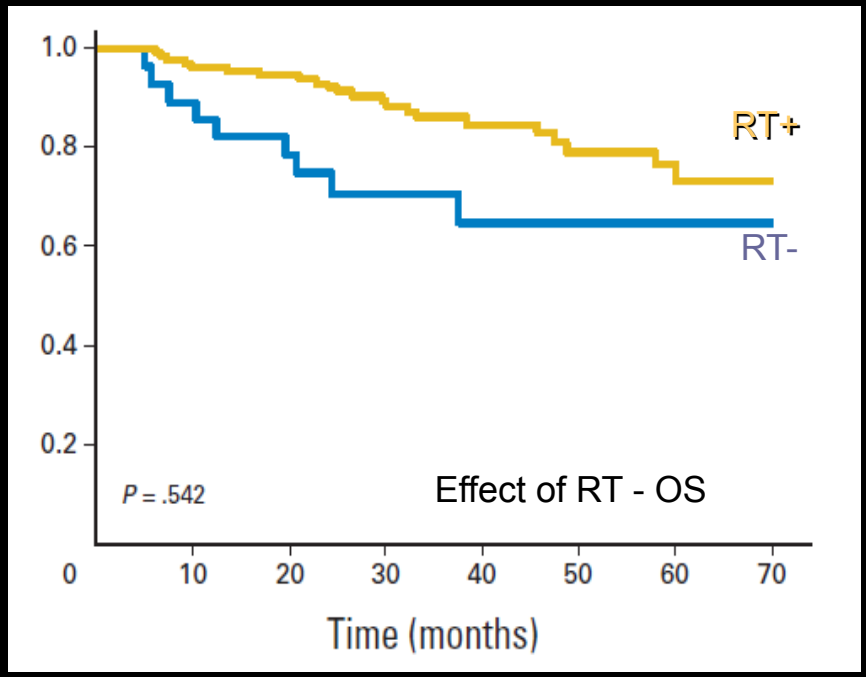
# Bone DLBCL: Rituximab & RT (3.840)

Effect of Rituximab - OS

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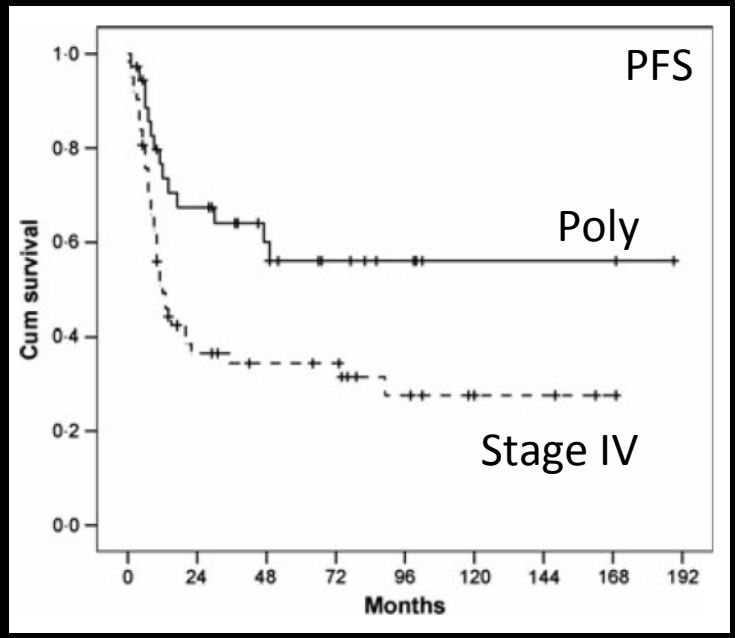
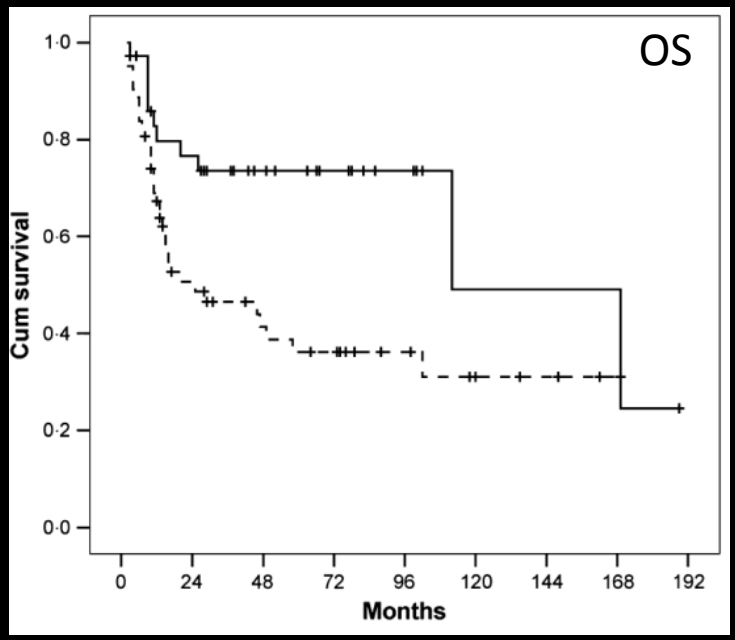
# Suggestions for RT use in PBL

- The choice of radiation volume should result from an accurate risk–benefit analysis (sensitive organs, late bone effects).
- Most radiotherapy experts favor whole-bone irradiation (WBI), but supporting evidence is limited.
- In the pre-rituximab era, results with WBI are slightly better than PBI.
- Flat bones (a.e., vertebra) should be entirely irradiated.
- In cases where WBI appears risky, 3–5-cm margins on pre-chemo tumour borders is advisable.
- Margins around the soft tissue or extra-osseous borders can be further restricted to 1–2 cm around post-chemotherapy volumes.
- Dose depends on the irradiated volume size, the anatomical area and response to chemo.
- A dose of 30 Gy is not associated with loss of efficacy.

# Polyostotic Ly.

| | MB-DLBCL ($n$ = 37) | Controls* ($n$ = 63) | $P$ |
|---|---|---|---|
| Males | 22 (59%) | 25 (40%) | NS |
| Median age; years (range) | 53 (17–75) | 62 (28–83) | 0·004 |
| Clinical presentation (%) | | | |
| ECOG-PS > 1 | 14 (38%) | 39 (62%) | 0·019 |
| High LDH serum level | 11 (30%) | 41 (65%) | 0·0006 |
| B symptoms | 9 (24%) | 20 (30%) | NS |
| Pain | 33 (92%) | 56 (90%) | NS |
| Swelling | 13 (45%) | 19 (34%) | NS |
| Bulky disease | 2 (15%) | 12 (32%) | NS |
| Fracture | 7 (25%) | 16 (29%) | NS |
| Sites of involvement (%) | | | |
| Skull | 12 (32%) | 12 (19%) | NS |
| Spinal cord | 24 (65%) | 32 (51%) | NS |
| Pelvis | 12 (32%) | 21 (33%) | NS |
| Humerus | 5 (13%) | 11 (17%) | NS |
| Forearm | 6 (16%) | 5 (8%) | NS |
| Femur | 14 (38%) | 15 (24%) | NS |
| Forefoot | 7 (19%) | 9 (14%) | NS |
| Lymph nodes | | 18 (28%) | |
| Cerebrospinal fluid | 1 (3%) | 1 (1%) | NS |
| Bone marrow | | 22 (35%) | |

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# Polyostotic Lymphoma

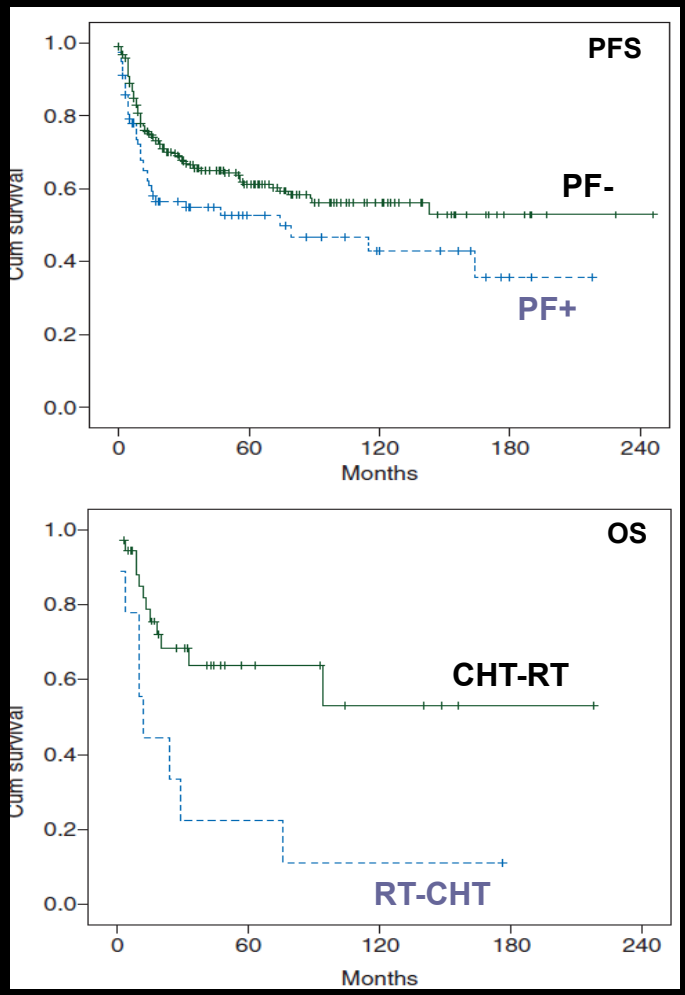
**Table IV.** Multivariate analyses.

| | Subgroups | Odds ratio | 95% CI | *P*-value |
|---|---|---|---|---|
| Whole series | | | | |
| Age | Continuous | 1·99 | 1·04–3·79 | 0·03 |
| ECOG-PS | 0–1 vs. 2–4 | 1·36 | 0·69–2·68 | 0·36 |
| LDH serum level | High vs. Normal | 0·97 | 0·49–1·96 | 0·93 |
| B symptoms | No vs. Yes | 0·69 | 0·32–1·49 | 0·35 |
| Fracture | No vs. Yes | 1·20 | 0·66–2·19 | 0·55 |
| MB-DLBCL | Controls vs. MB-DLBCL | 0·46 | 0·22–0·98 | 0·04 |
| MB-DLBCL | | | | |
| Age | Continuous | 1·03 | 0·99–1·07 | 0·12 |
| ECOG-PS | 0–1 vs. 2–4 | 9·58 | 0·45–20·21 | 0·14 |
| LDH serum level | High vs. Normal | 0·57 | 0·03–9·61 | 0·70 |
| B symptoms | No vs. Yes | 7·97 | 0·72–87·91 | 0·09 |
| Fracture | No vs. Yes | 1·93 | 0·21–17·72 | 0·56 |
| Radiotherapy | No vs. Yes | 0·08 | 0·01–0·88 | 0·03 |

# Pathological fracture

**Table 1.** Clinical features of patients with bone DLBCL divided according to the presence of pathological fracture (PF)

| | PF, *n* (%) | Without fracture, *n* (%) | *P* ($X^2$ test) |
|---|---|---|---|
| Number of patients | 78 | 295 | |
| Male | 41 (53) | 151 (51) | NS |
| Median age (range) | 61 (18–93) | 57 (17-85) | NS |
| ECOG PS >1 | 34 (44) | 82 (28) | 0.007 |
| Ann Arbor stage III and IV | 36 (46) | 122 (41) | NS |
| Elevated LDH serum level[a] | 25/49 (51) | 107/209 (51) | NS |
| B symptoms | 9 (11) | 50 (17) | NS |
| Pain | 68 (87) | 251 (85) | NS |
| Swelling | 24 (31) | 117 (40) | NS |
| Involved bones | | | |
| Single | 47 (60%) | 189 (64%) | |
| Multiple | 31 (40%) | 106 (36%) | NS |
| Osseous sites | | | |
| Skull | 6 ( 8) | 52 (18) | 0.03 |
| Spine | 30 (38) | 77 (26) | 0.03 |
| Pelvis | 13 (17) | 73 (25) | NS |
| Upper limb | 21 (27) | 45 (15) | 0.01 |
| Lower limb | 38 (49) | 95 (32) | 0.006 |
| Extra-osseous sites | | | |
| Regional lymph nodes | 9 (12) | 50 (17) | NS |
| Distant lymph nodes | 8 (10) | 35 (12) | NS |
| Extranodal organs | 20 (26) | 74 (25) | NS |

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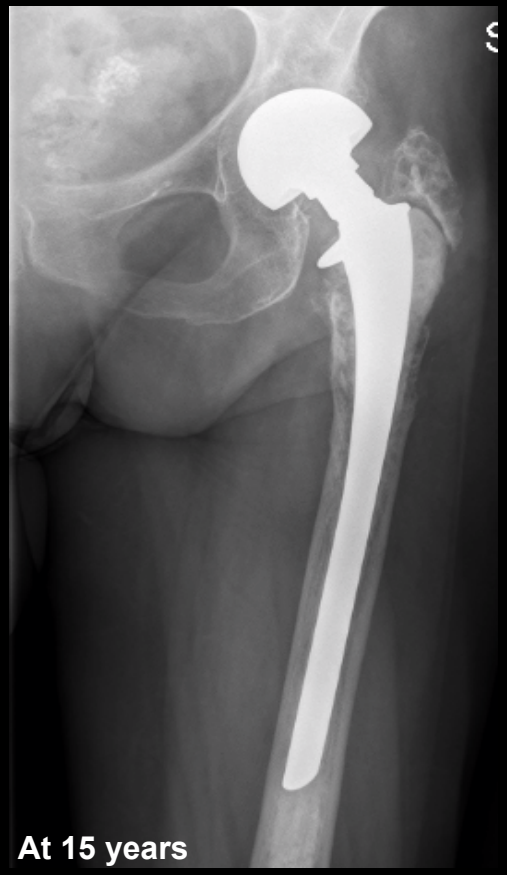
# Pathological fracture

**Table 3.** Multivariate analyses

| Whole series ($n = 373$) | Subgroups | HR | 95% CI | $P$ values |
|---|---|---|---|---|
| Age | Continuous variable | 1.04 | 1.02–1.05 | <0.001 |
| ECOG-PS | 0–1 versus 2–4 | 2.61 | 1.79–3.78 | <0.001 |
| Stage of disease | I–II versus III–IV | 1.97 | 1.38–2.81 | <0.001 |
| LDH serum level | Normal versus high | 1.97 | 1.23–3.17 | 0.005 |
| B symptoms | No versus yes | 0.94 | 0.57–1.54 | 0.824 |
| PF | Yes versus no | 0.61 | 0.41–0.91 | 0.015 |
| Use of anthracycline | No versus yes | 0.40 | 0.17–0.92 | 0.032 |
| **PF-BL group ($n = 78$)** | **Subgroups** | **HR** | **95% CI** | **$P$ values** |
| Age | Continuous variable | 1.05 | 1.02–1.08 | 0.001 |
| ECOG-PS | 0–1 versus 2–4 | 2.34 | 1.08–5.07 | 0.030 |
| Stage of disease | I–II versus III–IV | 2.26 | 1.14-4-47 | 0.019 |
| LDH serum level | Normal versus high | 2.14 | 0.80–5.72 | 0.127 |
| B symptoms | No versus yes | 0.8 | 0.29–2.40 | 0.747 |
| Initial radiotherapy | Yes versus no | 0.31 | 0.12–0.77 | 0.012 |
| Initial surgical stabilization | No versus yes | 1.39 | 0.71–2.69 | 0.326 |
| Fracture radiation dose | ≤30 Gy versus >30 Gy | 0.45 | 0.21–0.98 | 0.045 |
| Radiation field | Whole bone versus partial bone | 1.34 | 0.66–2.69 | 0.412 |
| Use of anthracycline | No versus yes | 0.15 | 0.04–0.47 | 0.001 |




**Any initial surgical stabilization should be kept to a minimum, and used to improve patient's QoL and prevent bone disintegration only if chemotherapy delays can be avoided.**

Govi S, et al. Ann Oncol 2014

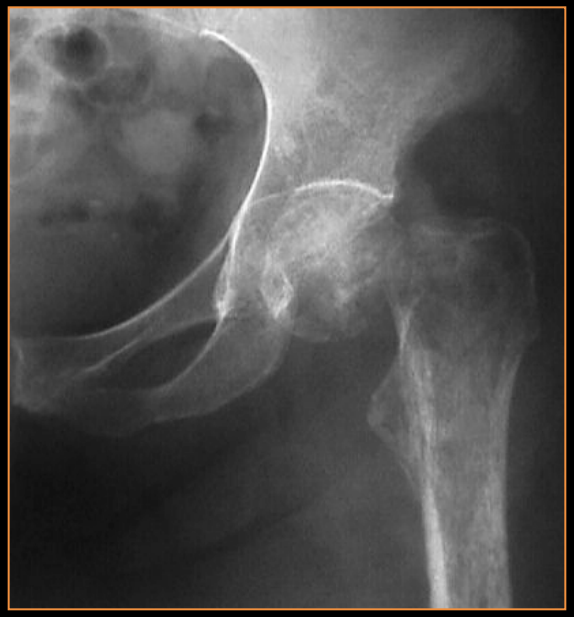
# CNS relapse in Bone DLBCL

| Condition | N° pts | CNS relapse | Notes |
|---|---|---|---|
| PB-DLBCL | 161 | 4 (2%) | Pelvic bones (single lesion) |
| Polyostotic | 37 | 2 (5%) | Spinal cord (multiple les.) |
| Stage IV | 158 | 8 (5%) | IPI ≥3; skull/spinal cord |

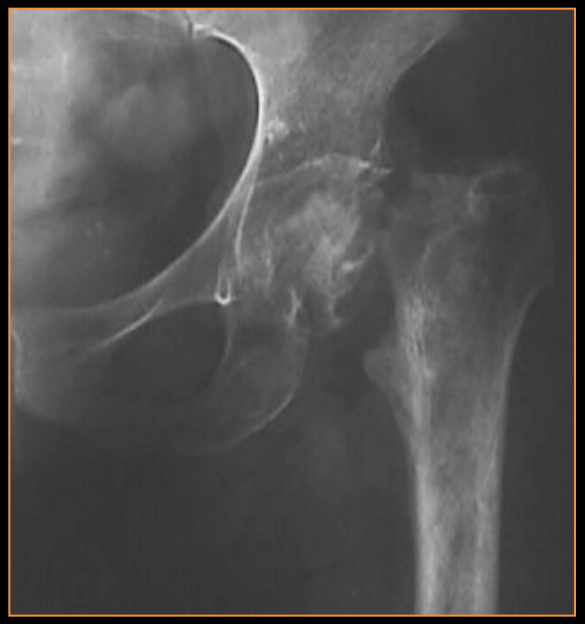
Bruno-Ventre M, *et al.* Oncologist 2014; Messina C, *et al.* BJH 2014; Govi S, *et al.* Ann Oncol 2014

- A few events = undetected predictors
- Lower risk in rituximab era
- CSF assessment, brain MRI and prophylaxis are advised in pts with disseminated DLBCL and involvement of bones close to the CNS (skull and/or spine). CNS recurrence occurs in 7% of these pts.

# Tumor Response - Rx

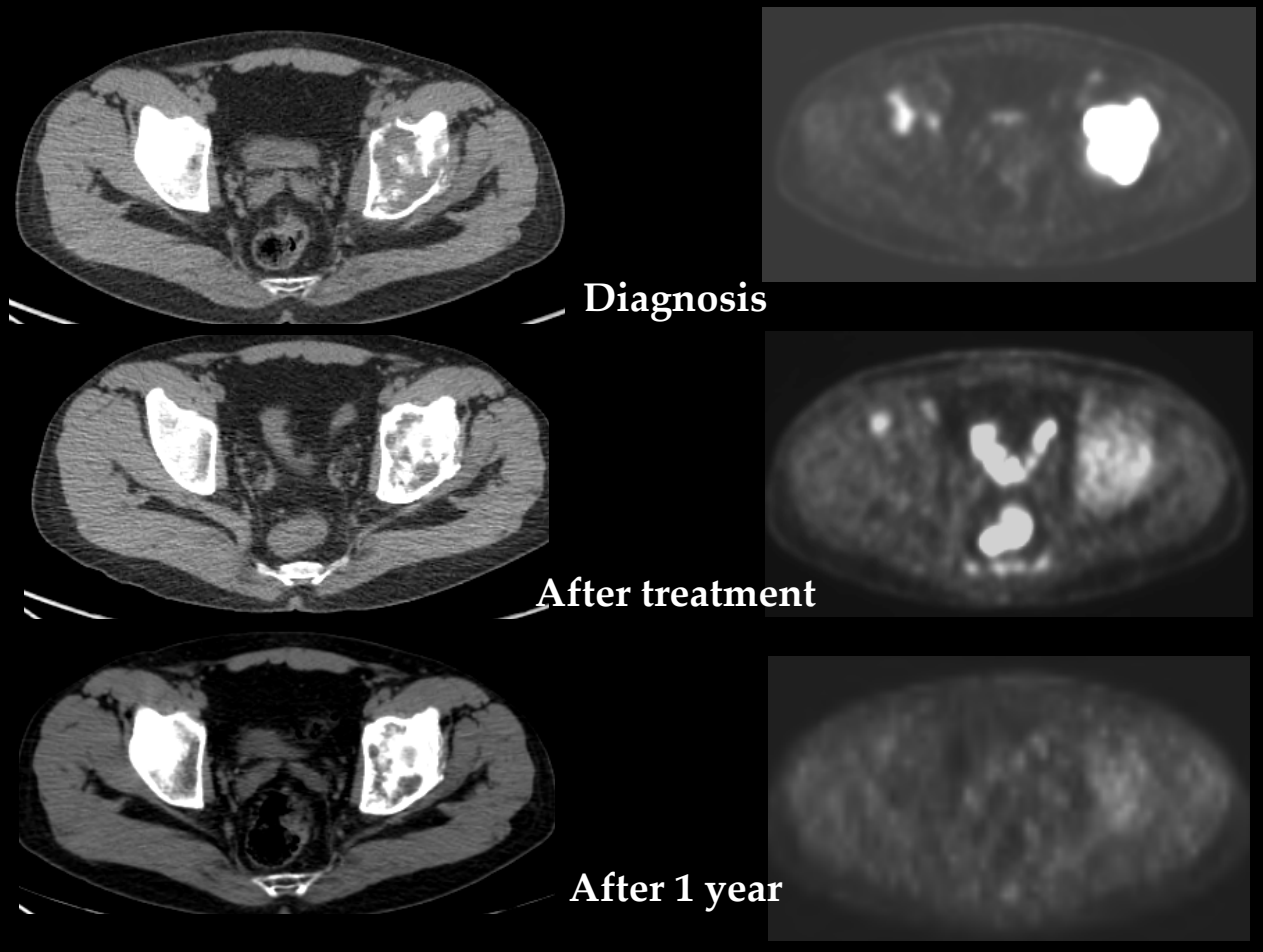


**Diagnosis**



**After treatment**

# Tumor Response – CT vs. PET



# Late iatrogenic sequelae

- Chronic pain, limb dysfunction, late PF (10%), osteonecrosis, osteomyelitis, avascular bone necrosis, and second cancers.
- Risky sites: femur, pelvis and the spine.
- Late PF can occur in the absence of local recurrence and can lead to persisting non-union and disability (lower limb).
- Contributing factors: previous tumour, PF before treatment and the existence of other medical conditions (osteomyelitis, Paget's disease and osteoporosis).
- Bone health preventative measures:
  - To avoid large biopsies at diagnosis and relapse.
  - To monitor bone density
  - To use calcium and vitamin D. Bisphosphonates ?
  - To avoid corticosteroids.
  - To avoid large radiation fields, fractions and doses.
  - To monitor accurately subsequent pain or disability.