

Adult Osteogenic Sarcoma

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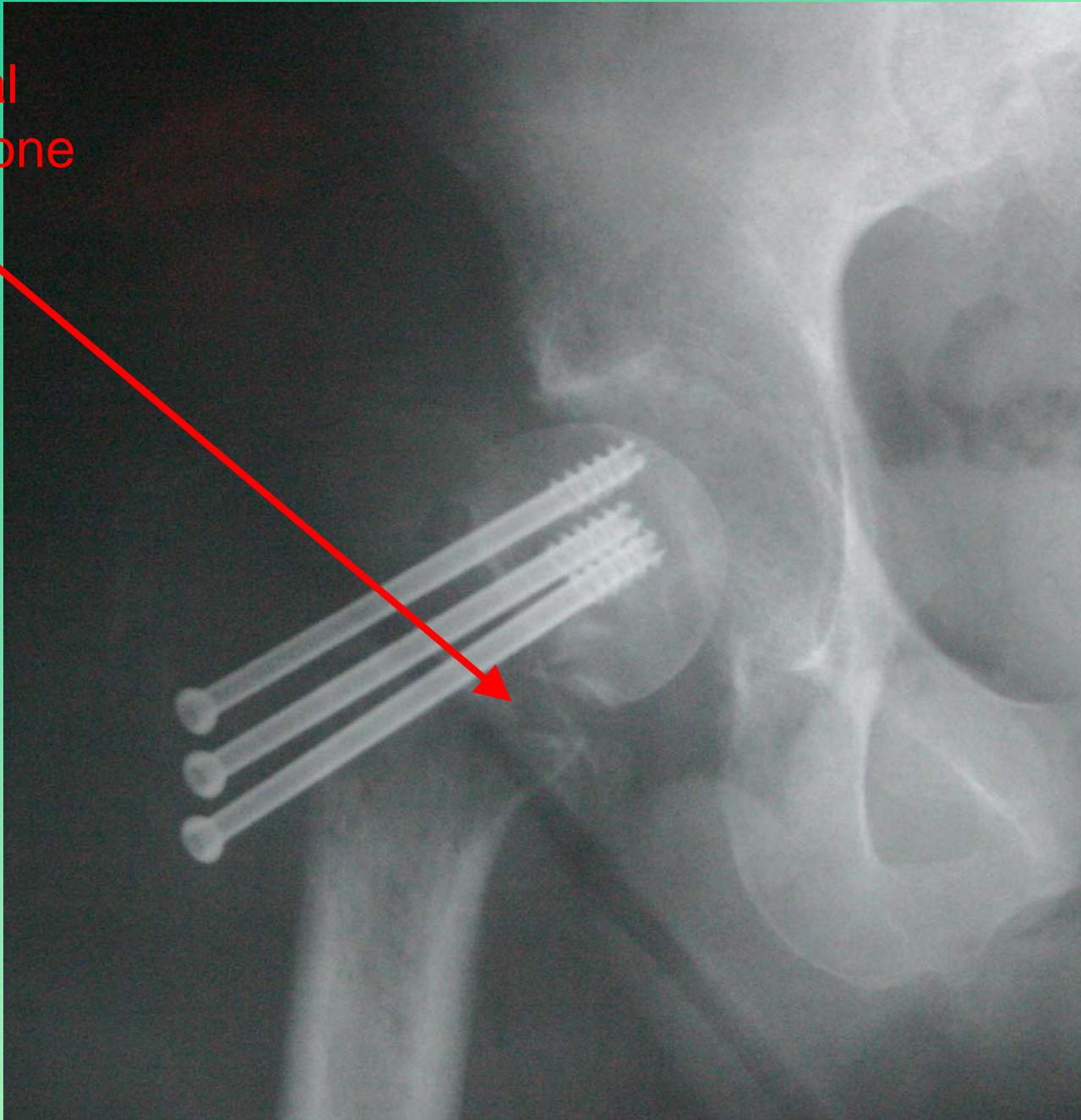


Case Presentation

- 34 y.o. man had hip pain for three months, put off having x-rays done
- Felt his hip “pop” while working as a plumber; no real trauma
- Quickly developed excruciating pain
- X-ray: fracture of right femoral head...pathologic fracture with benefit of hindsight
- Underwent nailing of hip
- Post-op X-ray....



Abnormal
part of bone



Case Presentation, continued

- Upon admission had undergone urinary drug screen: positive for LSD, benzodiazepines, opiates, amphetamines
- Continued to complain of pain post-op; question of drug-seeking behavior raised
- Two months later nails started working their way out of bone; bone fragments shifted; orthopedic surgeon temporized



Case Presentation, cont.

- Sought second orthopedic opinion
- Underwent total hip replacement
- Pathology: Telangiectatic Osteogenic Sarcoma
- Examples.....





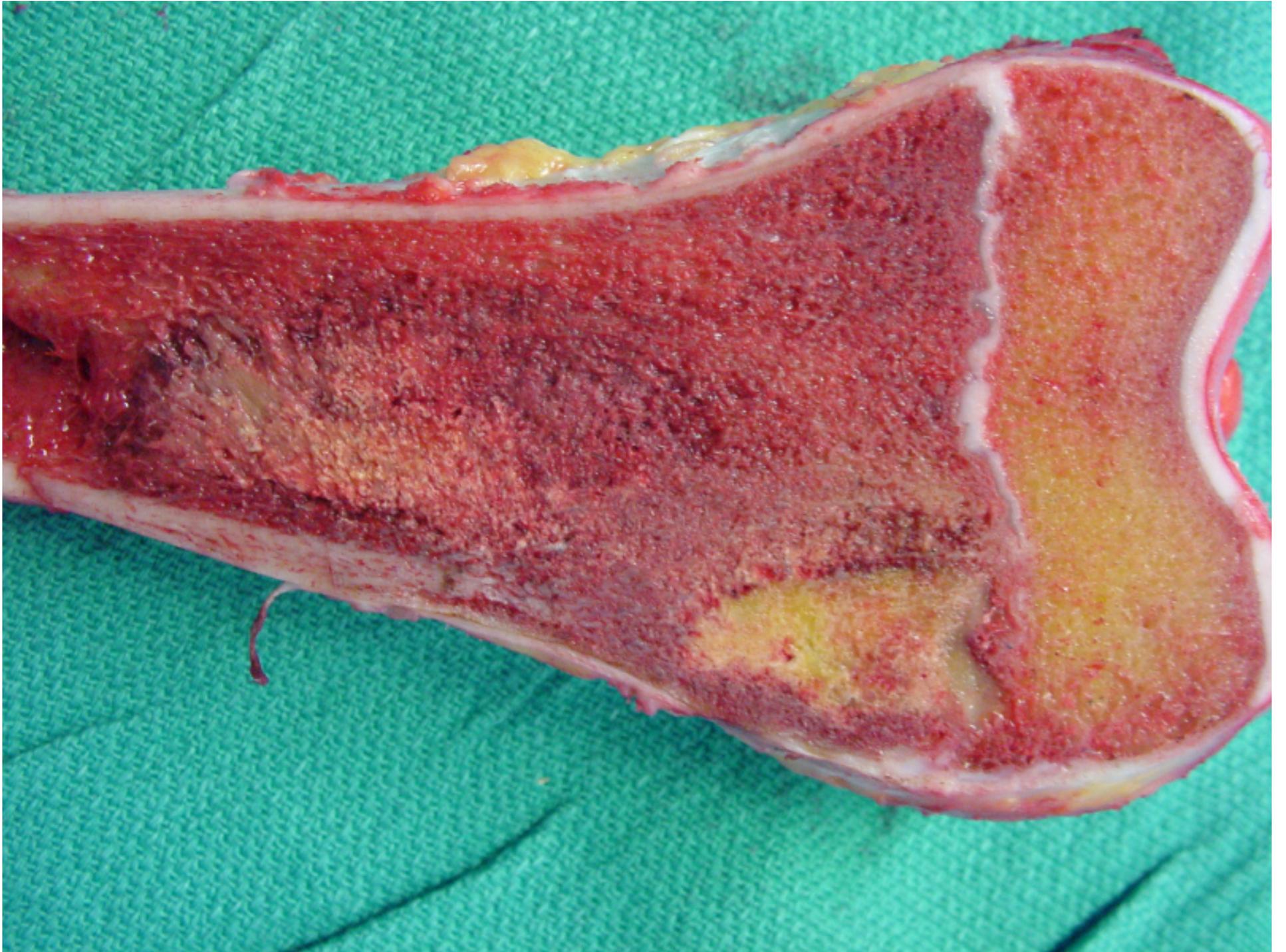
AND NOW FOR PATHOLOGY...



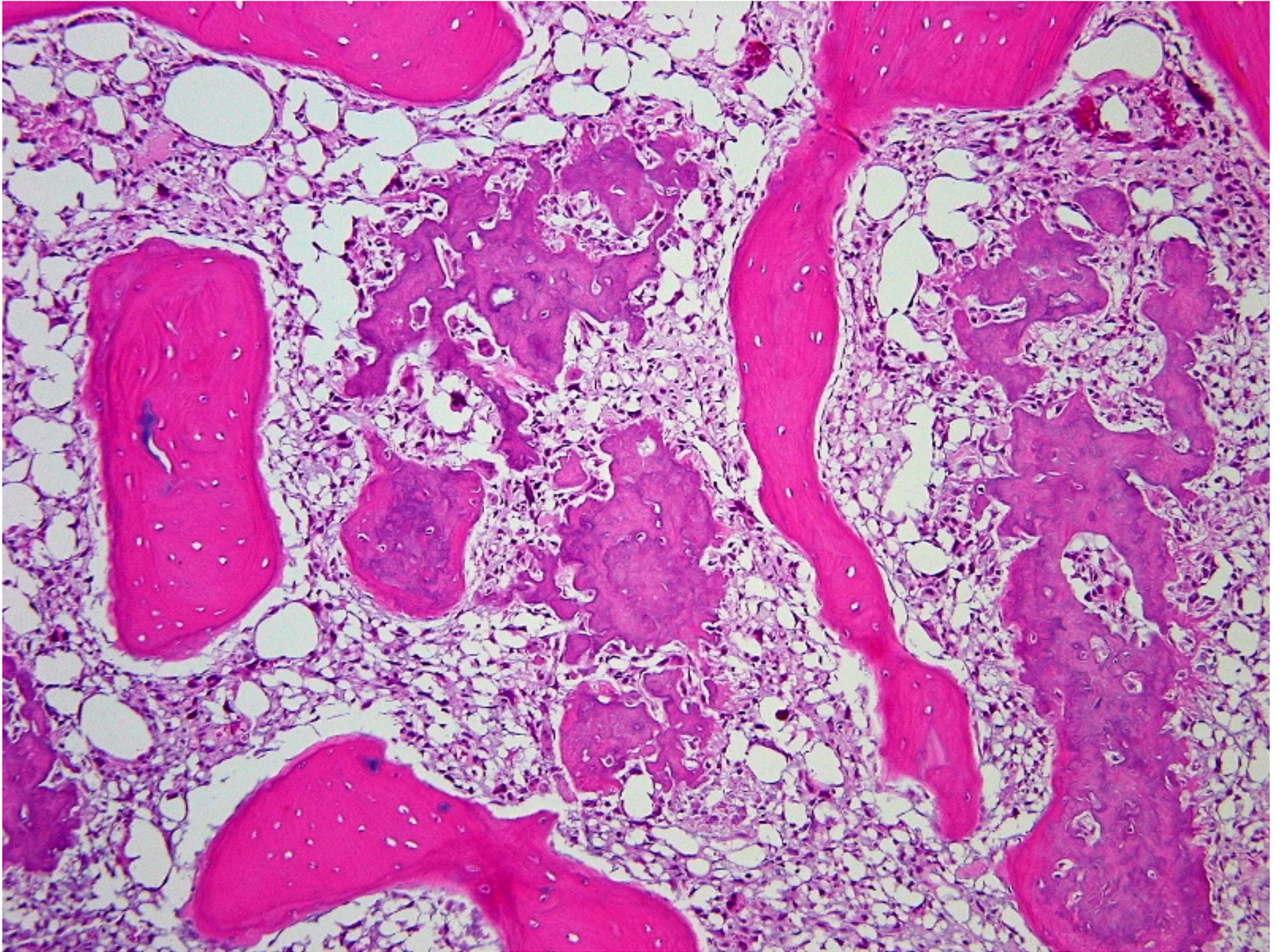
Osteosarcoma

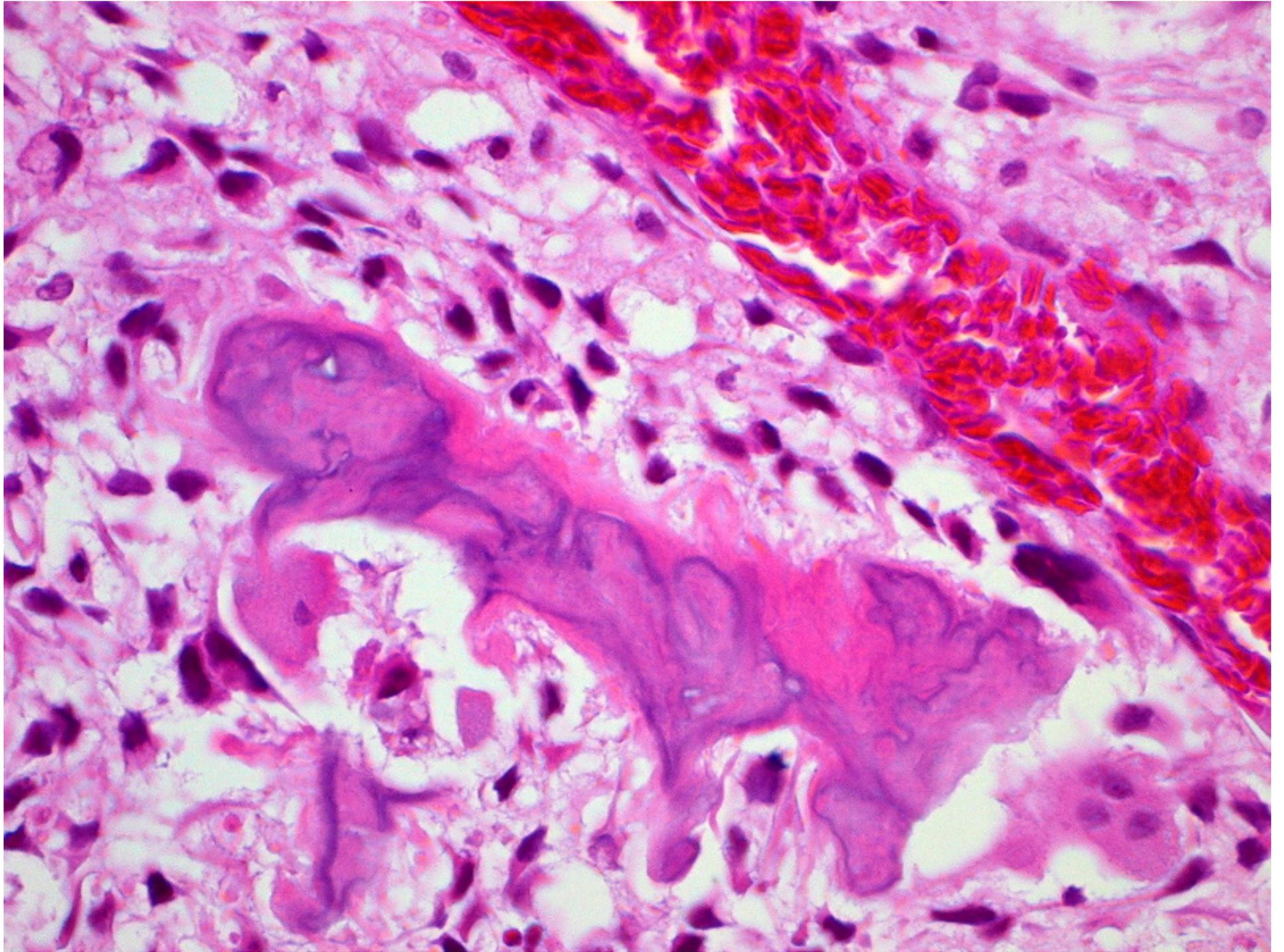
- At least focal osteoid production by neoplastic cells
- Conventional intramedullary
 - Osteoblastic, Chondroblastic, Fibroblastic, Giant cell rich, MFH-like
- Other patterns are less common

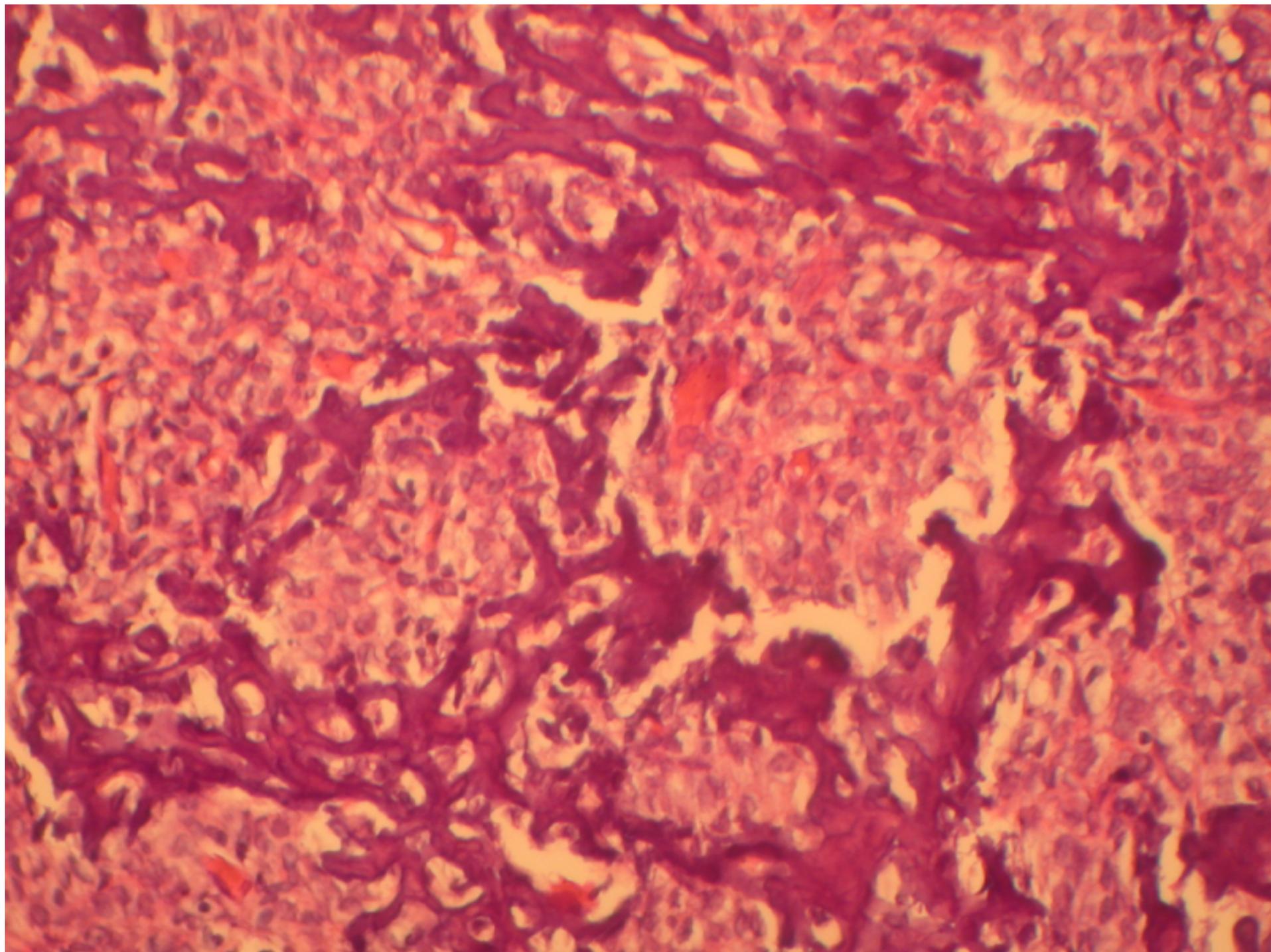


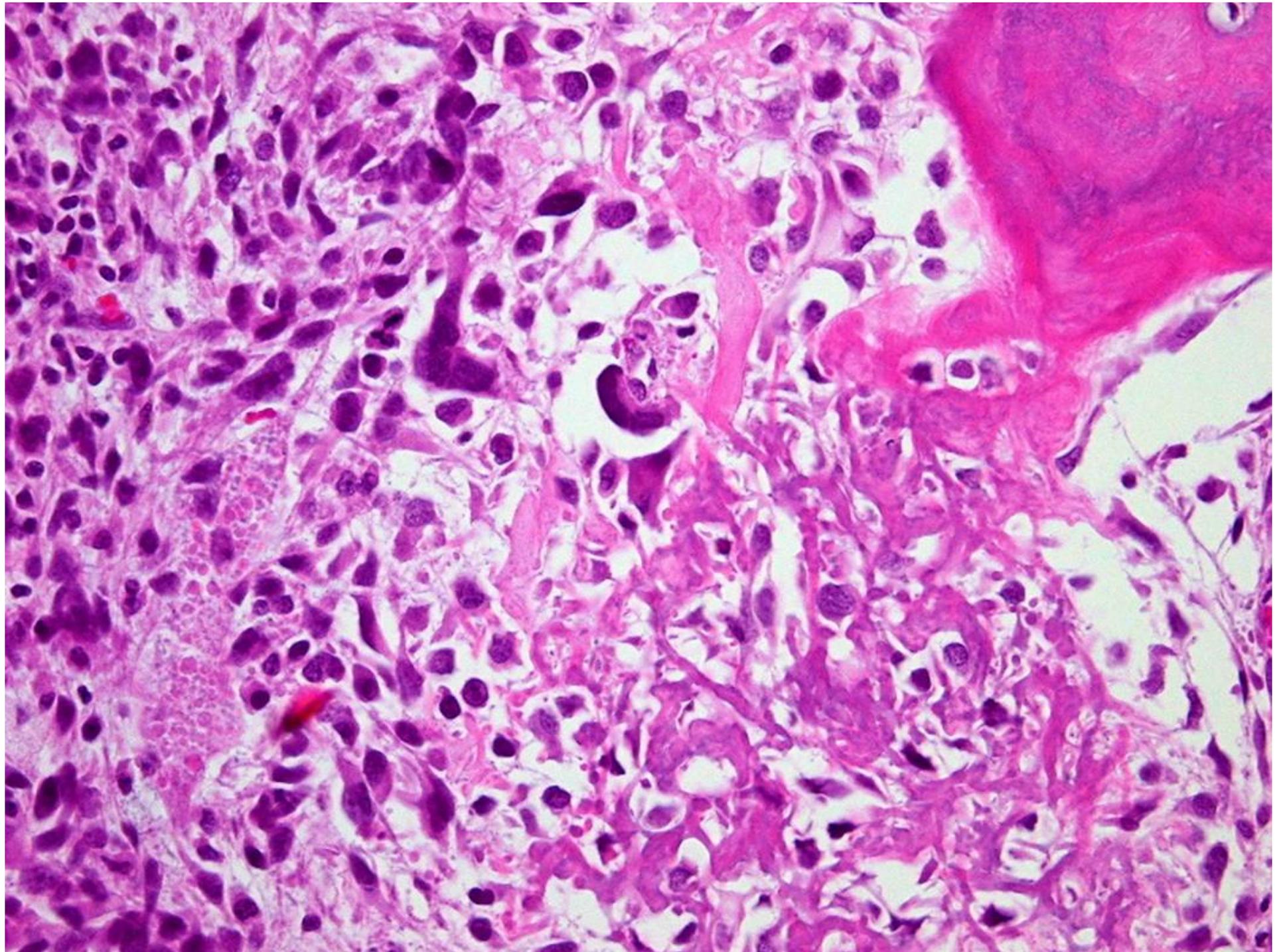


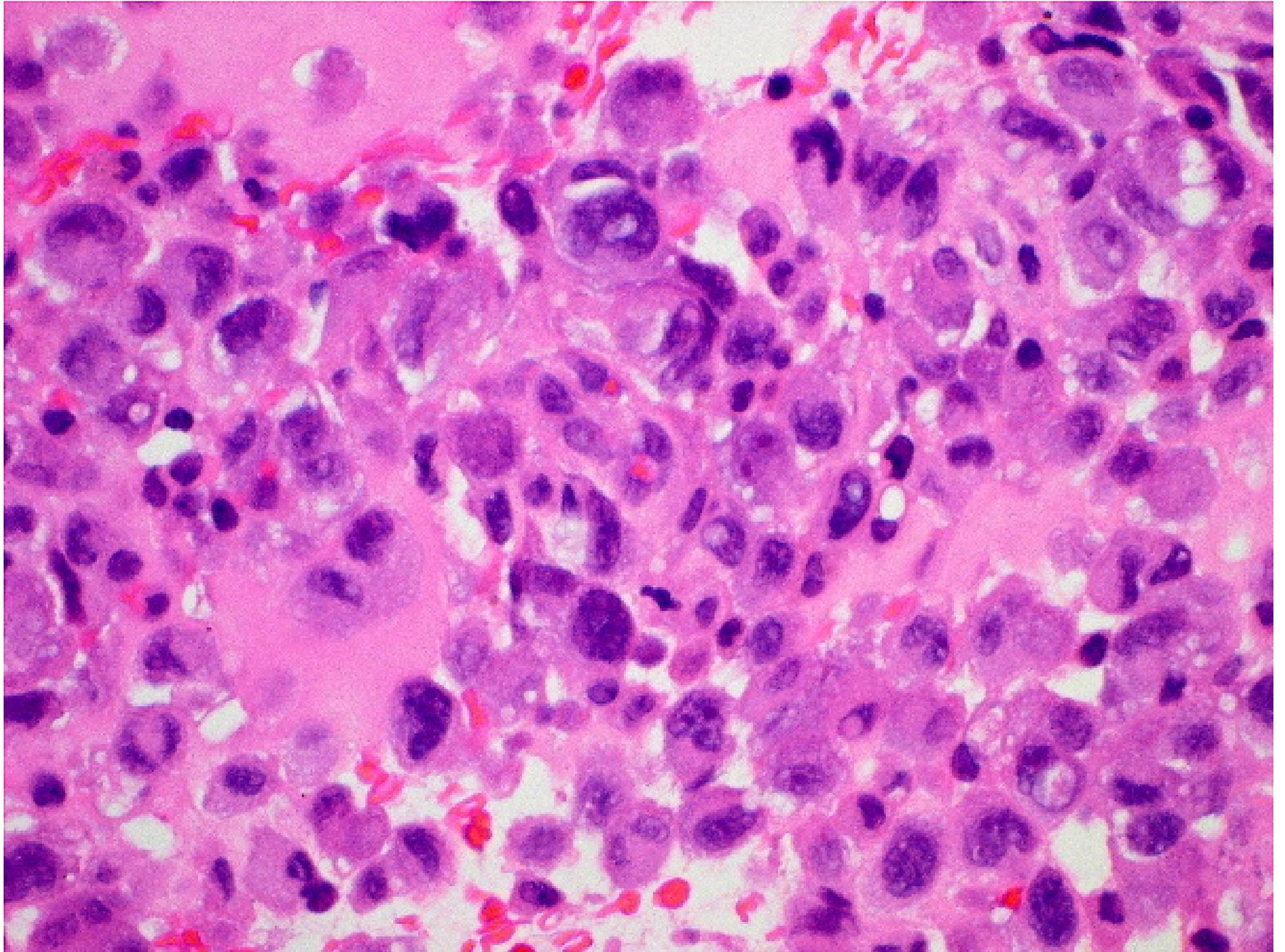


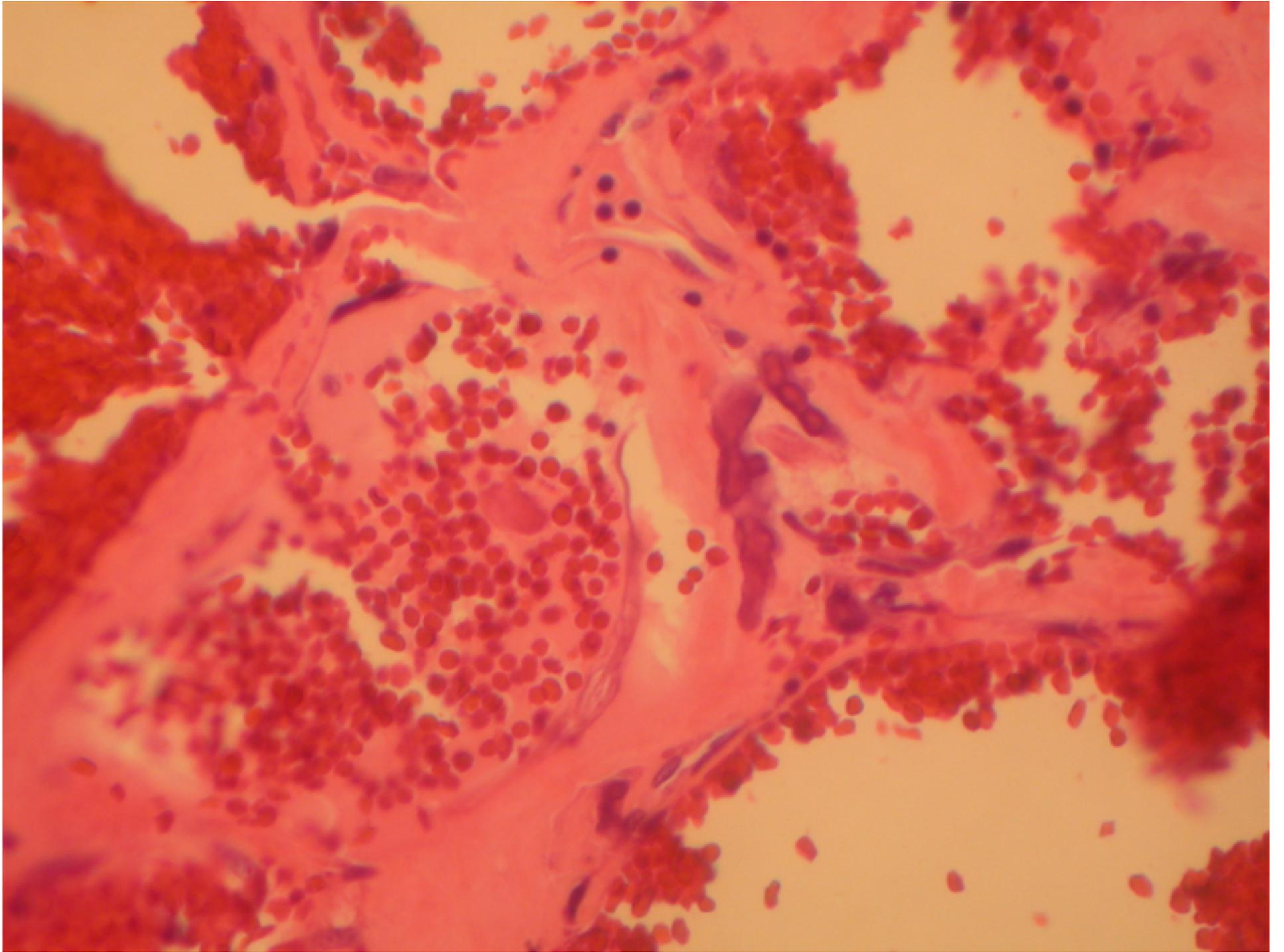


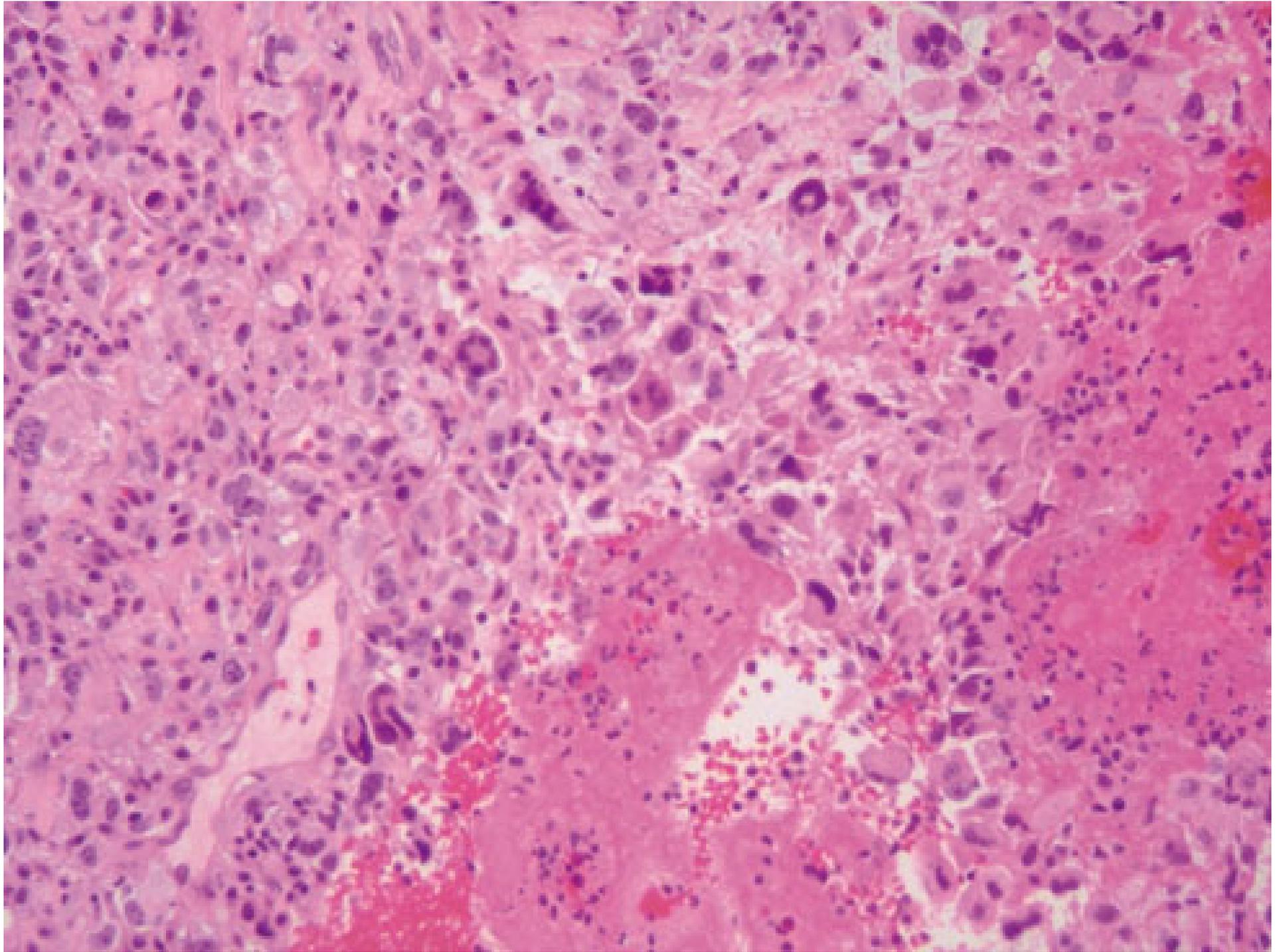


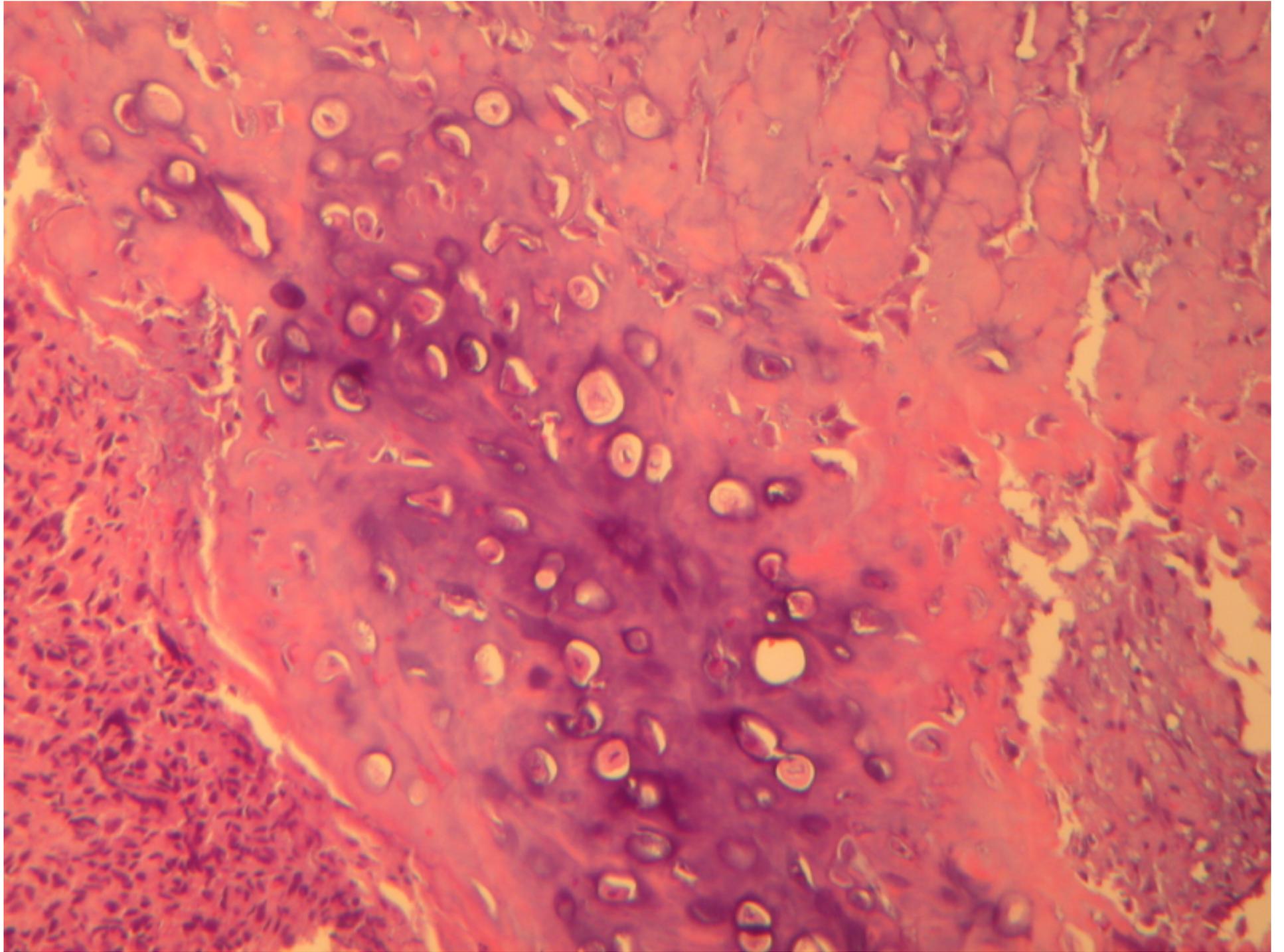


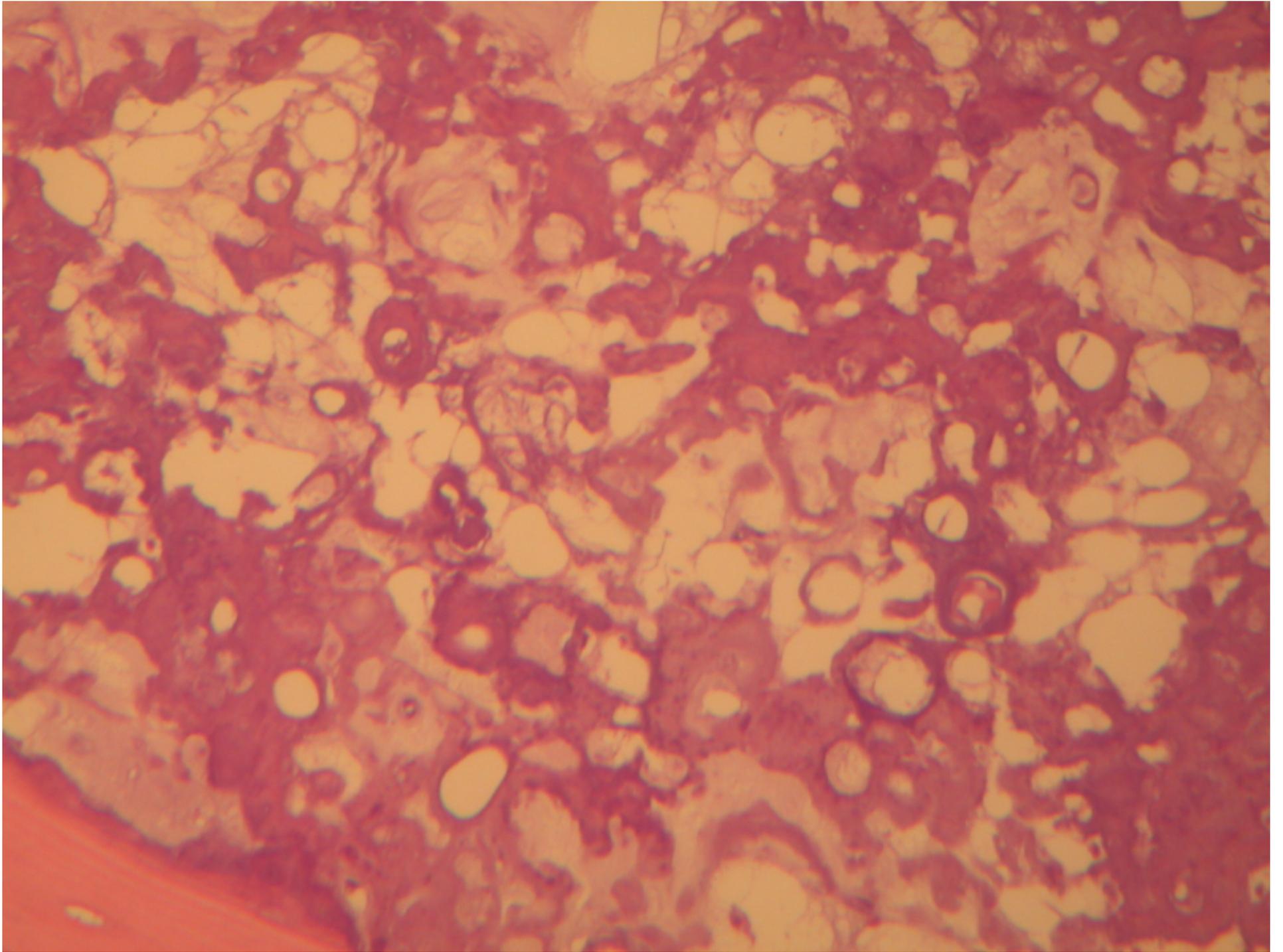












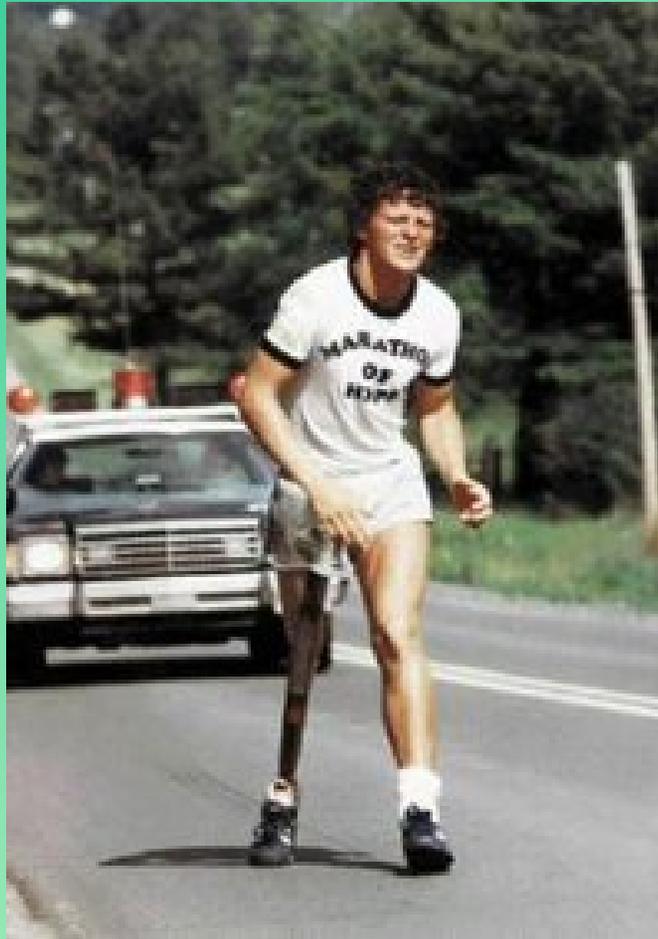


Case, continued

- Referred to tertiary-care cancer center for therapy; upon arrival was noted to have tiny pulmonary metastases and additional bone lesions
- Chemotherapy started: lung metastases regressed, bone lesions worsened (raising question of multi-focal osteosarcoma)
- Died fifteen months after diagnosis of overwhelming metastatic disease



Osteogenic Sarcoma



Terry Fox: developed OS at age 18 in 1976, ran across Canada to publicize his illness, died of lung metastases before he could finish.

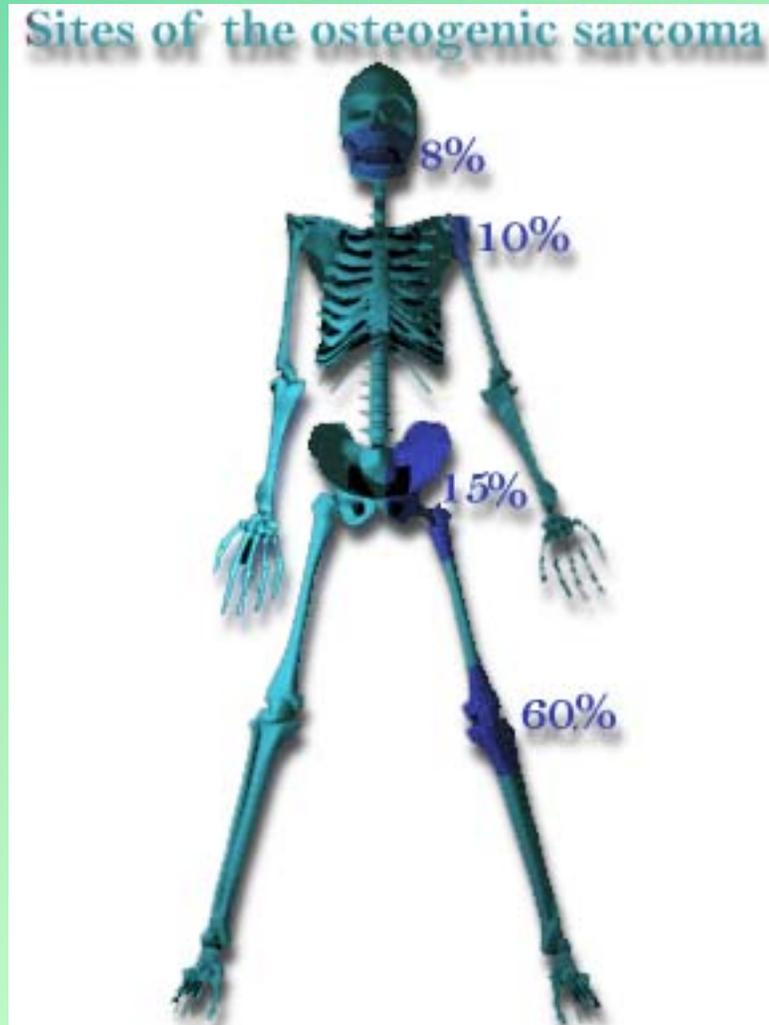
Voted Canada's most famous citizen of the 20th century

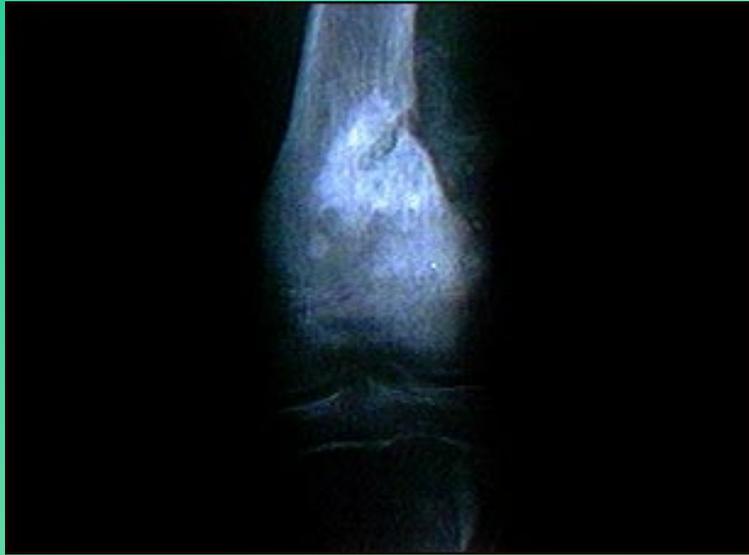
Who is this?



Characteristics of O.S.

- Typically a disease of adolescents
- Typically develops in distal femur or proximal tibia, but site can vary...
- Typical X-rays...





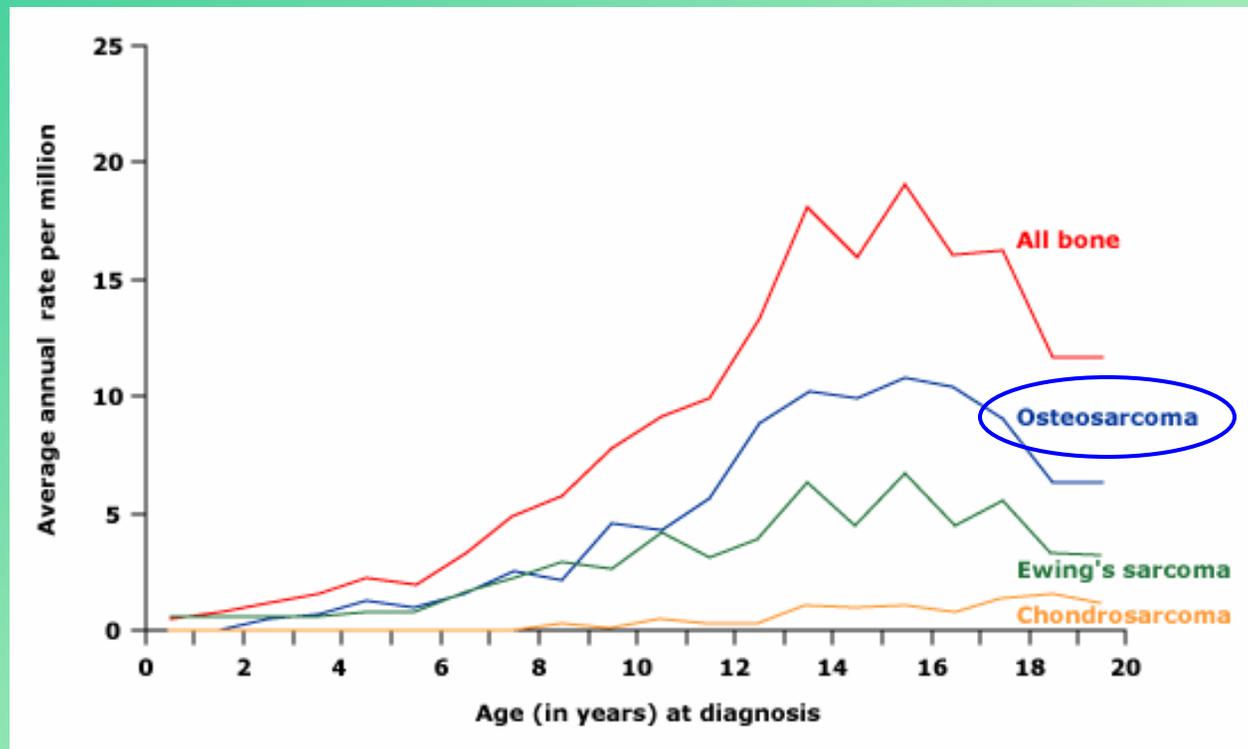
**Pathologic
fracture in O.S.**

Typical X-rays in
Osteogenic
Sarcoma



Clinical Spectrum of O.S.

- 400 cases/year in U.S.A.
- Typically between ages 13 and 16



Gurney, JG, et SEER Program 1975-1995



Characteristics of O.S.

- Bimodal distribution (second peak over age 65)
- Epidemiology:
 - Can arise in area of previous irradiation up to 40 years later (average 15 yrs)
 - Risk may be heightened by concomitant chemotherapy
 - Can arise in area of long-standing Paget's disease (rare)
 - Genetic diseases which predispose to O.S.....



Genetic Predisposition to O.S.

- Hereditary retinoblastoma
- Li-Fraumeni Syndrome
 - Variety of cancers associated with mutation of P-53 tumor suppressor gene
- Rothmund-Thomson Syndrome (Poikiloderma Congenitale)
- Bloom and Werner Syndromes
 - Last 3 associated with mutation of RecQ gene group



History of the Treatment of O.S.

- Pre-chemotherapy era (before 1970)
 - 80-90% of patients died, most relapsing in the first 12-18 months after diagnosis
- In early 1970's principles of cancer chemotherapy were applied to patients with newly diagnosed disease primarily in the adjuvant setting (immediately after definitive surgery) to eradicate microscopic metastases
 - Data since then, primarily derived from study of disease in adolescence:
 - 70% survival if chemo started before overt metastasis
 - 50% of patients with limited lung metastases can be cured with thoracotomy plus chemotherapy
 - 25% of patients with advanced metastatic disease can be cured with chemotherapy alone



Closer Look at Impact of Adjuvant Chemotherapy

- Naysayers criticized outcomes data because of improved index of suspicion and earlier diagnosis in general
- Mayo Clinic investigators reported survival increase from 20 to 50% between 1960 and 1975 with earlier diagnosis alone*
- Rarity of disease made it difficult to do randomized control trials to assess impact of chemo on cure rate
- Best series finally published in 1987, fifteen years after therapy began...

***Taylor et al *Mayo Cl Proc* 53:695, 1978**



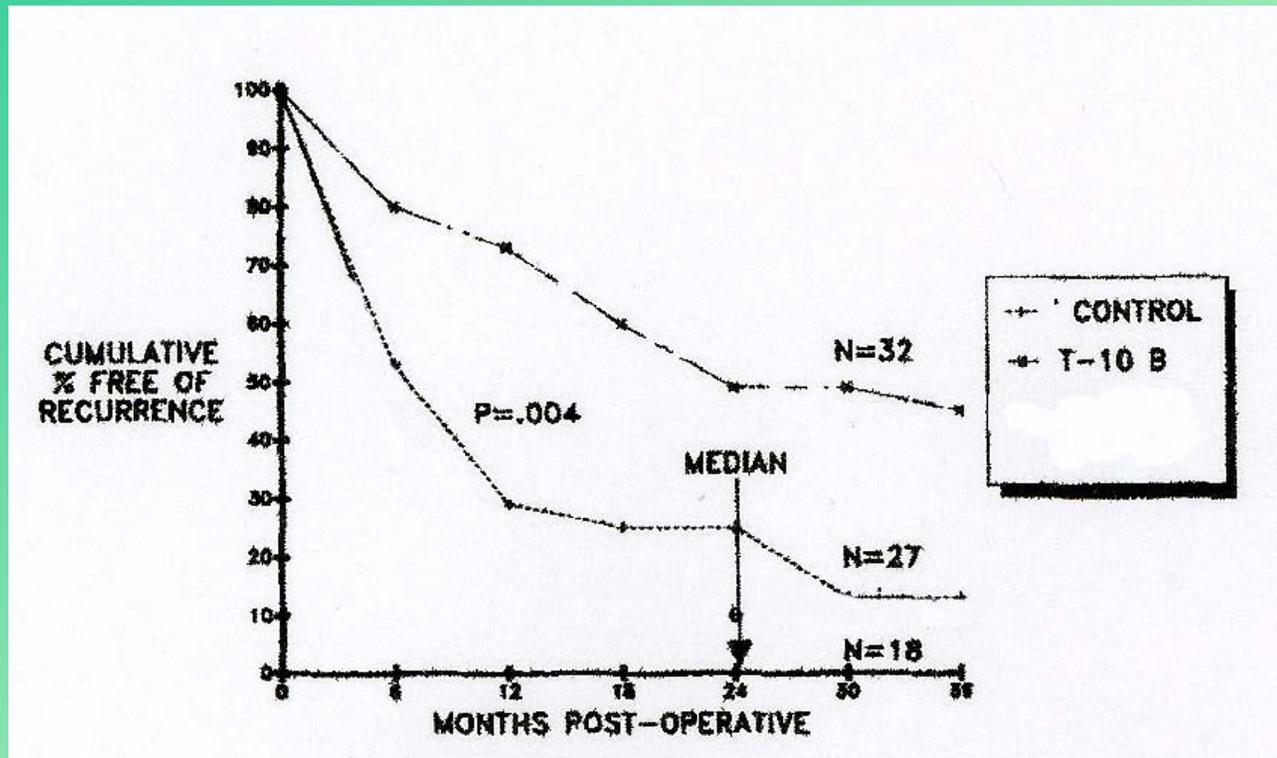
Eilber randomized trial from UCLA*

- 59 patients randomized: 32 treated, 27 observed
- Groups matched for age, gender, location of tumor
- Median age 16
- All patients received pre-op intra-arterial chemo and radiation; randomization occurred after surgery (curious design!)
- Limb salvage done where feasible; same percentage in control and post-op chemo groups
- Post-op chemo complex and included high-dose methotrexate and leucovorin rescue

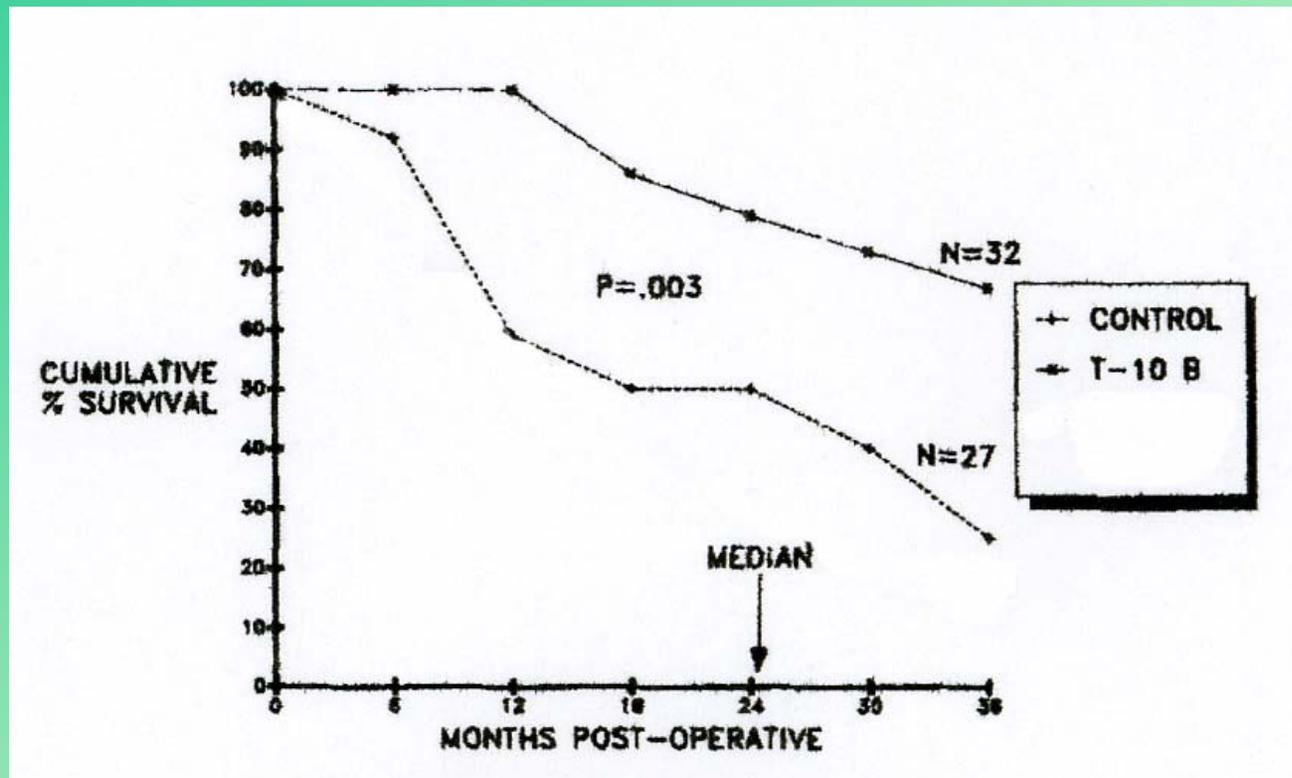
*Eilber et al *J Clin Oncol* 5 (1): 21-27, 1987



Disease-Free Survival



Overall Survival



Question of survival drift explored

- Patients from the 1970's who received no chemotherapy either before or after surgery were compared to control group in study...



Survival drift

Calls into question value of neo-adjuvant intra-arterial chemo

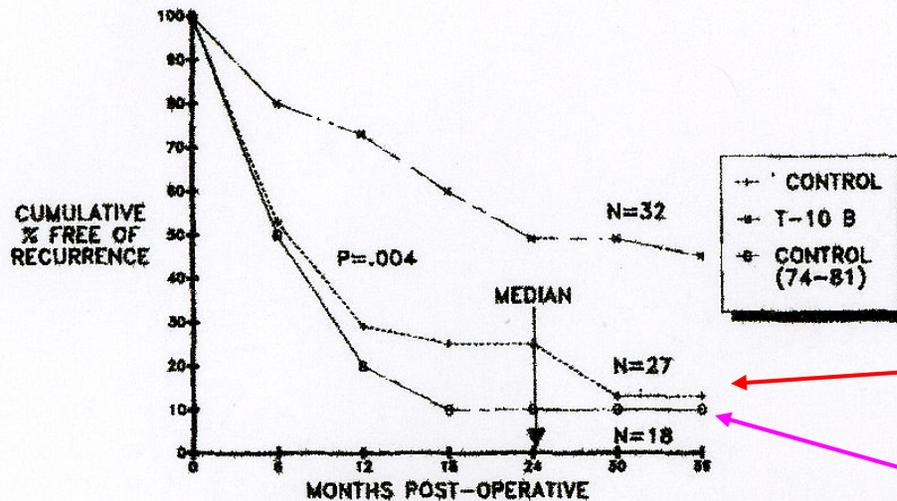


Fig 3. Disease-free survival.

Current Study

Historical controls

Tends to refuse key Mayo Clinic assertion that natural history of disease was changing because of earlier diagnosis



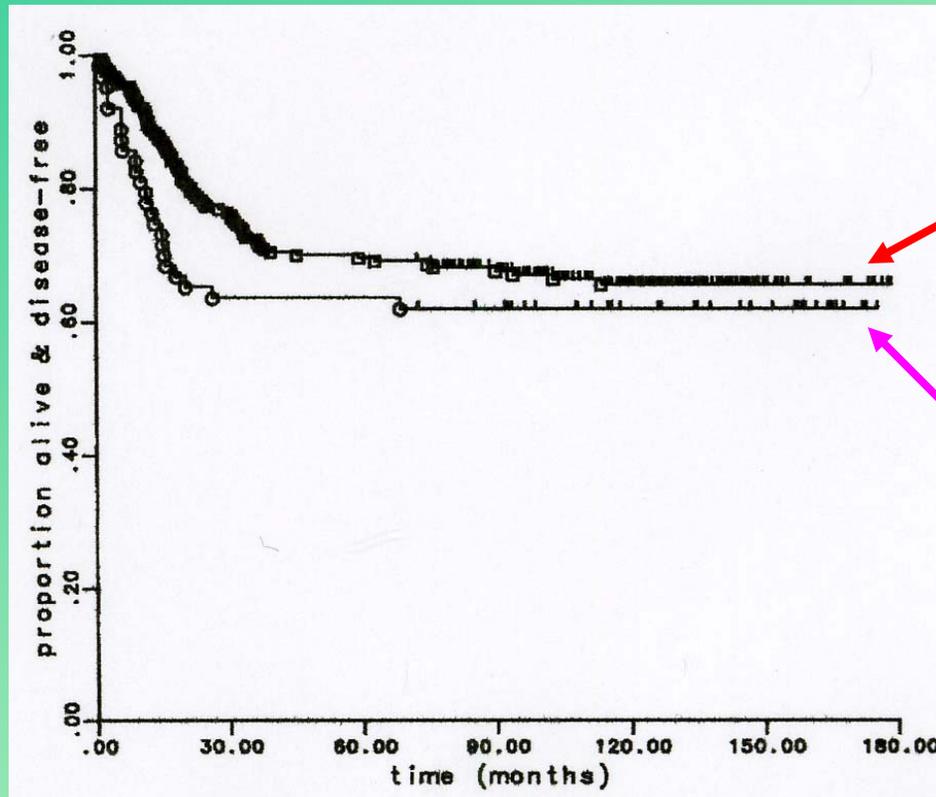
Predictors of Survival

- Memorial Sloan Kettering Cancer Center retrospective analysis of results*
- Looked at:
 - Value of pre-operative chemotherapy;
 - Survival with amputation versus limb-sparing surgery
 - Histologic response to pre-op chemo as predictor of survival
 - Site of primary tumor as predictor of survival
 - Influence of age at diagnosis on outcome

***Meyers et al *J. Clin. Oncol.* 10:5-15, 1992**



Value of Pre-Operative Intra-Arterial Chemotherapy



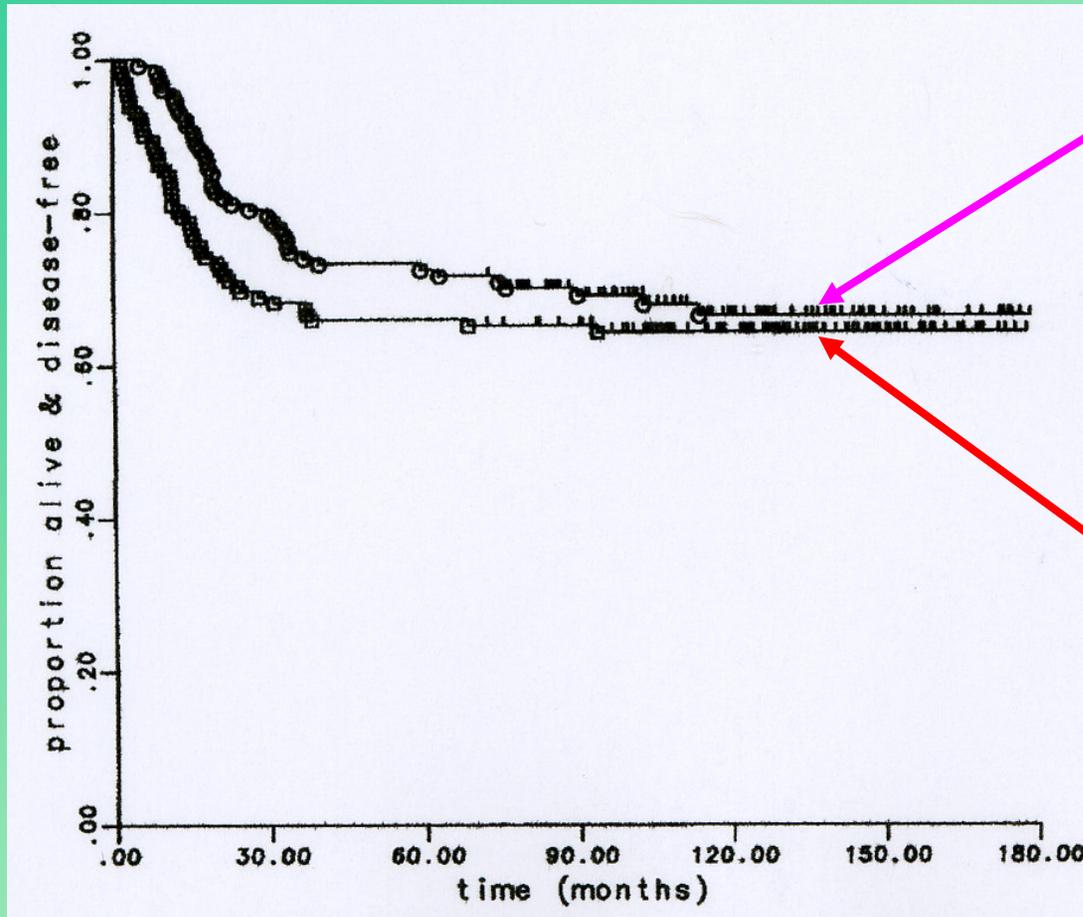
Chemo

No Chemo

No significant difference ($p=0.29$) between groups



Amputation versus Limb Salvage



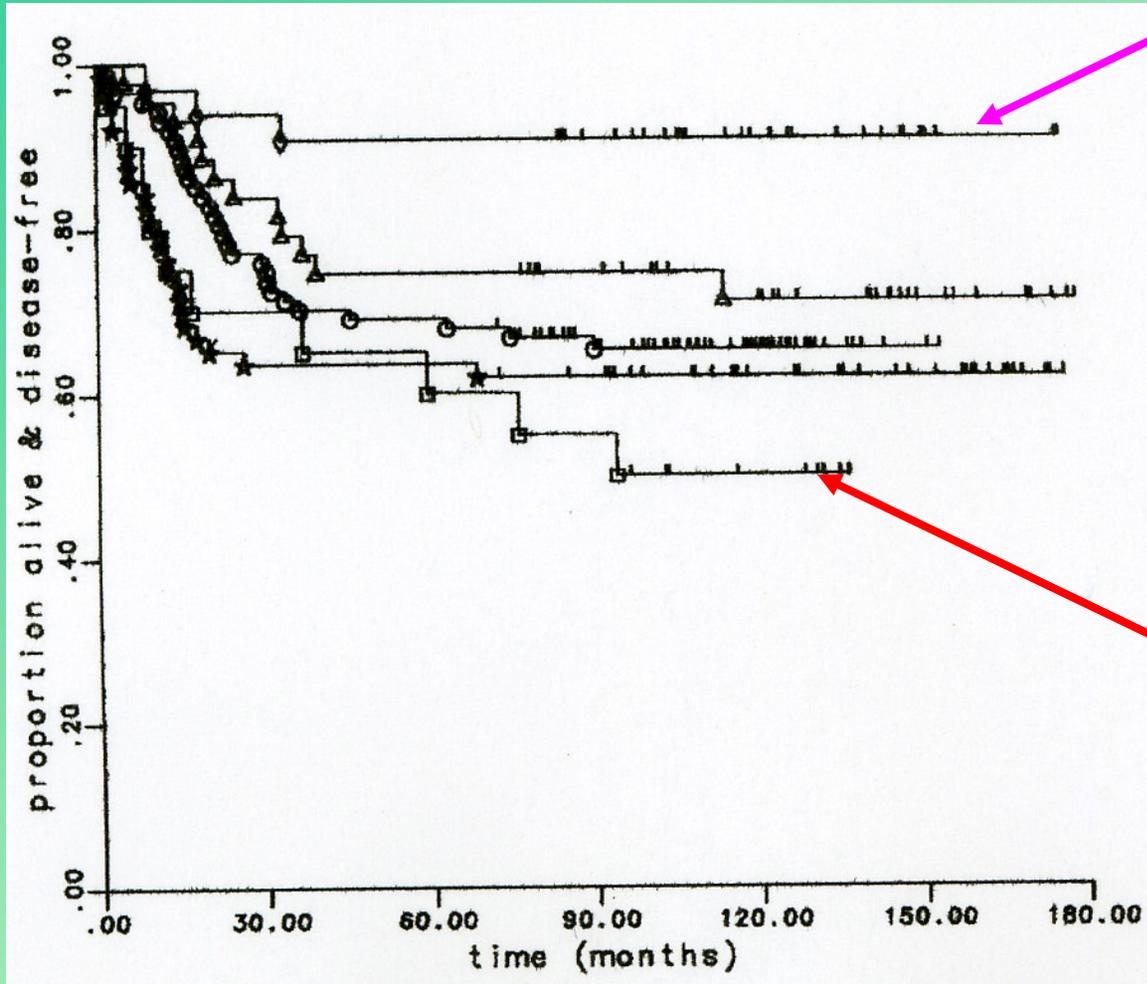
Limb Sparing

Amputation

$P = 0.34$ (N.S.)



Impact of Response to Pre-Op Chemo

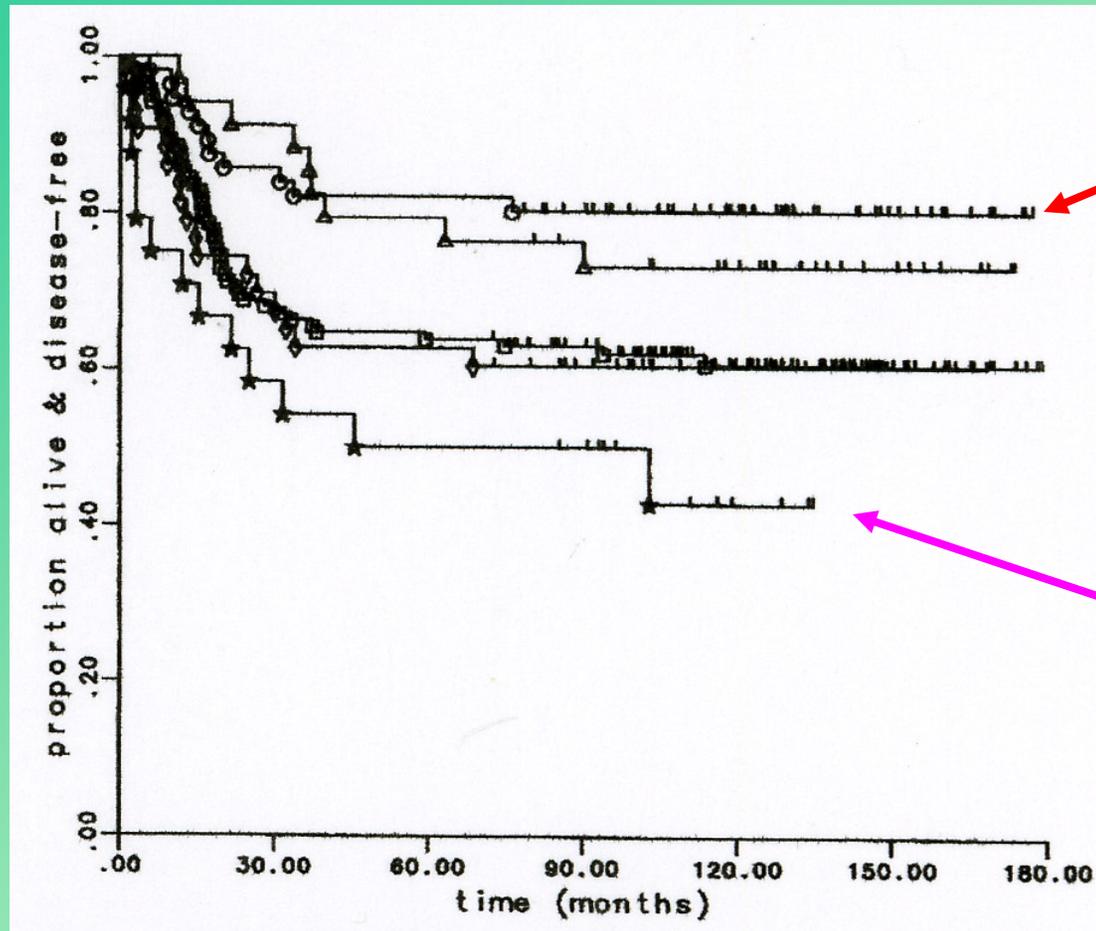


Excellent response

No response



Importance of Site of Primary

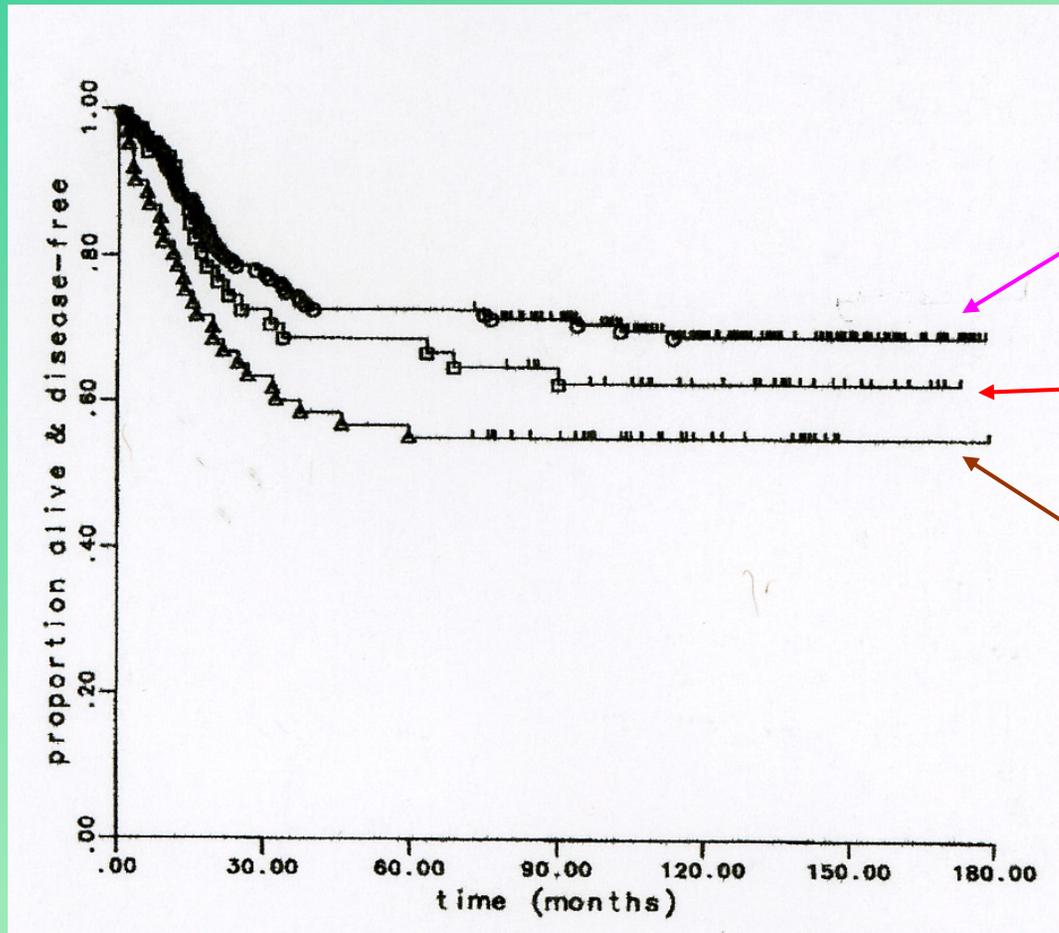


Proximal tibia

Axial skeleton



Significance of Age at Diagnosis



12-21

<12

>21



What About Osteosarcoma in Adults?

- Best data from Korean study*
- Looked at survival in patients younger and older than 40
- Looked at primary tumor sites in older patients

***Jeon J. *Korean Med Sci* 21:715, 2006**



Jeon study, continued

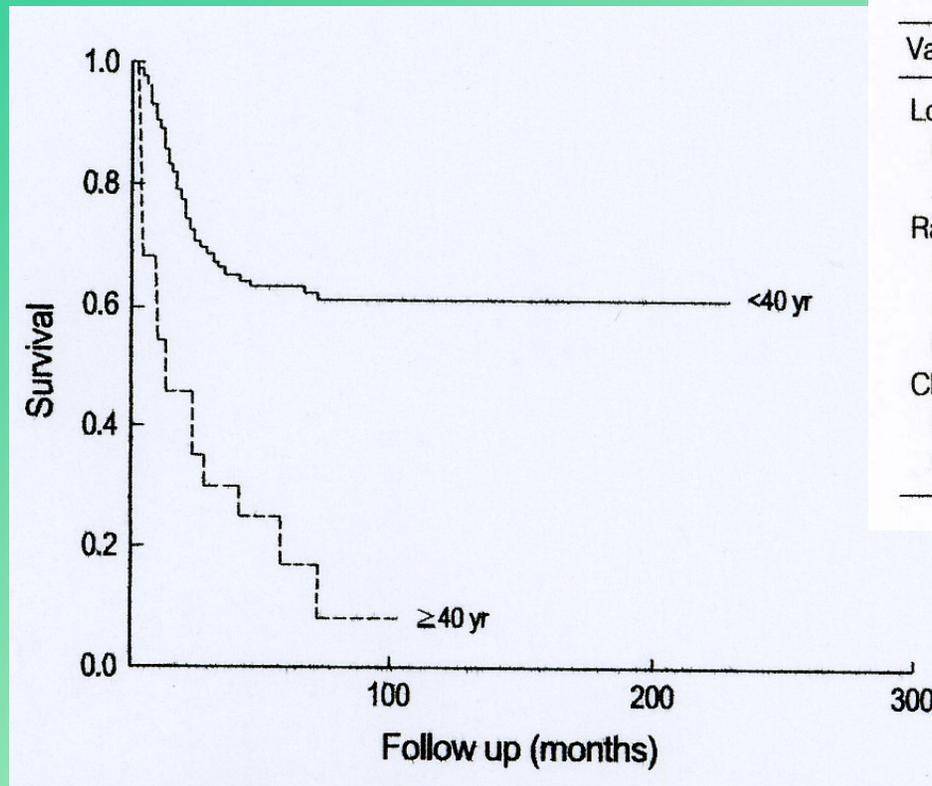


Table 2. Statistically significant comparisons between older patients and adolescent patients

Variable	Older patients	Adolescent patients	p value
Location			0.035
Extremity	31 (79.5%)	41 (95.3%)	
Axial Bone	8 (20.5%)	2 (4.7%)	
Radiological findings			0.031
Osteolytic	19/29 (65.5%)	10/43 (23.3%)	
Osteoblastic	3/29 (10.4%)	27/43 (62.8%)	
Mixed	7/29 (24.1%)	5/43 (13.9%)	
Chemotherapy-induced tumor necrosis			0.035
Good responder	3 (16.7%)	18 (42.2%)	
Poor responder	15 (83.3%)	25 (57.8%)	

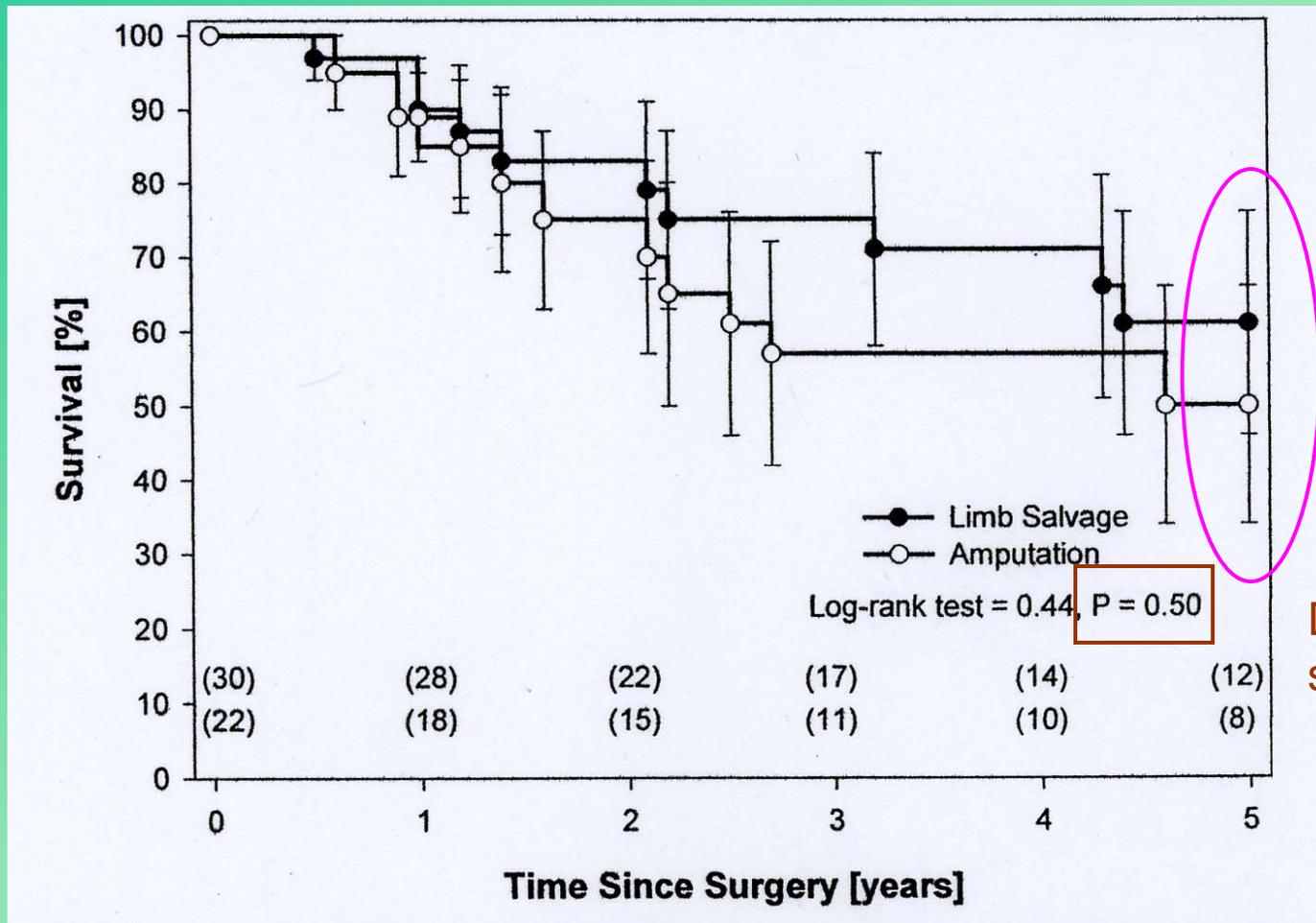


Pathologic Fracture

- Our patient presented with pathologic fracture
 - Can you still save the limb after fracture?
 - If so, does this impact adversely the outcome?
 - What is the overall impact of fracture on outcome?



Survival after Fracture with and without Limb Salvage



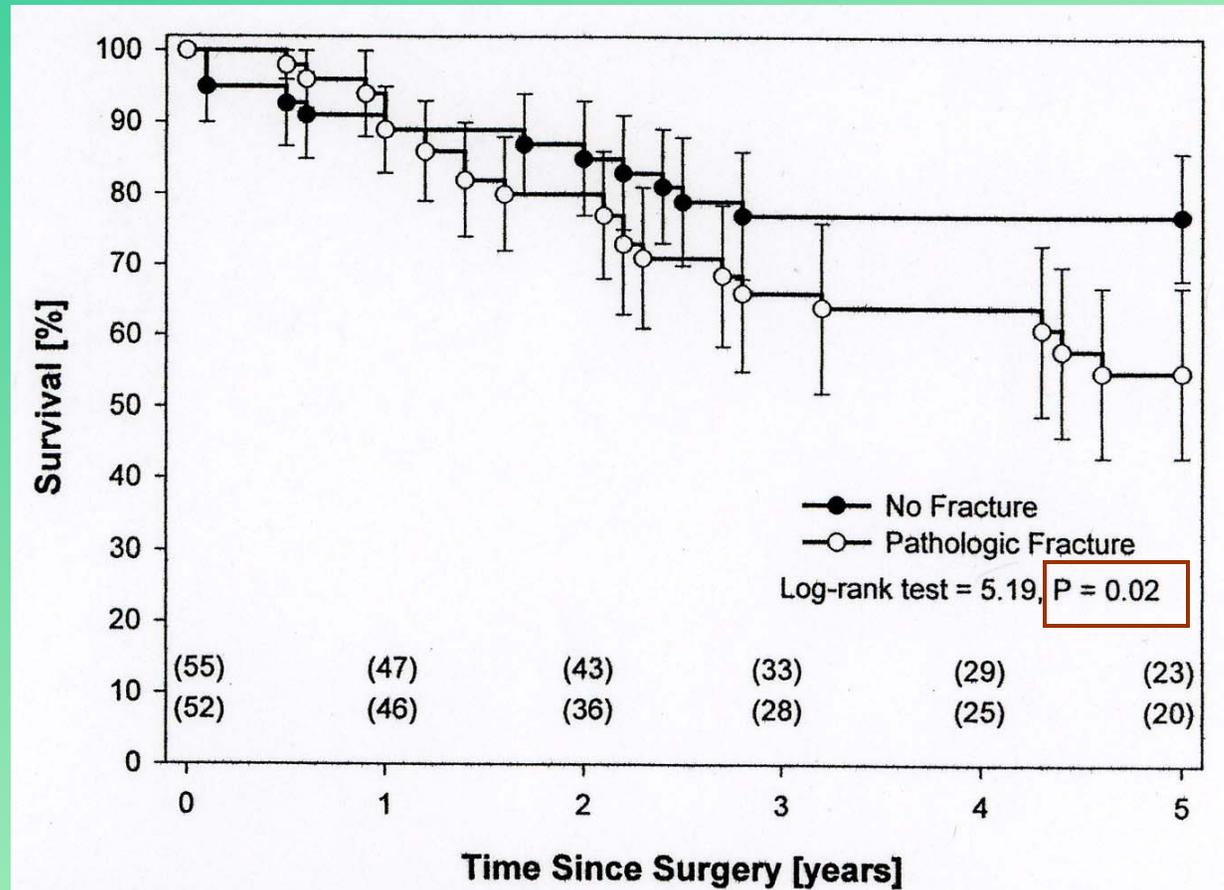
Confidence limits overlap

Difference not significant

Scully *J Bone Joint Surg Am* 84:49-57, 2002



Survival with and without Fracture



Difference highly significant



Conclusions

- Pre-Op intra-arterial chemotherapy yields in-vivo evidence of chemo sensitivity and predicts for, but does not affect, outcome
- Post-Op chemo has markedly enhanced survival
- Limb salvage is possible and does not worsen outcome
- Adults, especially those with presentation in atypical location, do much worse than adolescents with typical O.S.
- Fracture (as seen in our patient) predicts for a bad outcome



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