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FOS Expression in Osteoid Osteoma and Osteoblastoma

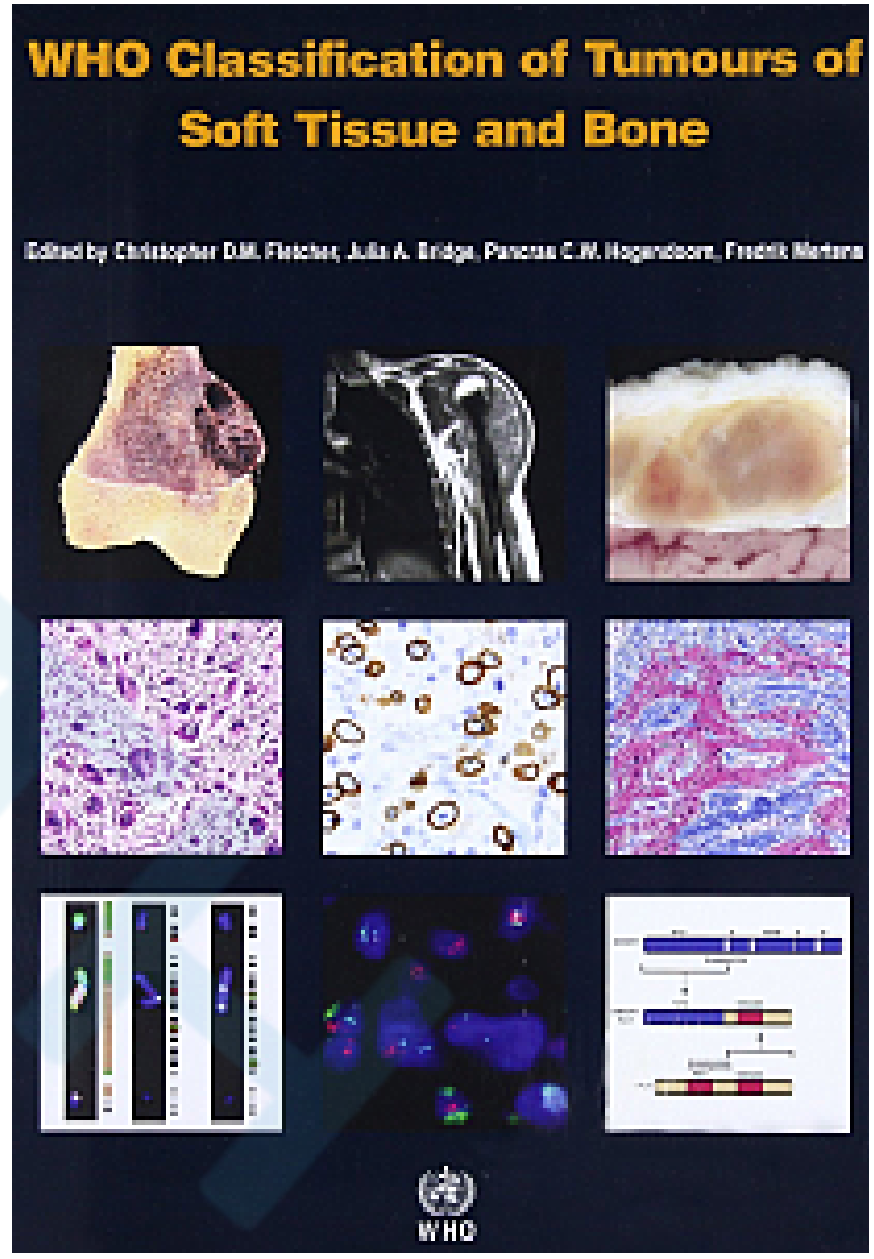
A Valuable Ancillary Diagnostic Tool

Fernanda Amary, MD, PhD,† Eva Markert, MD,* Fitim Berisha, MSc,* Hongtao Ye, PhD,* Craig Gerrand, MD,* Paul Cool, MD,‡ Roberto Tirabosco, MD,* Daniel Lindsay, MD,* Nischalan Pillay, MD, PhD,*† Paul O'Donnell, MD,* Daniel Baumhoer, MD, PhD,§ and Adrienne M. Flanagan, MD, PhD*†*

汇 报 人：徐婉妮

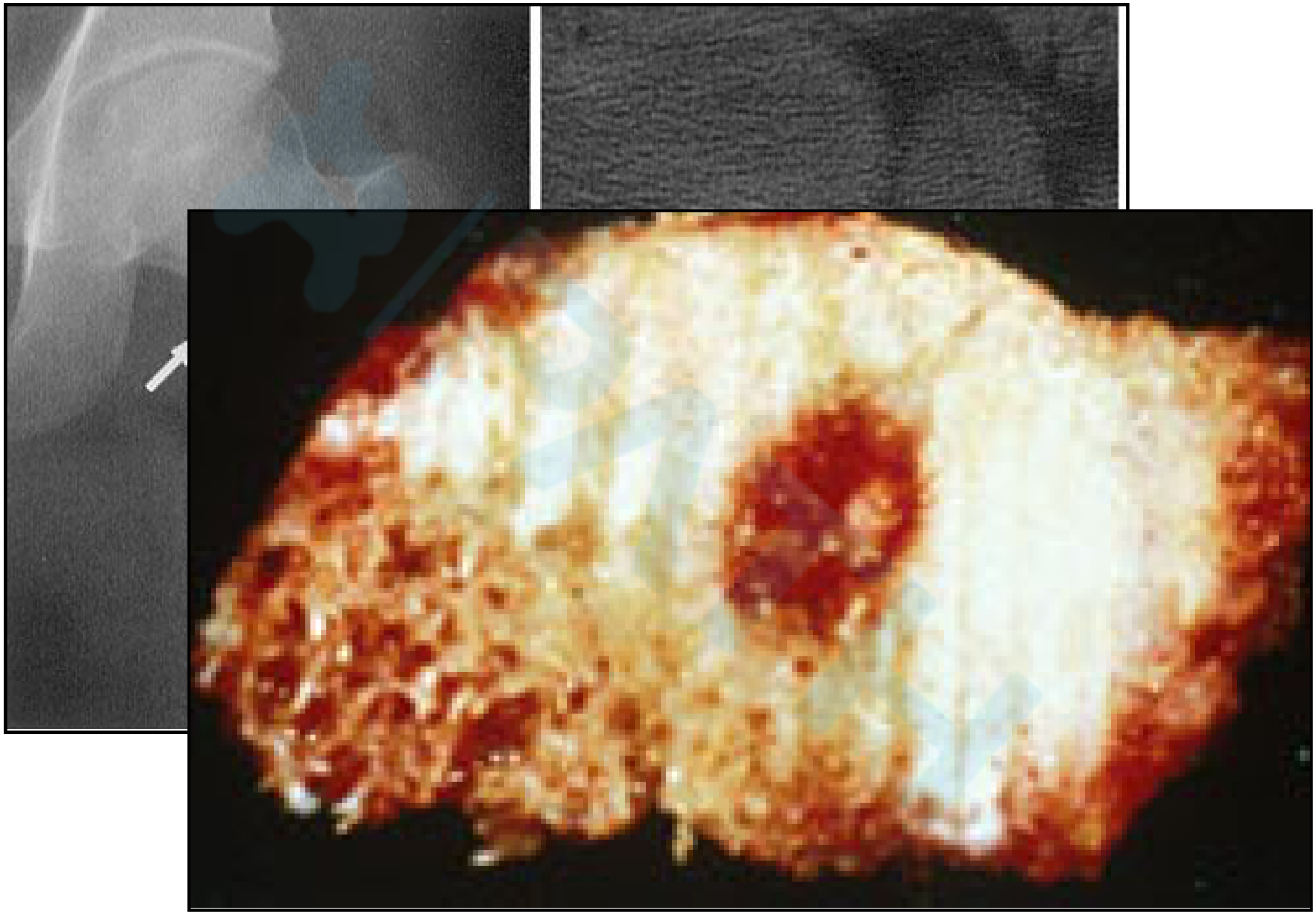
Osteogenic tumors

- **Benign**
  - Osteoma
  - Osteoid osteoma
- **Intermediate (locally aggressive)**
  - Osteoblastoma
- **Malignant**
  - Low-grade central osteosarcoma
  - Conventional osteosarcoma
    - Chondroblastic osteosarcoma
    - Fibroblastic osteosarcoma
    - Osteoblastic osteosarcoma
  - Telangiectatic osteosarcoma
  - Small cell osteosarcoma
  - Secondary osteosarcoma
  - Parosteal osteosarcoma
  - Periosteal osteosarcoma
  - High-grade surface osteosarcoma



Osteoid osteoma

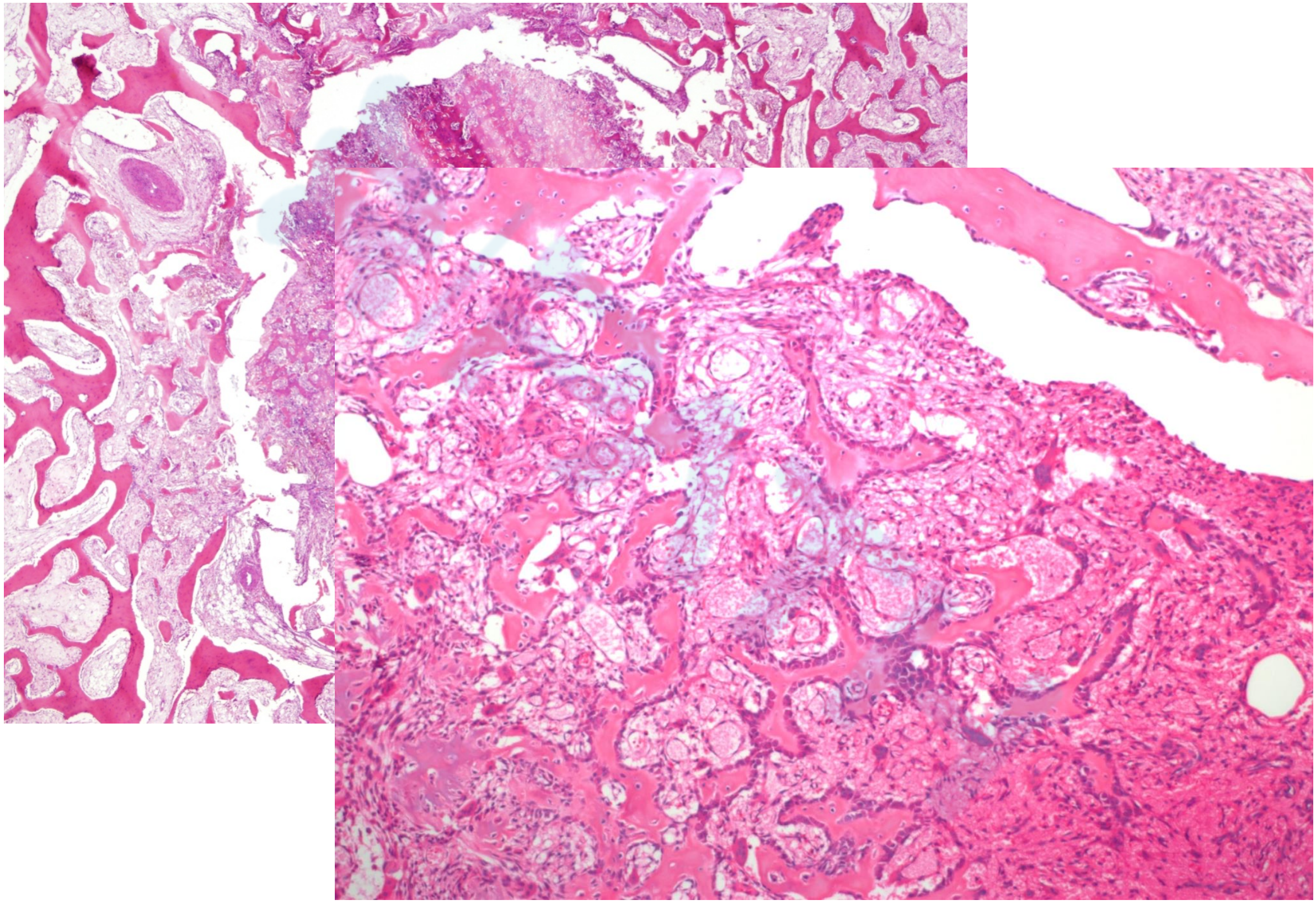
- **Definition**
  - A benign bone-forming tumor characterized by small size(＜2cm)，limited growth potential and disproportionate pain，usually responsive to non steroidal anti-inflammatory drugs
- **Epidemiology**
  - Children and adolescents
- **Sites of involvement**
  - Long bones,particularly in the proximal femur



摘自程虹教授课件

Osteoid osteoma

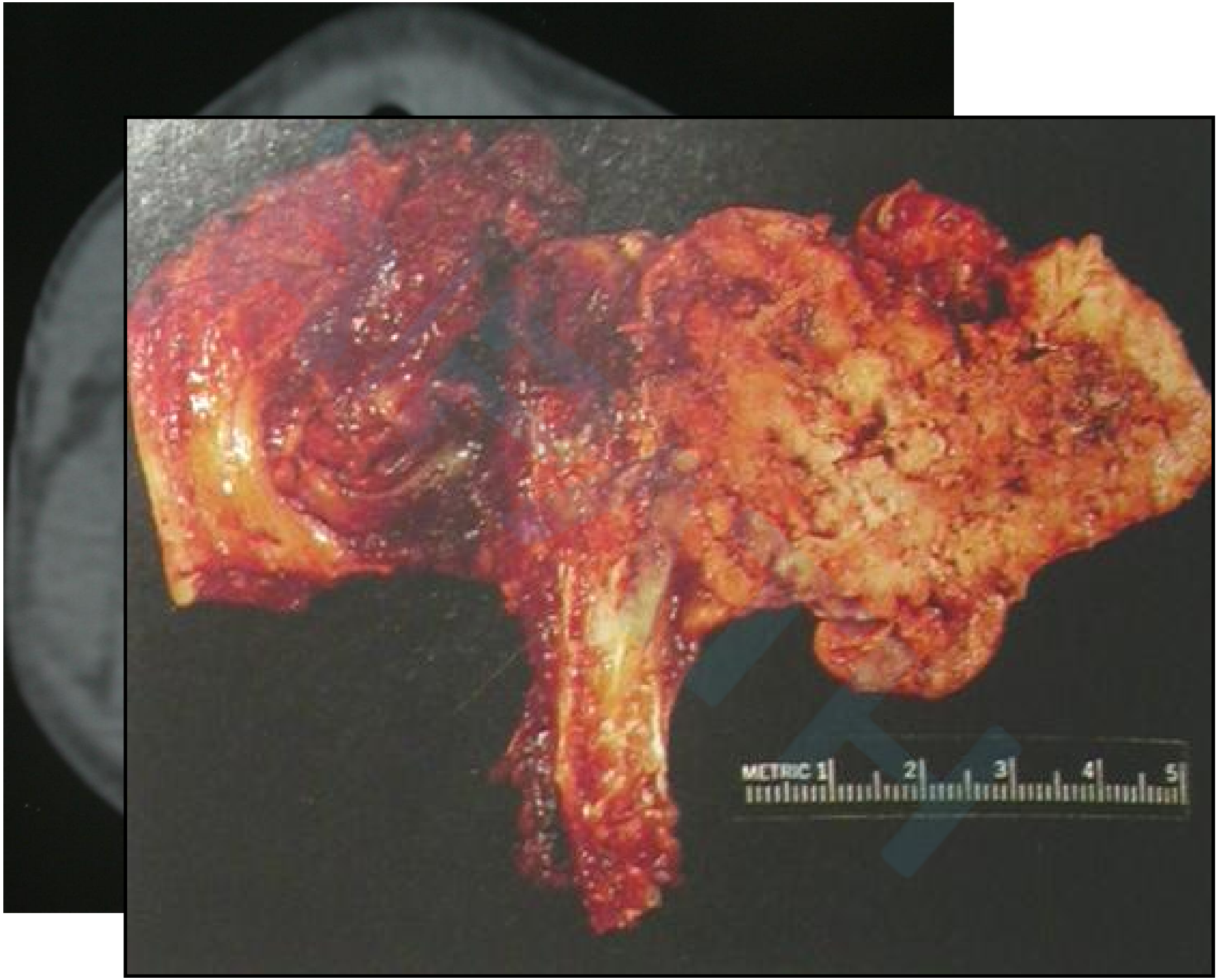
- **Histopatholohy**
  - Interconnecting trabeculae of woven bone rimmed by plump osteoblasts
  - The stroma is usually highly vascular with fibroblastic spindle cells and osteoclast-like giant cells
- **Prognostic factors**
  - Prognosis is excellent
  - Recurrences are uncommon



摘自程虹教授课件

Osteoblastoma

- **Definition**
  - A benign bone-forming neoplasm,＞2cm， which produces woven bone spicules,which are bordered by prominent osteoblasts
- **Epidemiology**
  - About 1% of all bone tumour
  - Age range of 10-30 years
  - More common in males(2.5:1)
- **Sites of involvement**
  - Posterior elements of the spine and the sacrum(40-55% of cases),proximal femur,distal femur



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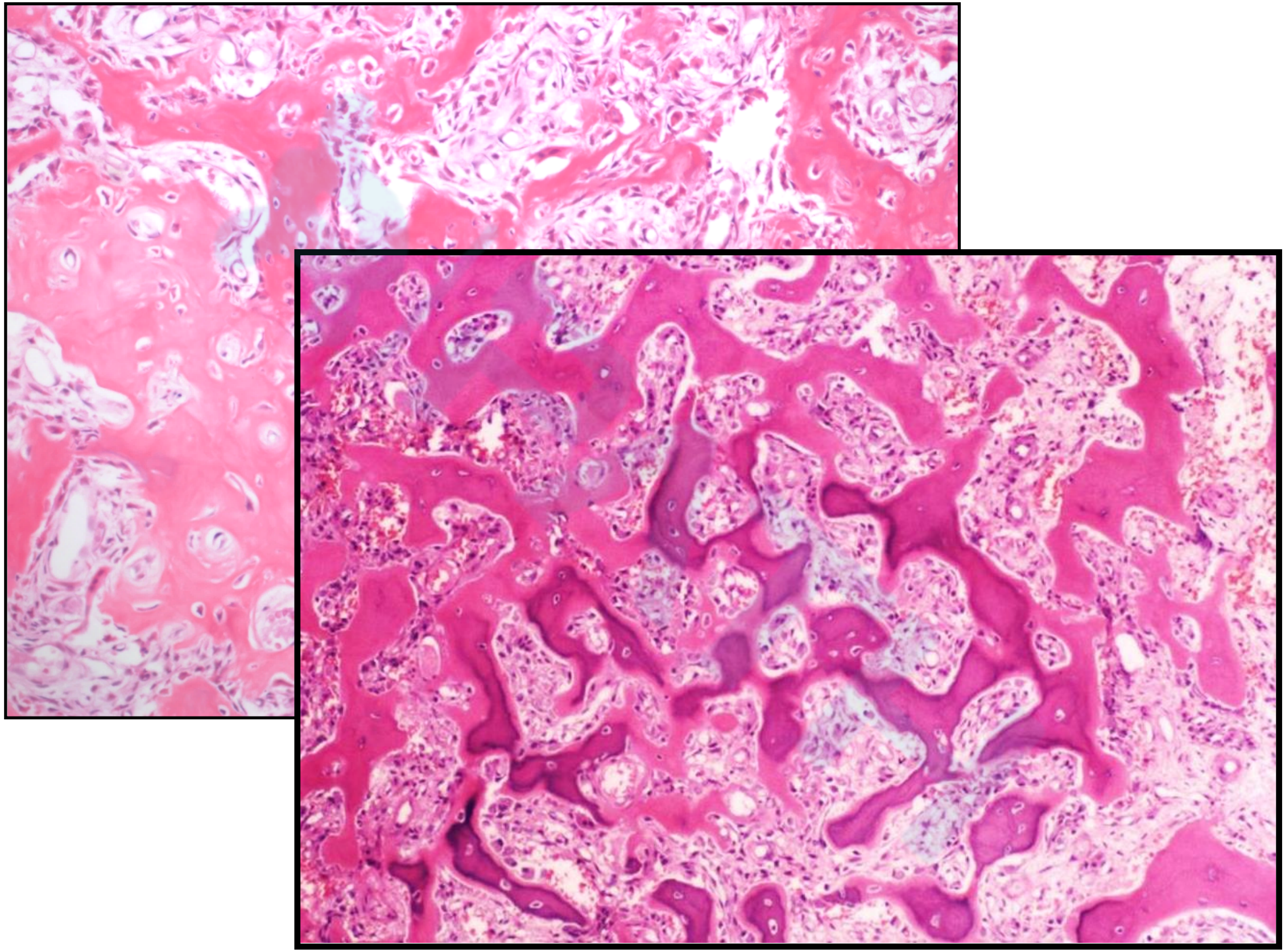

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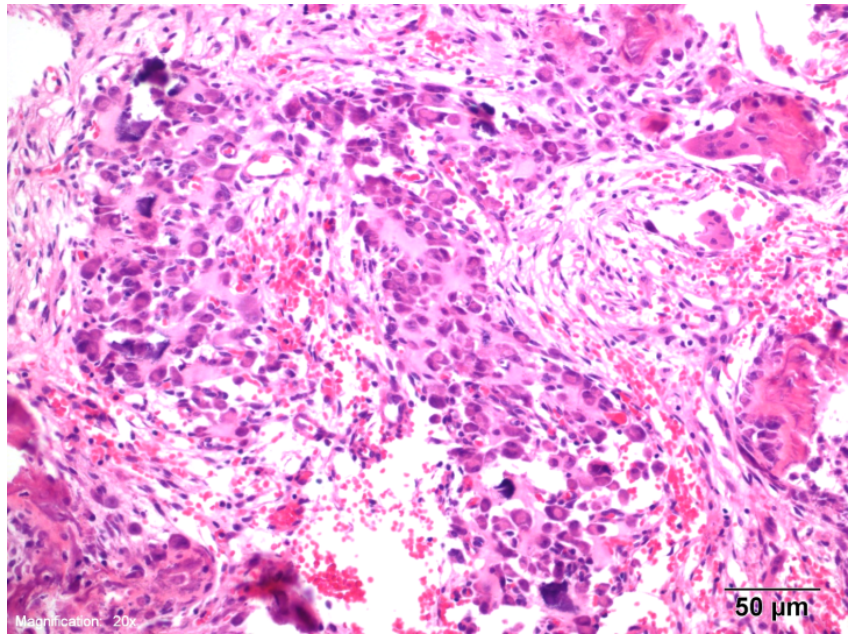
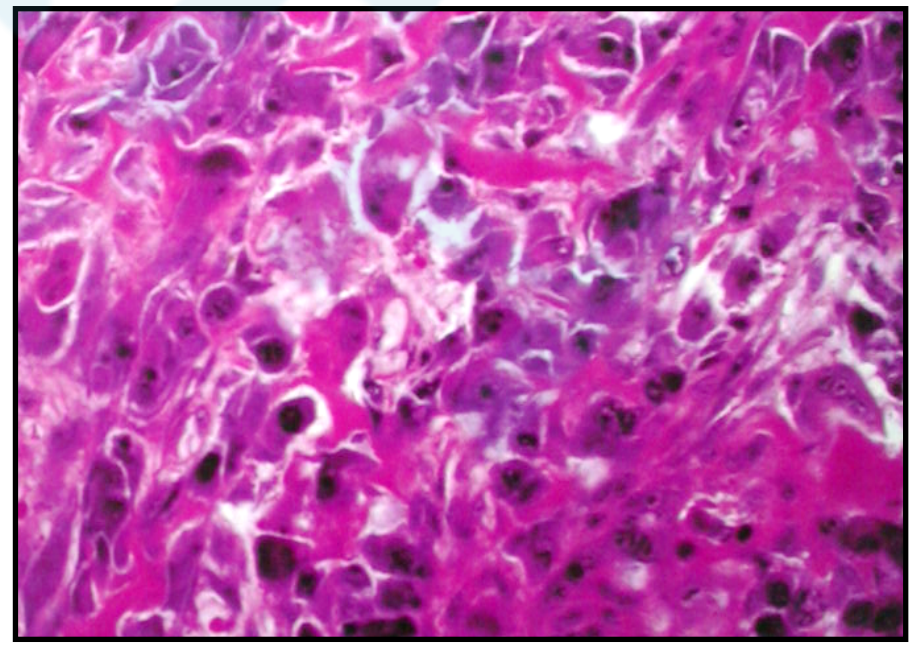
Osteoblastoma

- Prognostic factors
  - Often treated by curettage.Large lesions may have to be excised
  - The prognosis is excellent and recurrences are unusual

Differential diagnosis

- Aggressive osteoblastoma
  - Large,plump osteoblasts with a prominent nucleus and nucleoli,sometimes with mitoses
  - Larger than 4 cm, are associated with bone destruction and locally aggressive behavior
  - No evidence that epithelioid osteoblastoma has a worse prognosis





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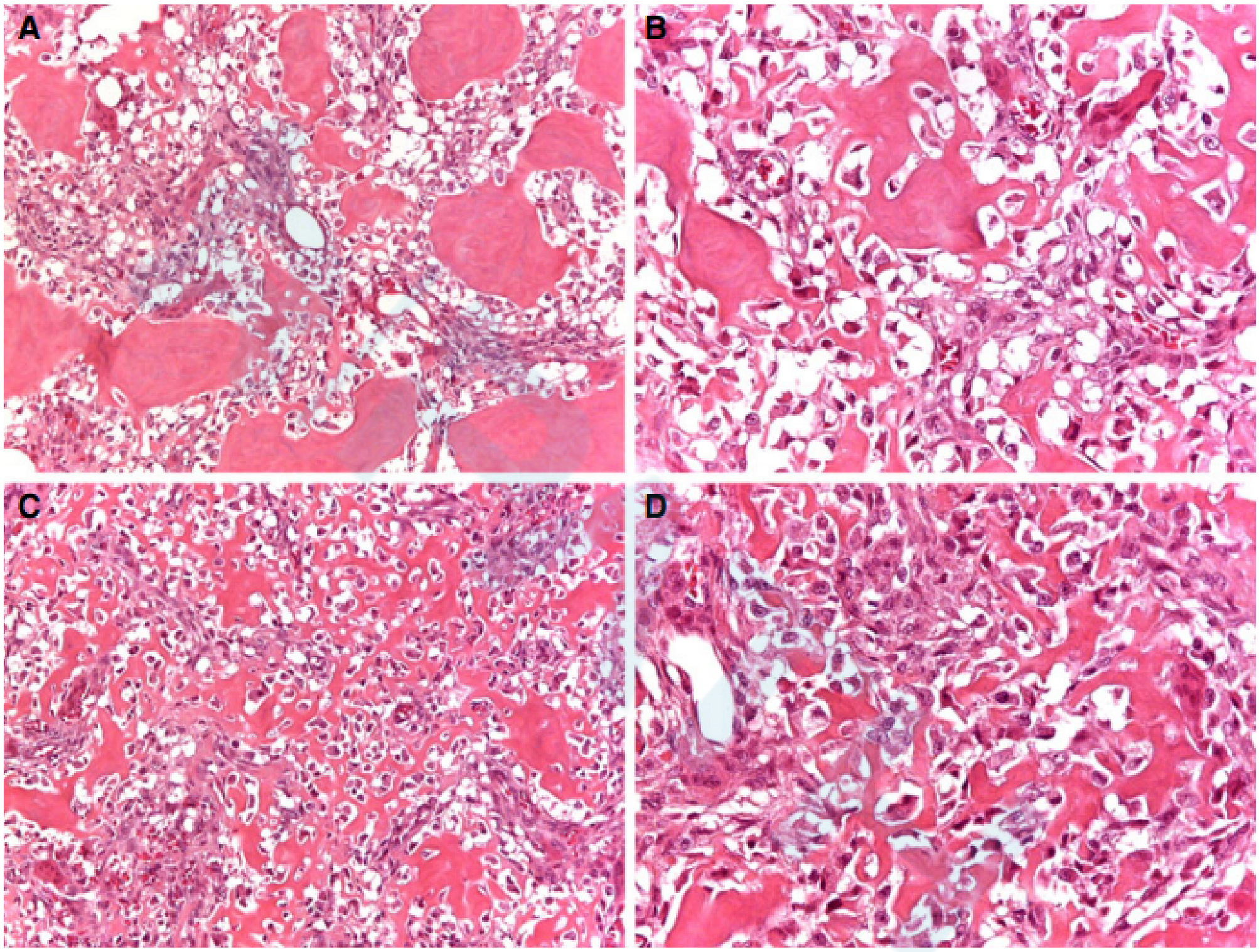
Differential diagnosis

- Osteoblastoma-like osteosarcoma
  - A rare variant of osteosarcoma
  - Sometimes described as a high-grade malignancy and at other times as a low-grade neoplasm, largely based on differing clinical behavior
  - Pathologic criteria
    - Peripheral permeation of the neoplasm into the surrounding bone
    - Cellular sheets of tumor cells devoid of vascular stroma
    - The presence of atypical mitotic figures



osteoblastoma-like osteosarcoma with areas similar to conventional osteoblastoma, but with disorderly architecture. Very abundant osteoid and areas similar to conventional highgrade osteosarcoma were also present.

- *FOS* and *FOSB*
  - Members of the activated protein-1 family of transcription factors
  - *c-FOS* was identified as an oncogenic element of the FBJ murine osteosarcoma virus in the development of osteosarcoma
  - The importance of the *FOS* gene in osteosarcoma was underscored when primary bone sarcomas developed in transgenic mice as a result of FOS overexpression

ARTICLE

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Recurrent rearrangements of *FOS* and *FOSB* define osteoblastoma

Matthew W. Fittall[1,2,3], William Mifsud[2,3,4], Nischalan Pillay[2,5], Hongtao Ye[5], Anna-Christina Strobl[5], Annelien Verfaillie[1], Jonas Demeulemeester[1,6], Lei Zhang[7], Fitim Berisha[5], Maxime Tarabichi[1,3], Matthew D. Young[3], Elena Miranda[2], Patrick S. Tarpey[3], Roberto Tirabosco[5], Fernanda Amary[5], Agamemnon E. Grigoriadis[8], Michael R. Stratton[3], Peter Van Loo[1,6], Cristina R. Antonescu[7], Peter J. Campbell[3], Adrienne M. Flanagan[2,5] & Sam Behjati[3,9]

The transcription factor *FOS* has long been implicated in the pathogenesis of bone tumours, following the discovery that the viral homologue, *v-fos*, caused osteosarcoma in laboratory mice. However, mutations of *FOS* have not been found in human bone-forming tumours. Here, we report recurrent rearrangement of *FOS* and its paralogue, *FOSB*, in the most common benign tumours of bone, osteoblastoma and osteoid osteoma. Combining whole-genome DNA and RNA sequences, we find rearrangement of *FOS* in five tumours and of *FOSB* in one tumour. Extending our findings into a cohort of 55 cases, using FISH and immunohistochemistry, provide evidence of ubiquitous mutation of *FOS* or *FOSB* in osteoblastoma and osteoid osteoma. Overall, our findings reveal a human bone tumour defined by mutations of *FOS* and *FOSB*.

- The pattern of c-FOS expression in a cohort of osteoblastoma and osteoid osteoma from 3 institutions
- Diagnostic value by analyzing c-FOS expression in a separate cohort of biopsy samples of consecutive osteosarcoma cases

MATERIALS AND METHODS

- A total of 337 cases
  - 84 osteoblastoma
  - 33 osteoid osteomas
  - 215 biopsies of osteosarcoma
  - 5 samples of reactive new bone formation
- Immunohistochemistry c-FOS
  - Nuclear expression in <10% or 10% or more of the osteoblastic cell component
- FISH
  - *FOS* and *FOSB*

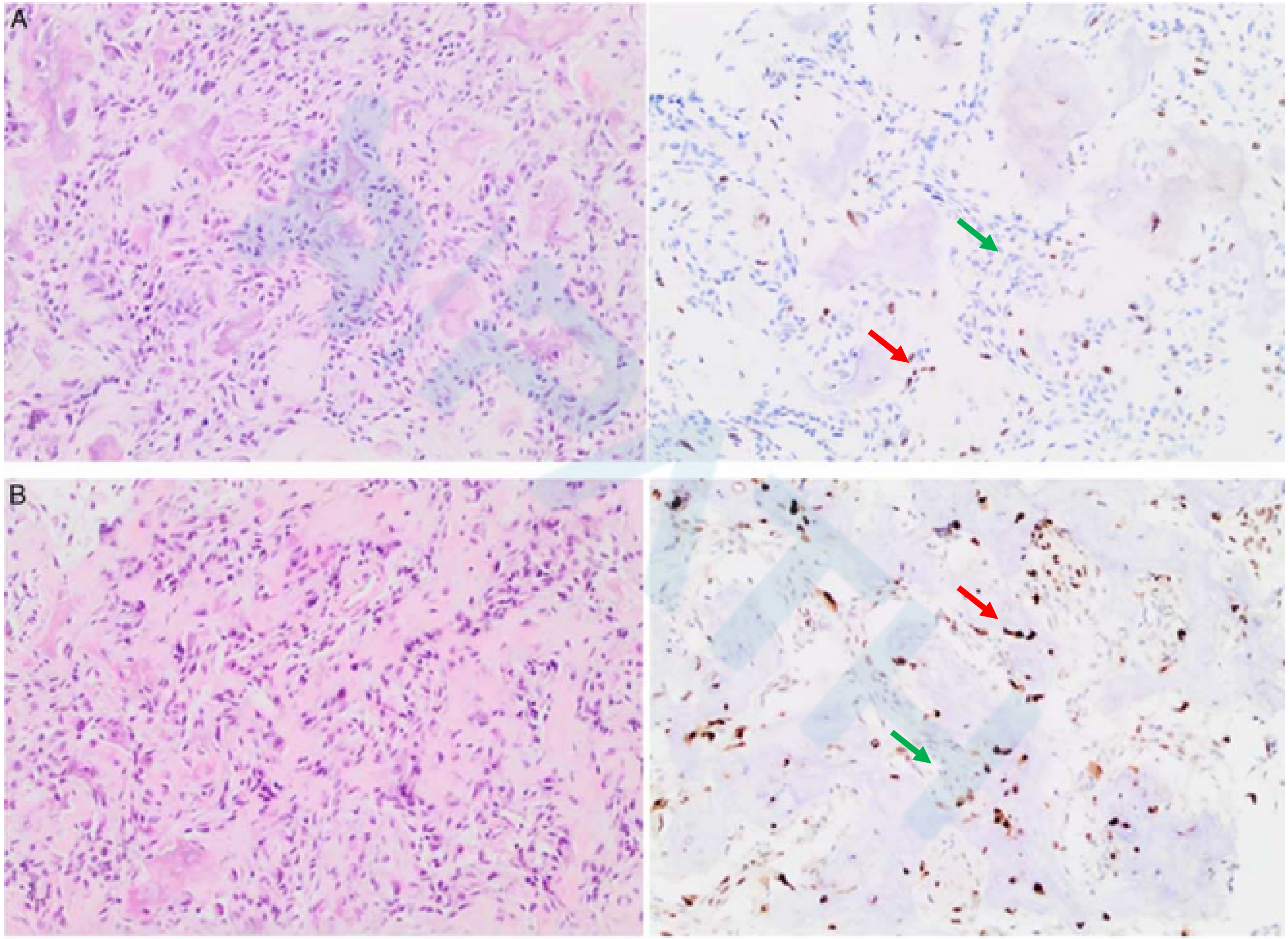
RESULTS

LESION	CASES	AGE	SEX (M : F)	BONES MORE COMMONLY AFFECTED
Osteoid osteoma	33	2–52(mean: 20 y)	2:1	long tubular bones(n= 15） , spine(n=12), bones of the hands or feet(n=5), pelvis(n=1)
Osteoblastoma	84	2–61(mean: 21 y)	2:1(59M:25F)	spine (n= 31; 37%), long tubular bones (n =17; 20%), feet(n = 13; 15%), bones of the jaw (n =9; 11%), and pelvis (n = 8; 10%)
Osteosarcoma	215	2–87(average: 26y)	1.3:1	long tubular bones(n=124) , spine(n=20), jaw bones(n=23)
Reactive new bone formation	5	29-46	4:1	Spine(n=2)， femur，foot，jaw

RESULTS

TABLE 1. Summary of c-FOS Immunohistochemistry

	No. of Cases Showing c-FOS Expression (%)	% of Tumor Cells	No. of Cases
Osteoid osteoma	24 (73)	< 10 (+)	5
		10-50 (++)	8
		> 50 (+++)	11
Osteoblastoma	70 (83)	< 10 (+)	6
		10-50 (++)	38
		> 50 (+++)	26
Osteosarcoma	31 (14)	< 10 (+)	23
		10-50 (++)	7
		> 50 (+++)	1


A
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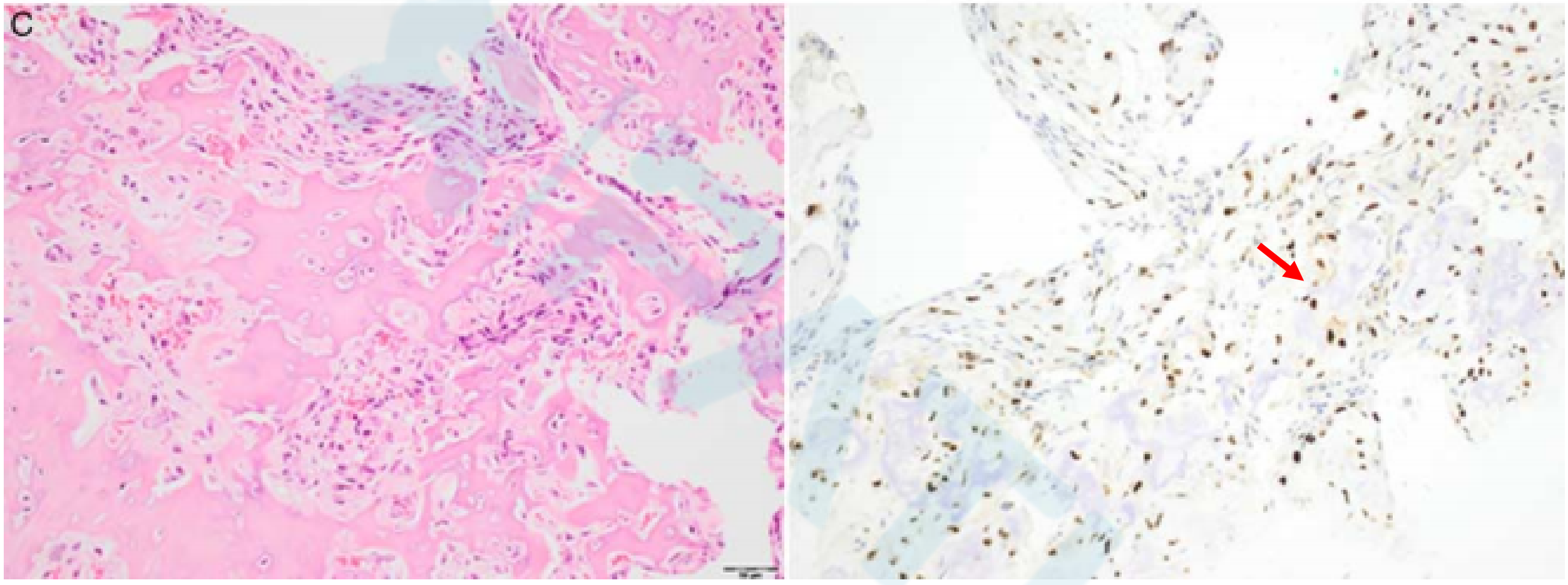
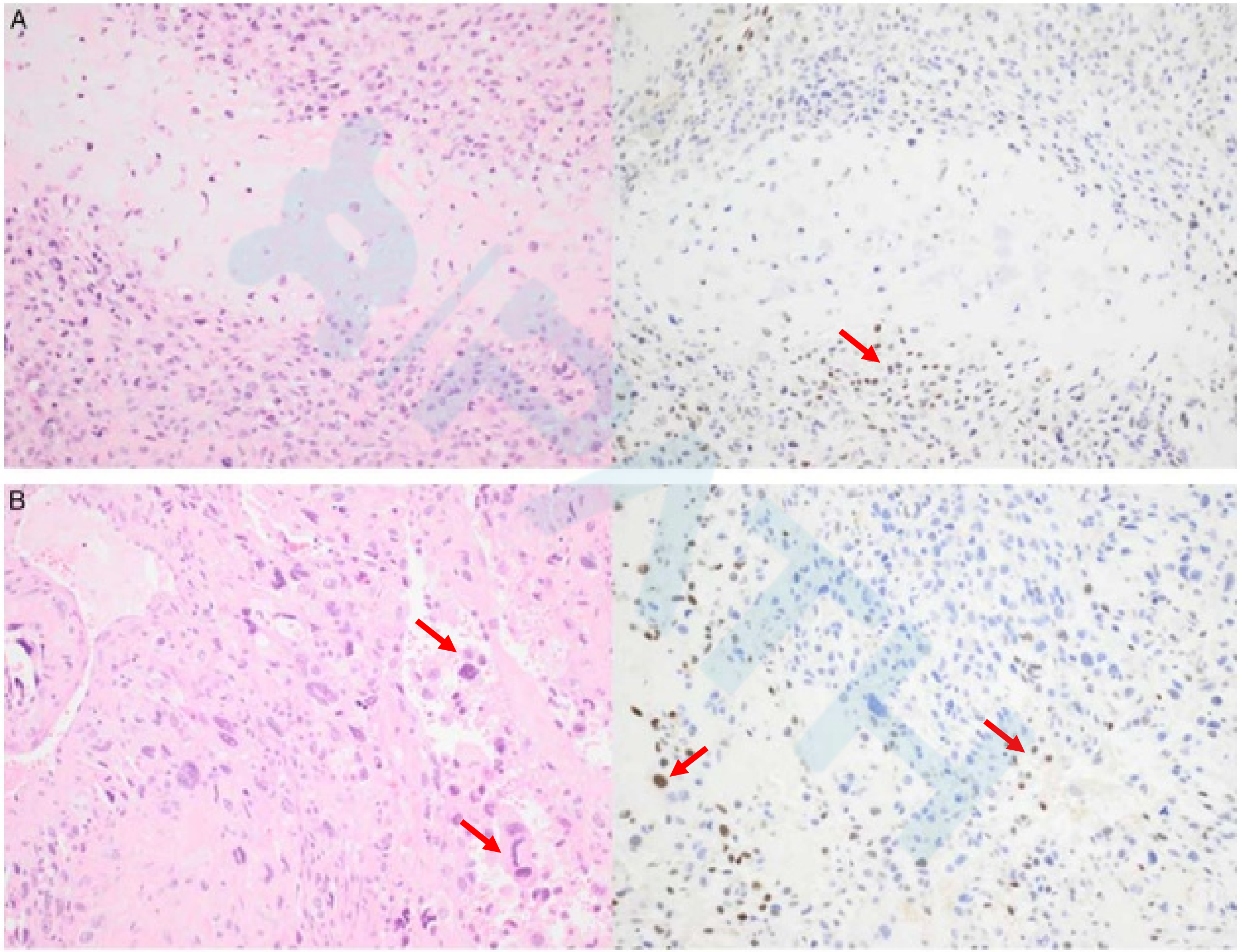


FIGURE 1. Photomicrographs of 3 different cases of osteoblastoma/osteoid osteoma (A–C) demonstrating the histological features and corresponding c-FOS expression limited to the plump osteoblastic cells. The stromal fibroblastic cells, endothelial cells and osteoclast-like giant cells are consistently negative for c-FOS


A
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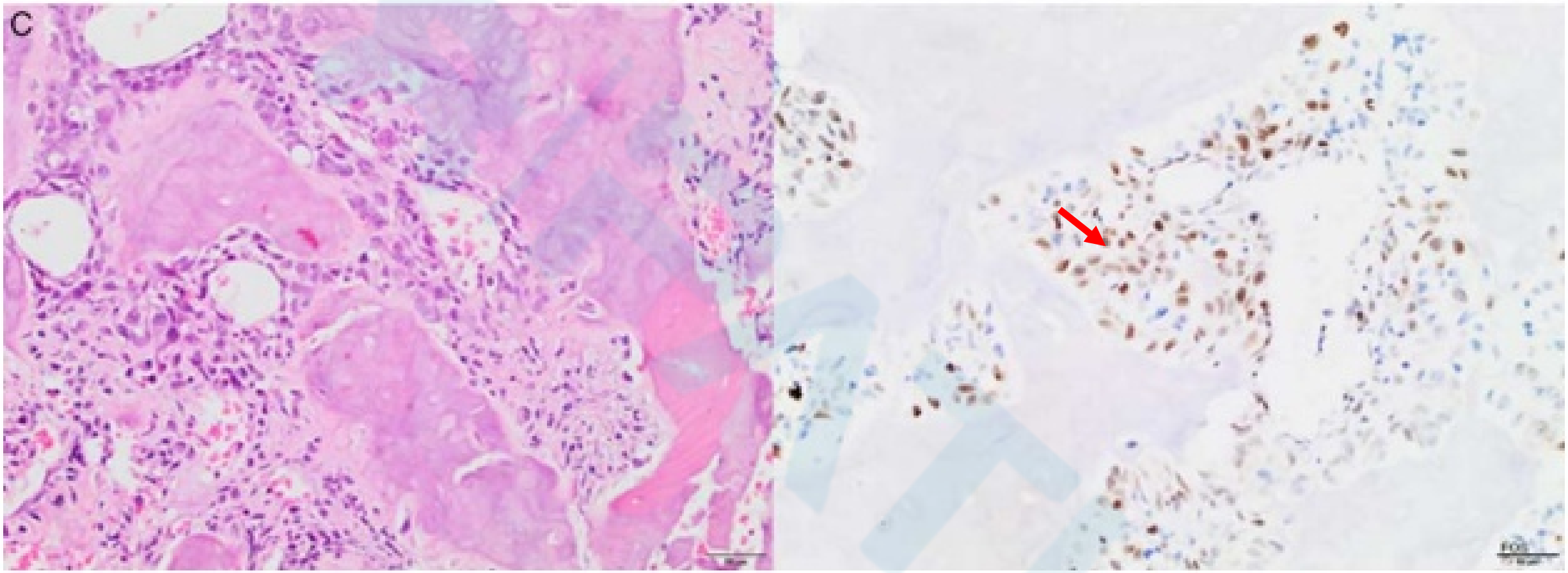
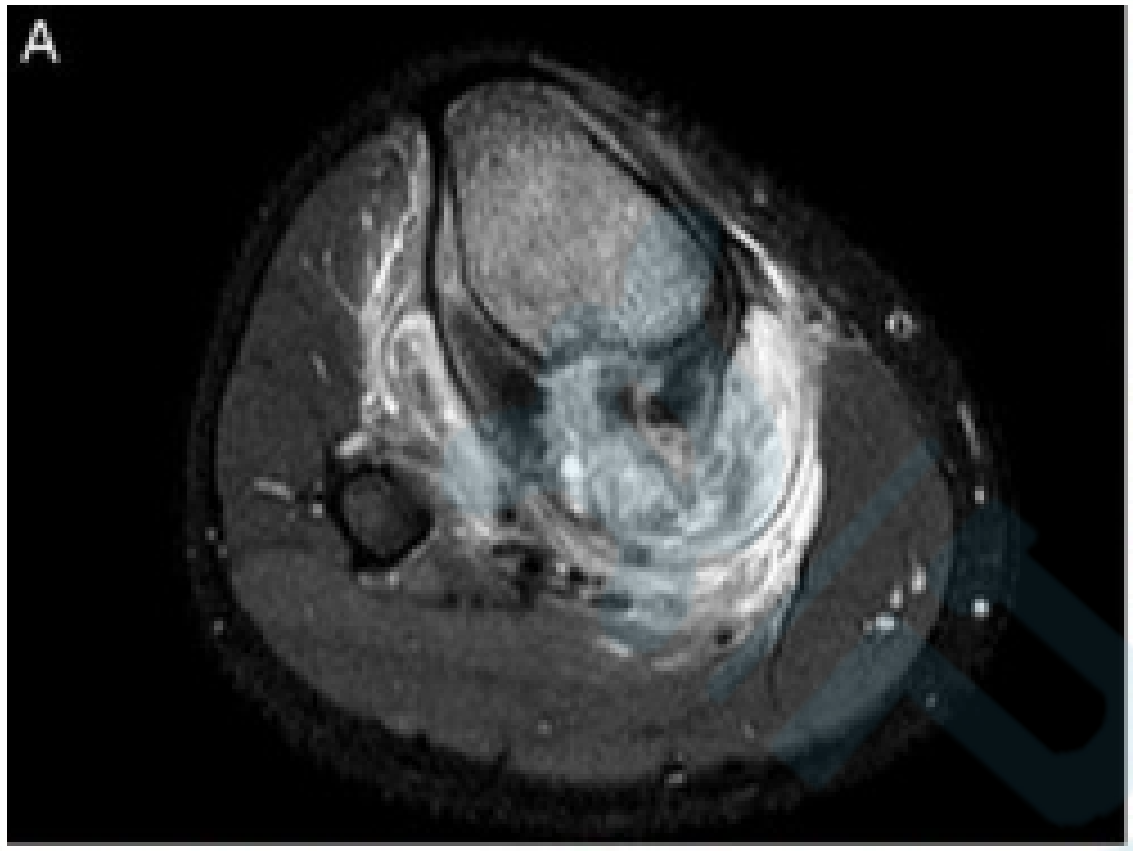
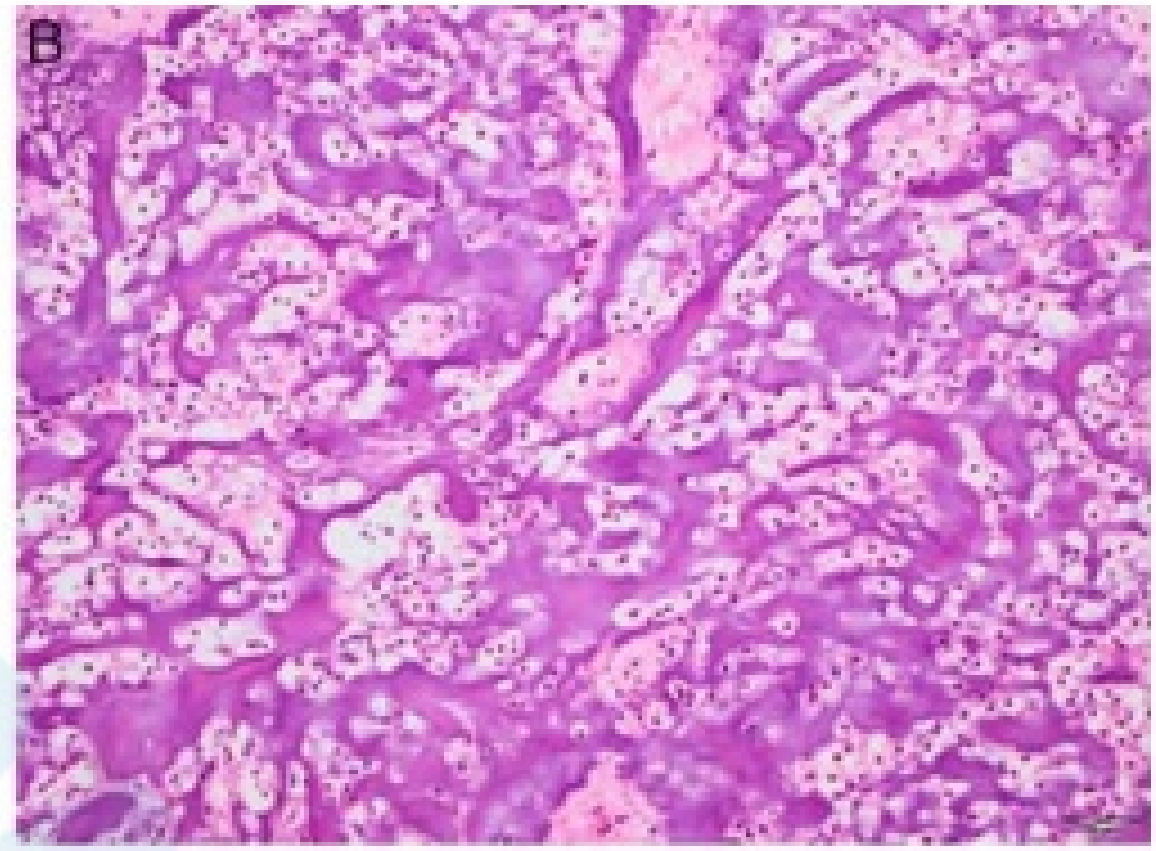


FIGURE 2. Photomicrographs of 3 different cases of osteosarcoma (A–C) showing different patterns of c-FOS expression (right panel).


A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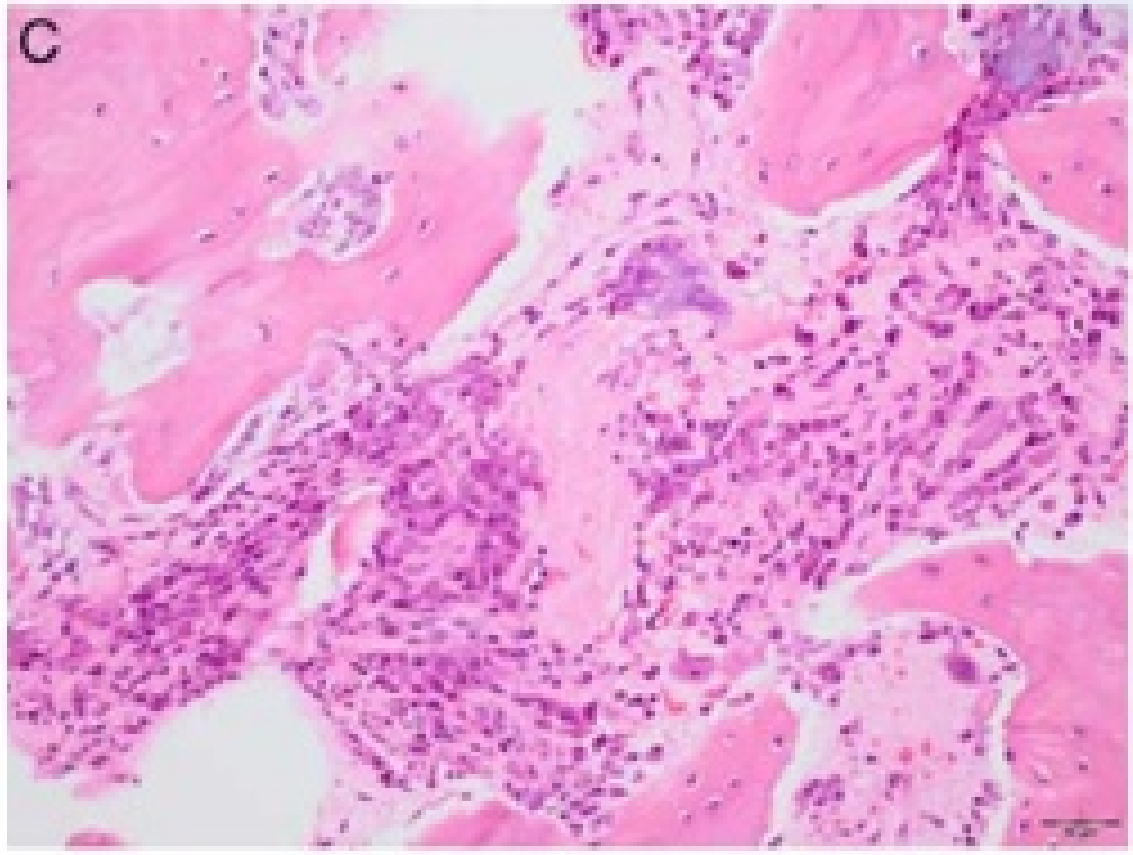
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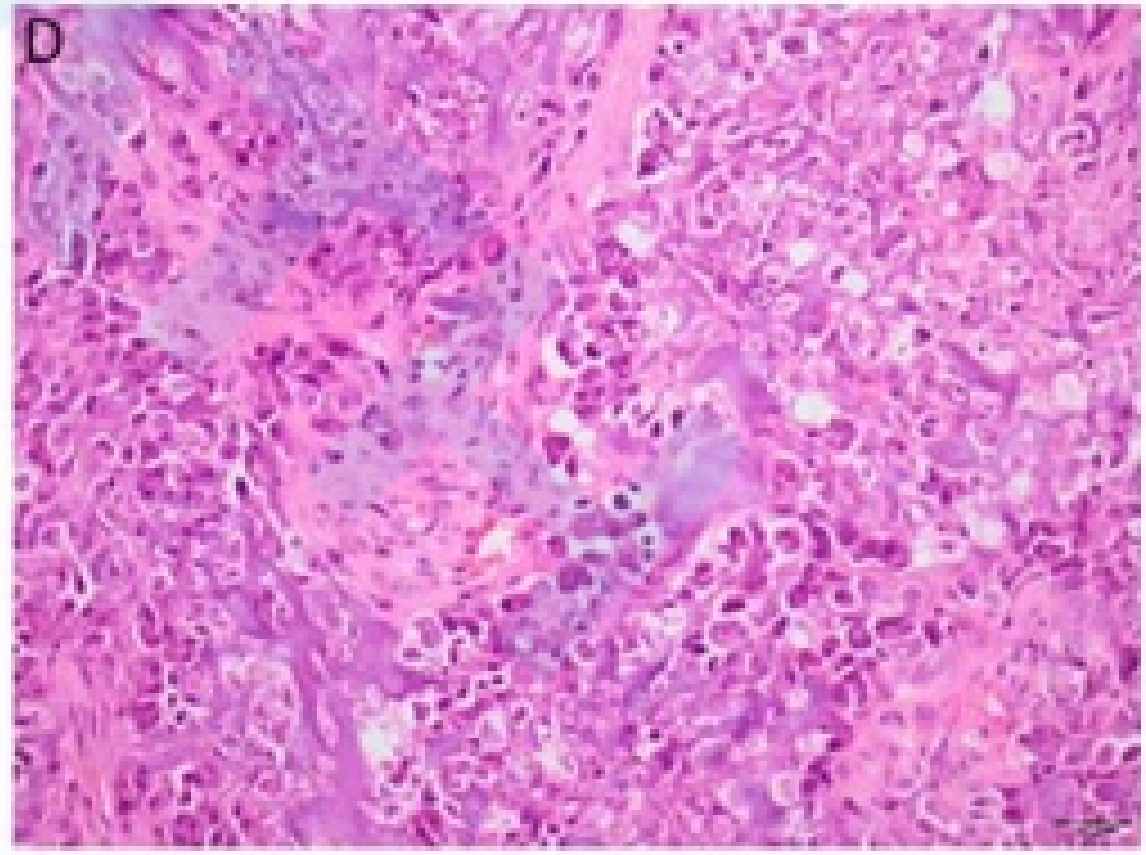
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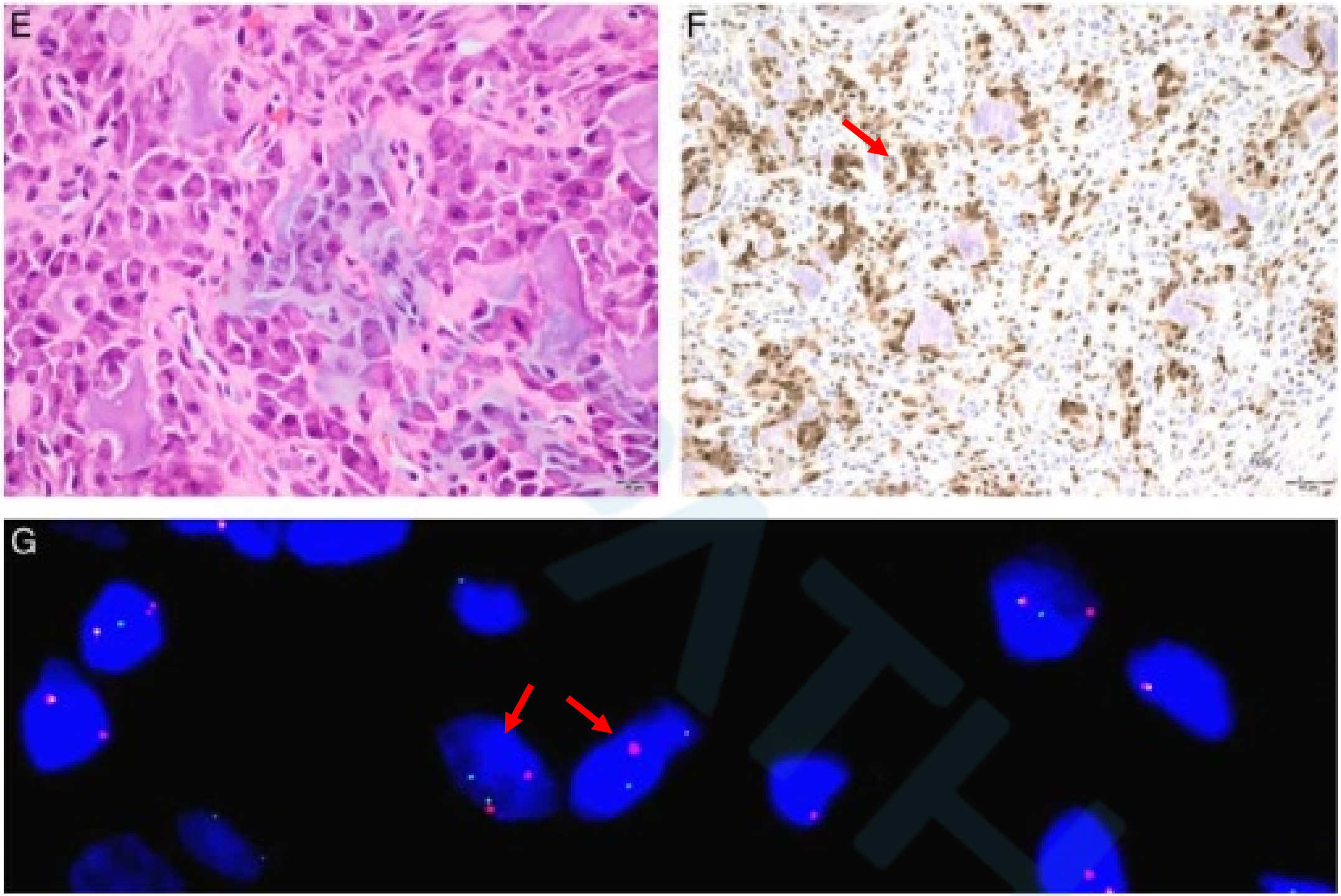

FIGURE 3. Tibial osteoblastoma: (A) axial magnetic resonance image of the right tibia showing focal cortical destruction posteriorly and a large associated hyperintense tumor, with a low signal mineralized margin and perilesional edema. Photomicrographs showing lace-like osteoid deposition (B), tumor growing within the cortical bone (C) and areas with epithelioid morphology (D, E).(F, G) FISH using FOS break-apart probes showing clear break-apart signals.

RESULTS

FOS and *FOSB* FISH

- 14 osteoblastomas negative for c-FOS
  - 6 were negative
  - 7 were noninformative
  - 1 (epithelioid osteoblastoma) was a consultation case with no extra slides available for FISH analysis
- 9 c-FOS negative osteoid osteomas
  - 2 showed FOS gene rearrangement
  - 5 were negative
  - 2 were noninformative
- None showed copy number gain or loss

RESULTS

FOS and *FOSB* FISH

•8 osteosarcoma cases showed a diffuse expression pattern (over 10% of the cells)

- Only 1, the osteoblastoma-like osteosarcoma， showed a *FOS* gene rearrangement
- Four cases were negative but showed multiple copies of the *FOS* locus
- No tissue available on the remaining 3 cases

DISCUSSION

- c-FOS has a distinctive pattern of protein expression in the majority of osteoblastomas and osteoid osteomas
  - A useful marker in the diagnoses of these tumor types
  - Similar pattern of expression seen in both these tumor types supports the genetic findings that they represent a spectrum of the same disease
- Minority of osteosarcomas (<4%)showed a more conspicuous expression of c-FOS in over 10% of the cells
- Immunohistochemistry,appropriate clinical, morphologic, radiologicinformation

DISCUSSION

- c-FOS expression was reported in osteosarcomas over 2 decades ago, although the antibodies used in these studies potentially recognized epitopes within the protein other than those using the current antibody
- The antibody used in the current study target the N terminus,present in the truncated c-FOS protein as a result of the rearrangement , similar to the mechanism described in cases of epithelioid hemangiomas harboring *FOS* gene rearrangement with breakpoints in the same exon 4 as described in osteoblastomas/osteoid osteomas

CONCLUSION

- c-FOS immunohistochemistry
  - Helpful ancillary tool in the diagnosis of osteoid osteomas and osteoblastomas
  - Present in a minority of osteosarcomas despite the lack of *FOS* gene rearrangements
  - Caution in distinguishing benign from malignant bone-forming tumors
- Detection of a *FOS* gene rearrangement is a safer means

THANK YOU