西京医院 XIJING HOSPITAL

PATH 西京病理

Dedifferentiated Chordoma

Clinicopathologic and Molecular Characteristics With Integrative Analysis

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BACKGROUND

BACKGROUND

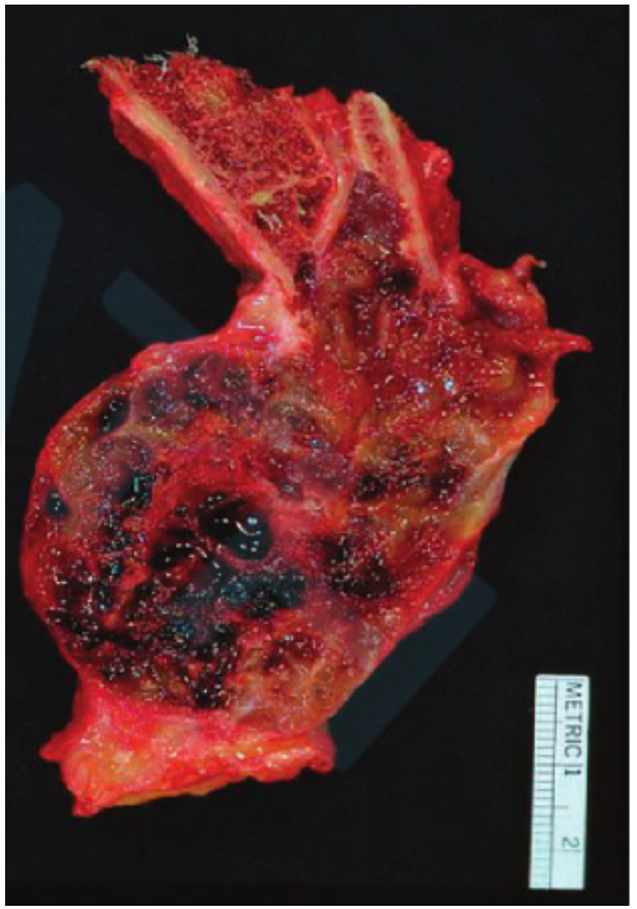
脊索瘤Chordoma

- 起源于原始脊索的残留物，脊索瘤生长缓慢，局部浸润，但远处转移相对少见
- 好发于中轴骨，如：骶尾部、颅底近蝶枕结合部
- 多见于男性（男：女≈1.8:1），50-60岁
- 肉眼：质地软，分叶状，浅灰色-半透明
- 分类：

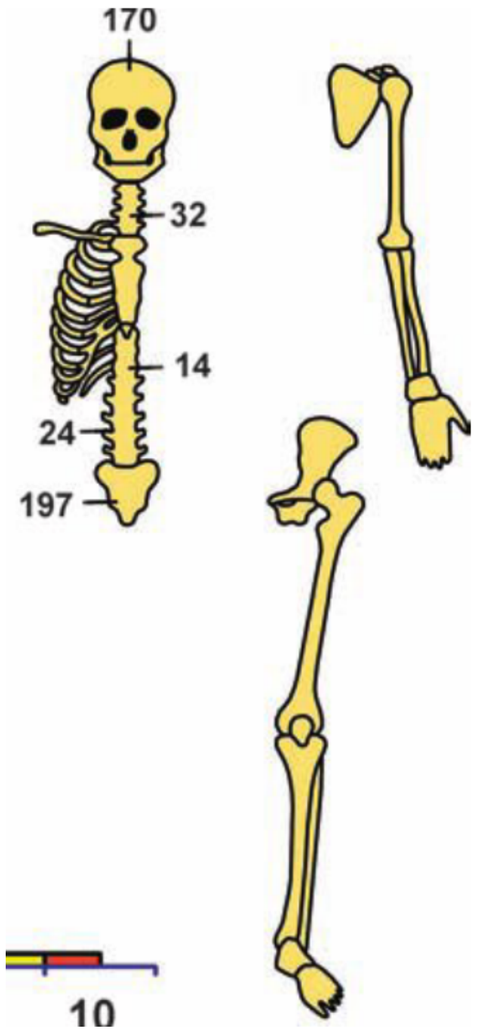
  普通型/软骨样脊索瘤

  低分化脊索瘤

  去分化脊索瘤



Dablin’s Bone Tumors, SIX EDITION



BACKGROUND

普通型脊索瘤Conventional Chordoma

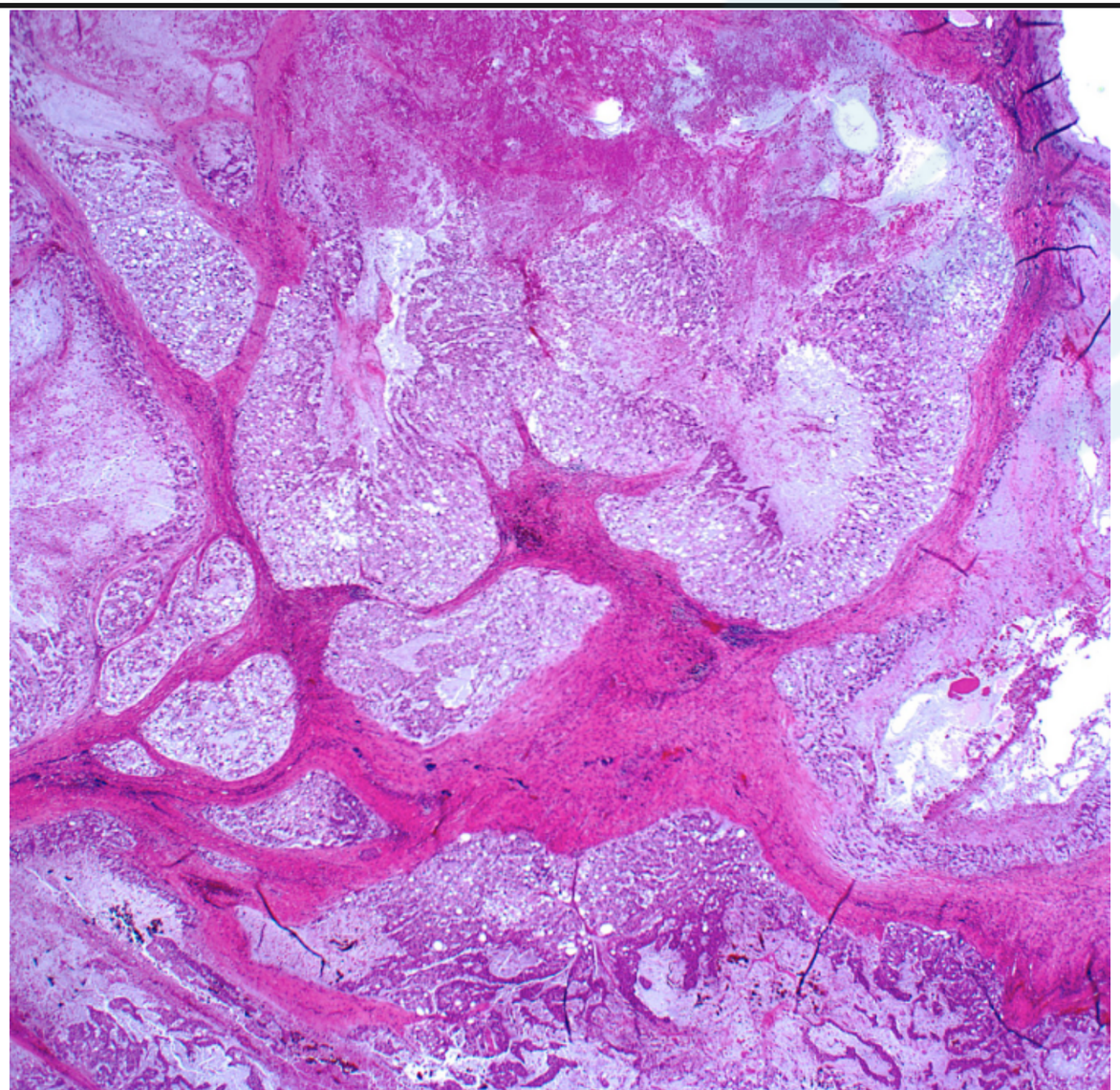
- 由纤维间隔分隔呈分叶状，间质软骨黏液样变性
- 细胞排列成条索状，分布于蓝染的黏液样基质中
- 细胞胞浆内常形成空泡，单个小空泡-多个空泡
- 胞浆淡染-淡嗜酸性
- 核轻度异型性，核分裂像少见
- 偶见多形性多核细胞

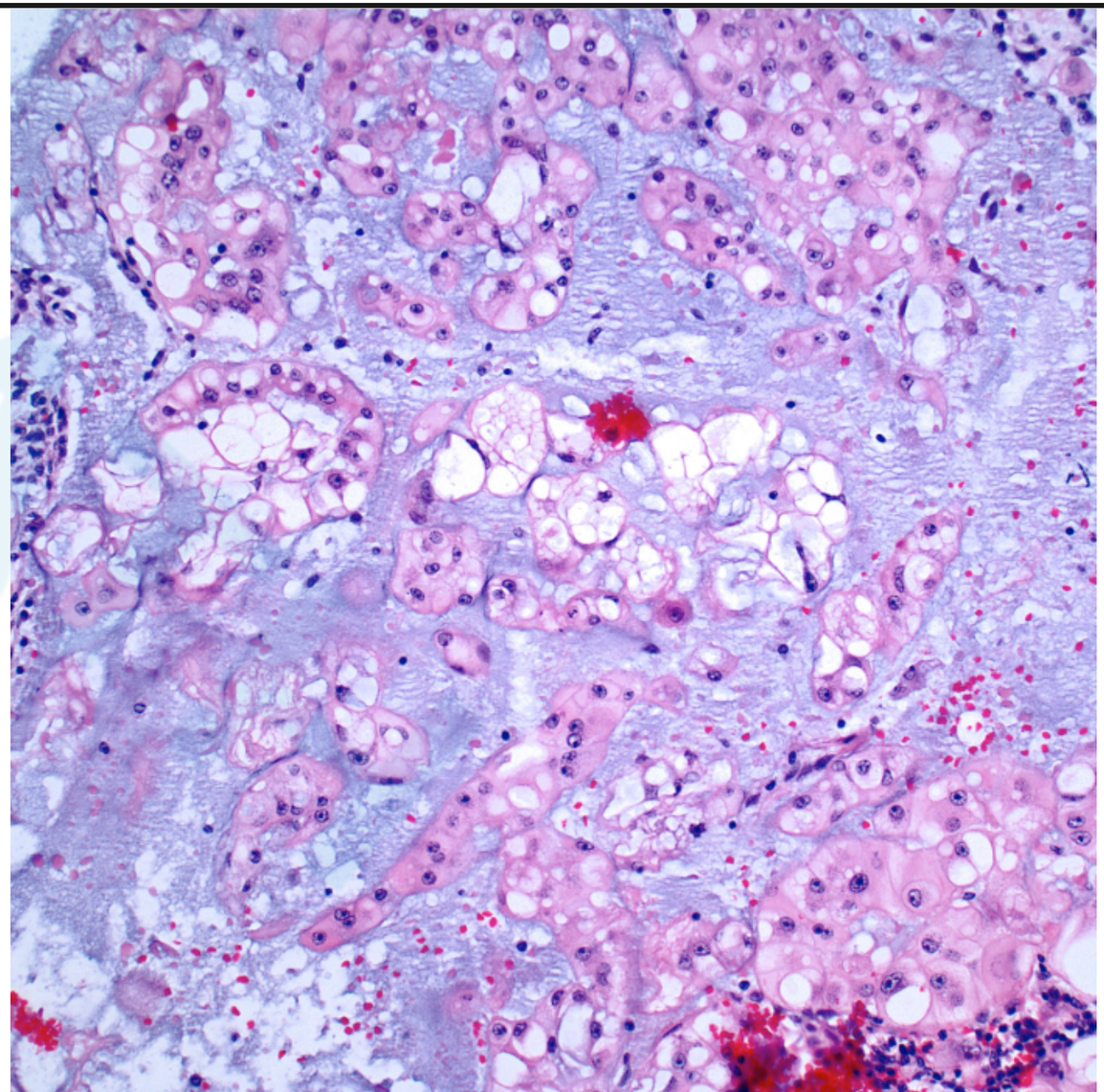
WHO Classification of Tumours· 5TH Edition Soft tissue and Bone Tumours

Dablin's Bone Tumors, SIX EDITION

BACKGROUND

普通型脊索瘤Conventional Chordoma





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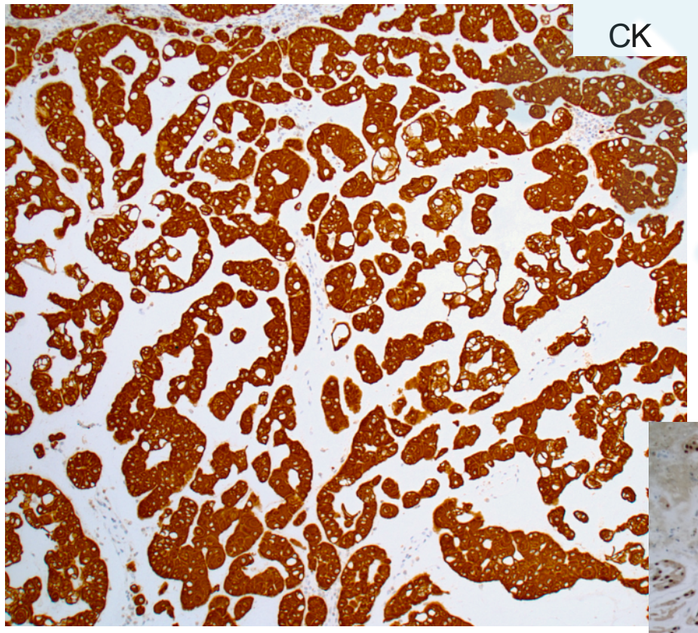
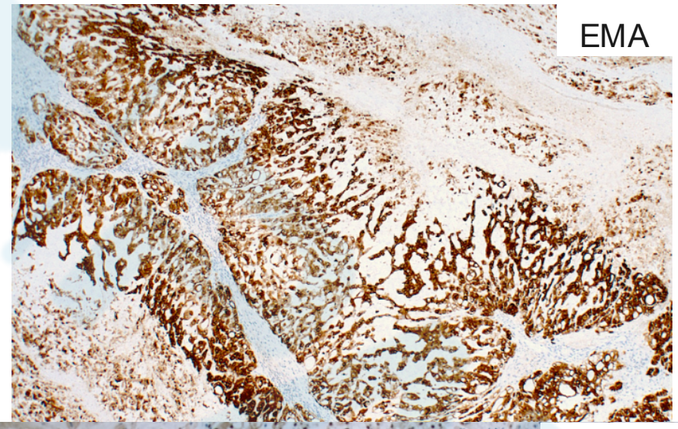
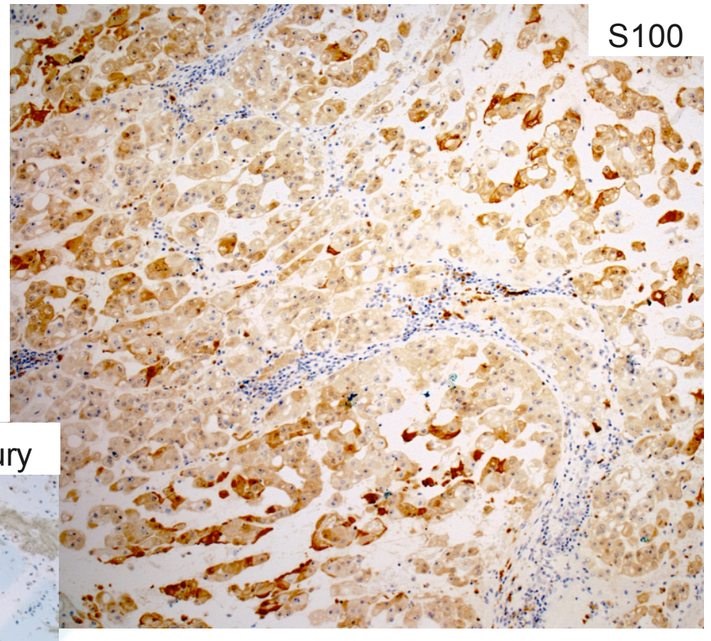
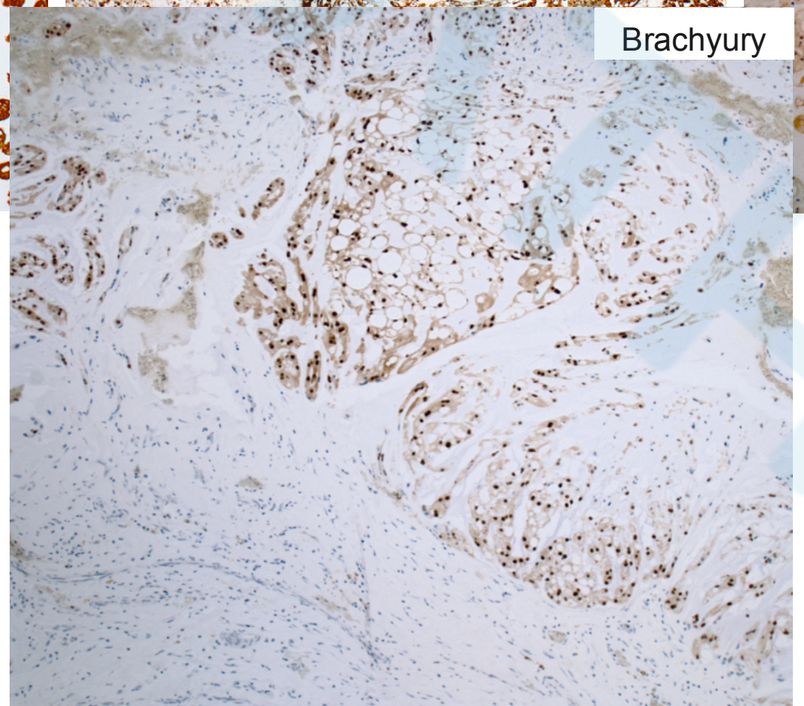
普通型脊索瘤Conventional Chordoma





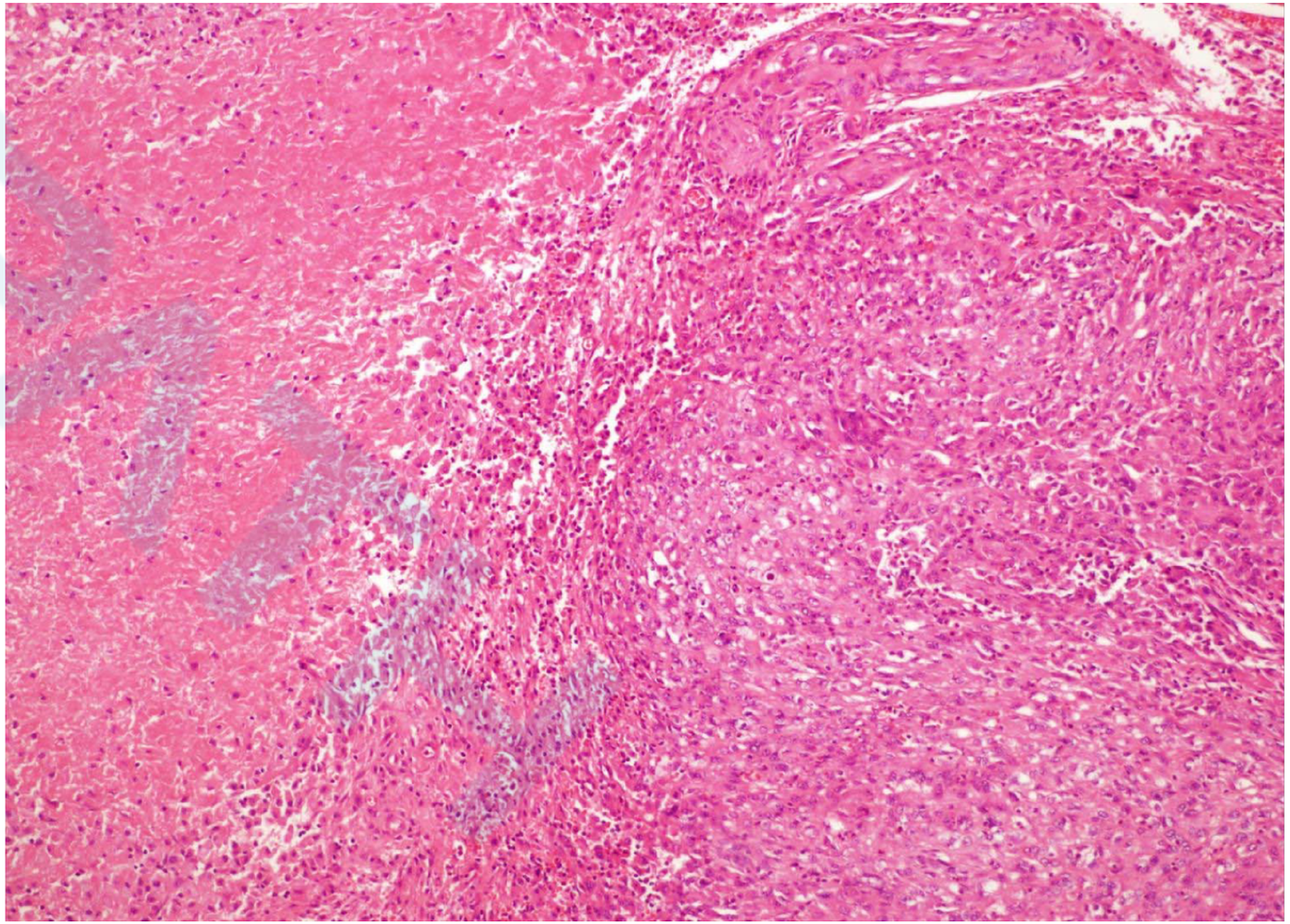




BACKGROUND

低分化脊索瘤Poorly Differentiated Chordoma

- 上皮样细胞排列呈片状或巢团状
- 胞浆丰富、嗜酸，散在胞浆内空泡
- 核圆形-卵圆形，呈空泡状
- 核轻-中度异型性，核分裂增多
- 地图样坏死
- 空泡细胞、黏液变间质少见



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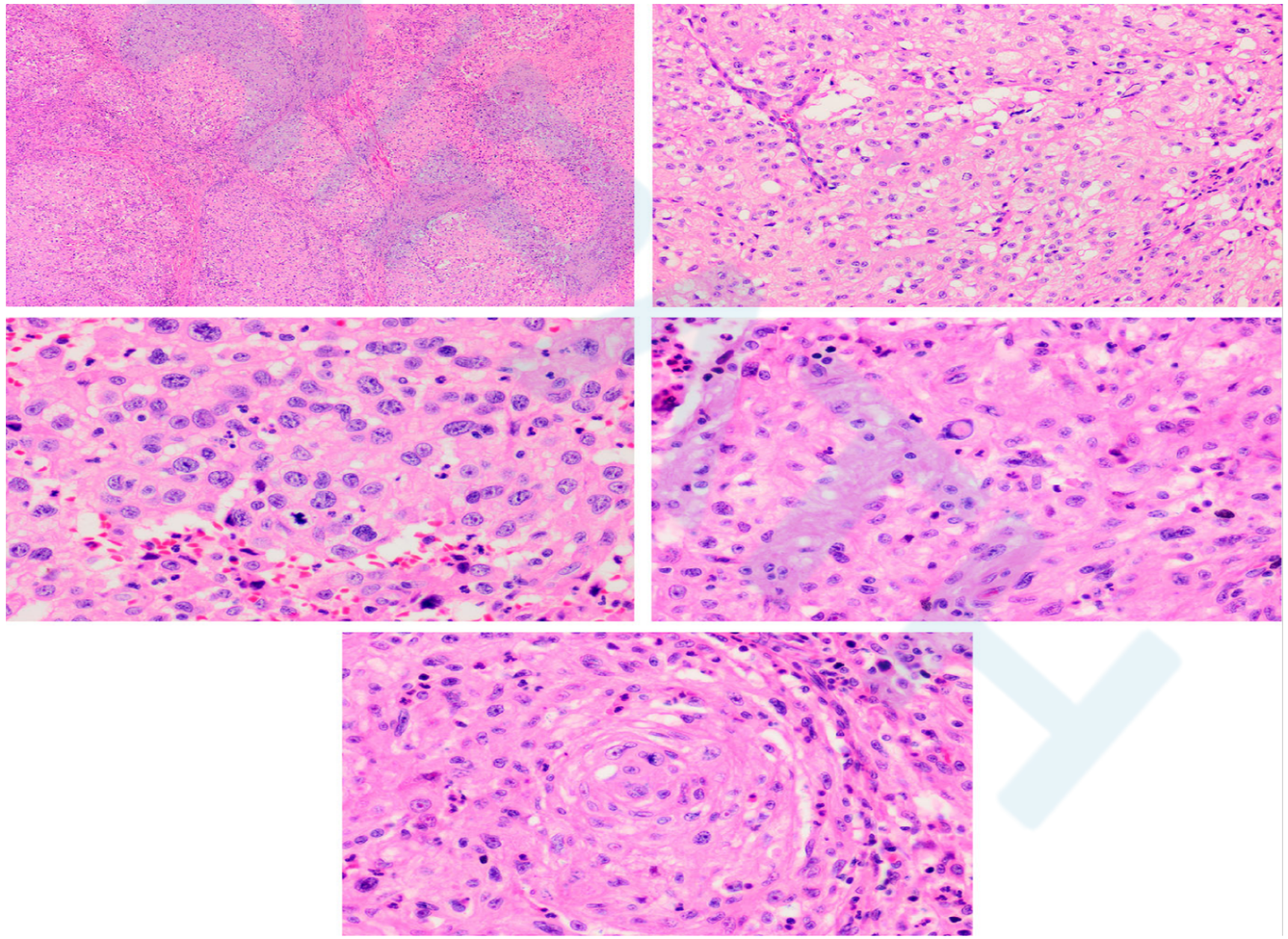
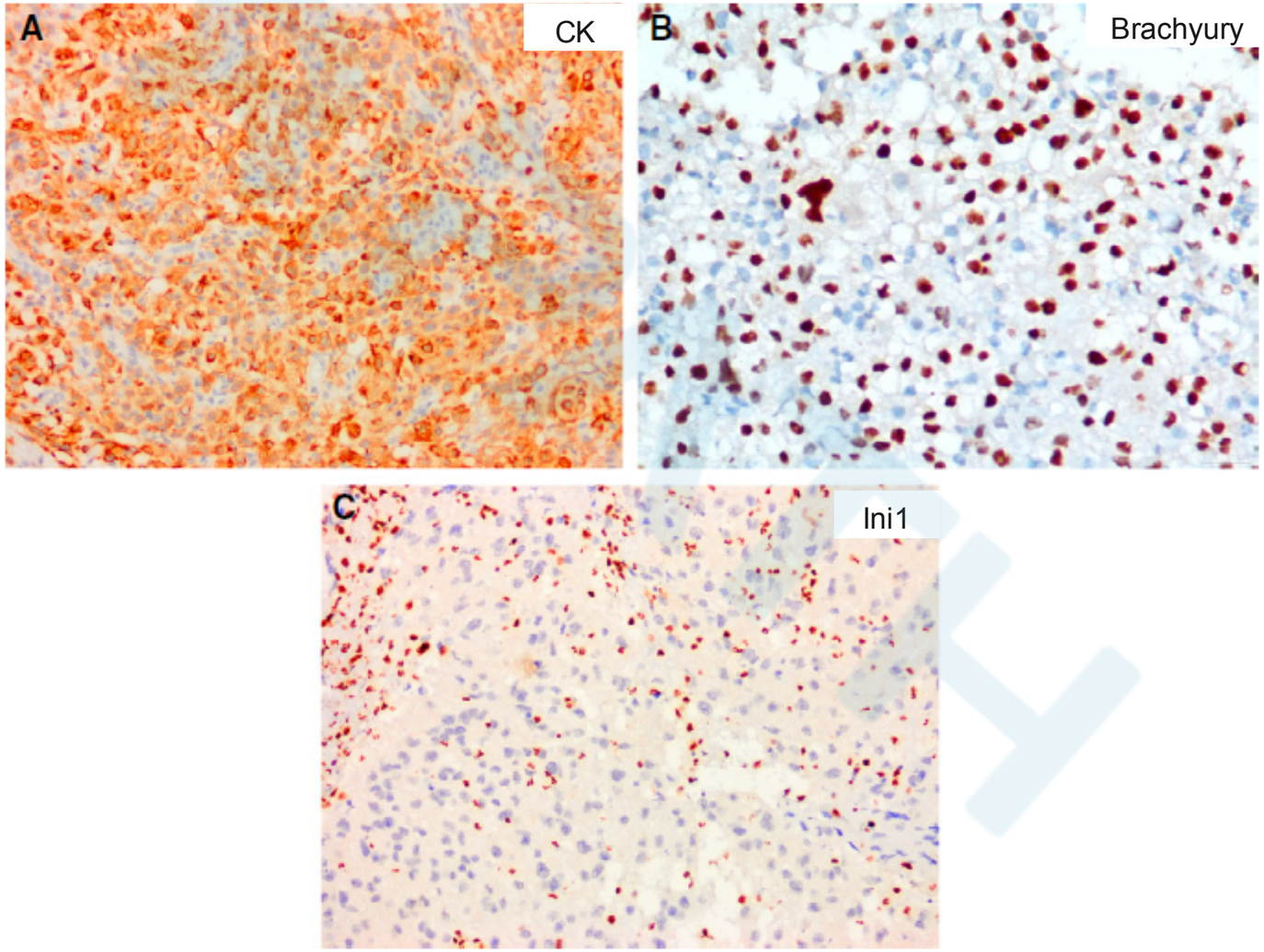
低分化脊索瘤Poorly Differentiated Chordoma



Gokce Yeter H. *APMIS* 2019; 127: 607–615.

BACKGROUND

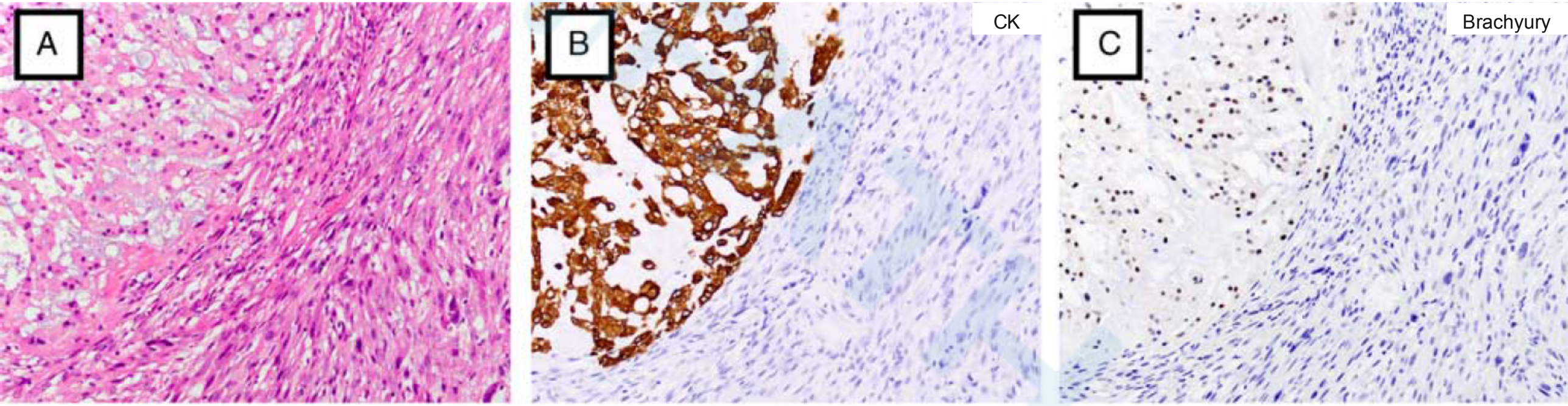
低分化脊索瘤Poorly Differentiated Chordoma



Gokce Yeter H. *APMIS* 2019; 127: 607–615.

BACKGROUND

去分化脊索瘤Dedifferentiated Chordoma



研究目的

研究多中心提供的10例去分化脊索瘤，总结已发表的关于去分化脊索瘤的病例报道，揭示去分化脊索瘤的临床病理学特征、分子特征

MATERIALS AND METHODS

MATERIALS AND METHODS

- ✓ Surgical pathology files from 1990 to 2019 of 2 institutions (Massachusetts General Hospital and University of Miami) and consultation files from 2 authors (G.P.N. and A.E.R.) were searched for cases of dedifferentiated chordoma.
- ✓ Immunohistochemistry was performed in select cases on 5- µ m-thick formalin-fixed paraffin-embedded wholetissue sections for the following targets: brachyury, INI1, cytokeratin, S-100
- ✓ Next-generation sequencing was performed successfully in 4 tumors (including both components in 3) but failed in 1 case, likely due to decalcification (from EDTA) and specimen age (over 6 y).

MATERIALS AND METHODS

For integrative analysis, all publications in English on dedifferentiated chordoma were analyzed by searching on the PubMed search engine of the Library of Medicine with the following terms: “chordoma” and “dedifferentiated,” “dedifferentiation,” “sarcomatous,” “sarcomatoid,” “anaplastic,” “transformation,” or “malignant fibrous histiocytoma.”

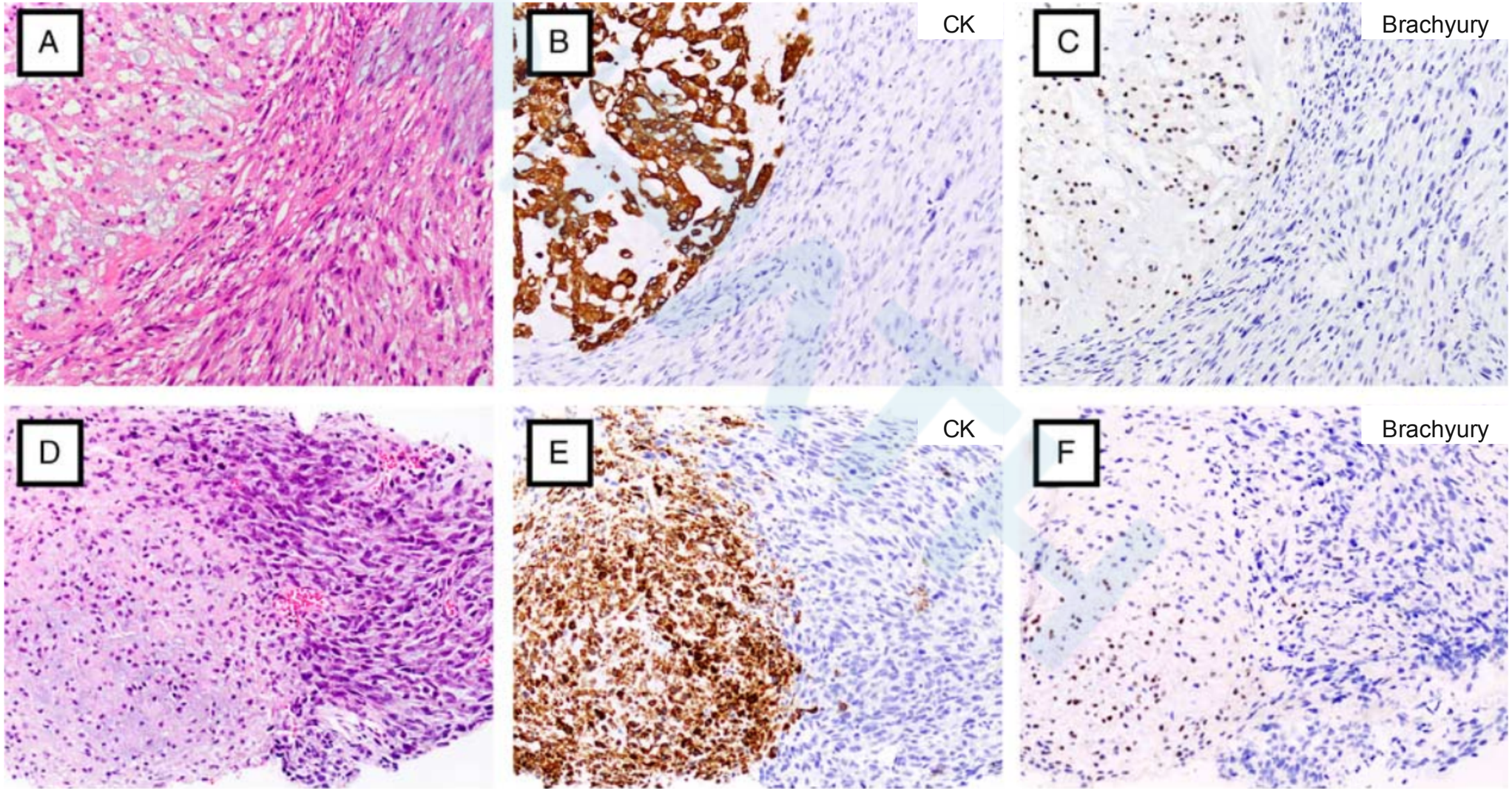
RESULTS

RESULTS

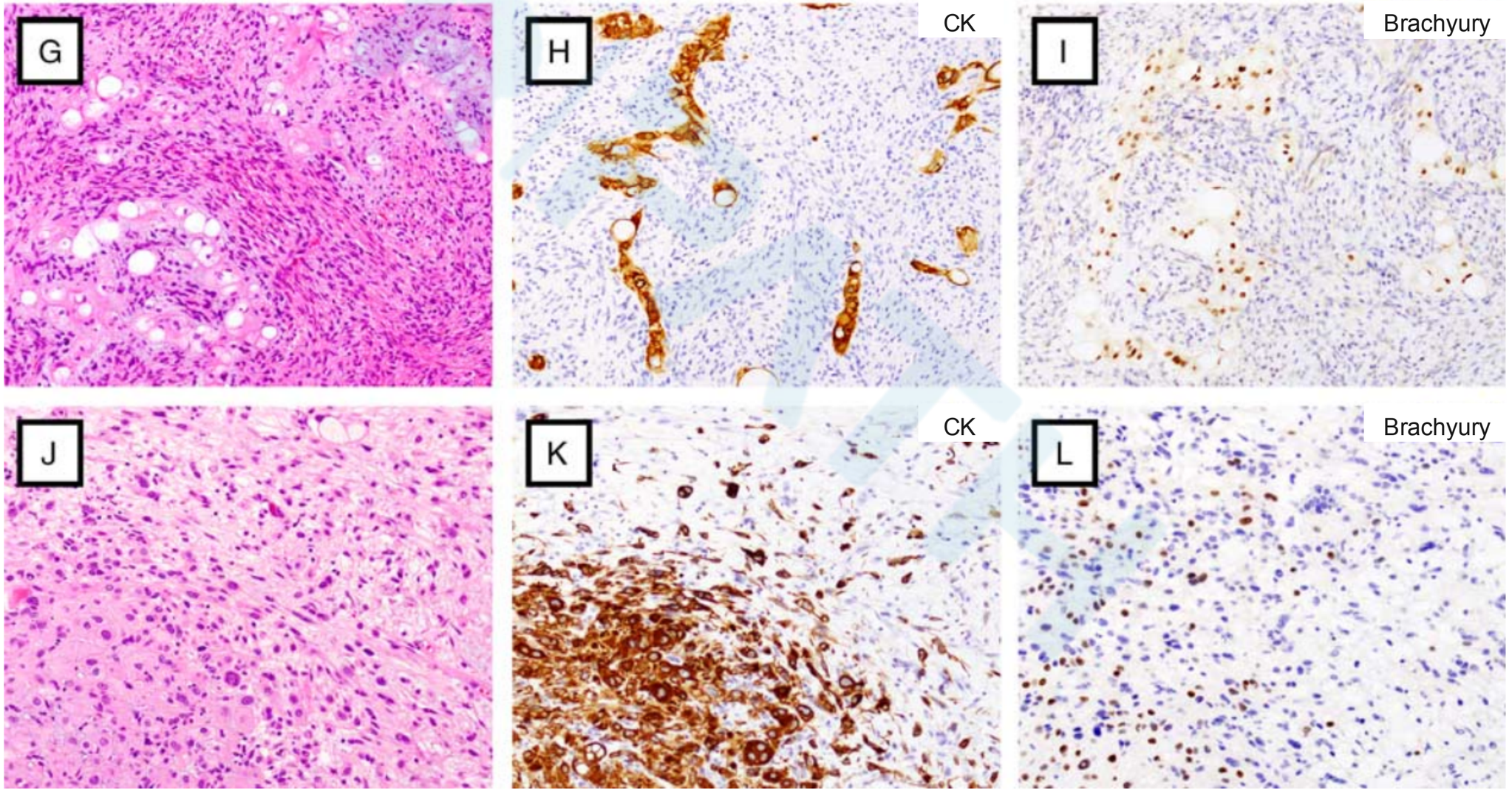
TABLE 1. Clinicopathologic Characteristics of Dedifferentiated Chordoma in This Study and in the Integrative Analysis

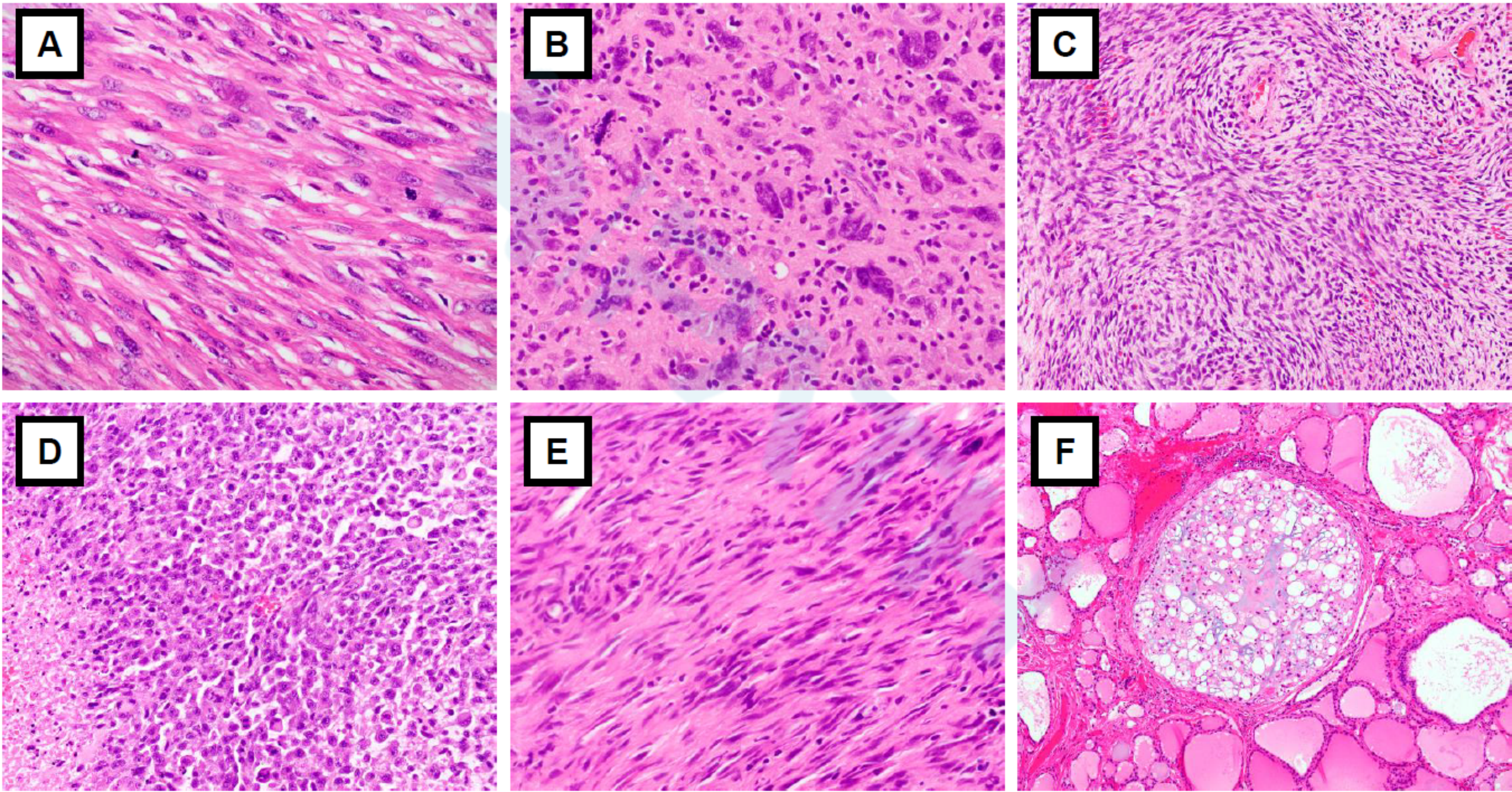
	n (%)		
	This Study (N = 10)	**Prior 45 Studies (N = 77)**	**Combined (N = 87)**
Age			
Median (range)	54 (15-80)	58 (16-81)	58 (15-81)
Sex			
Female	3 (30)	29 (38)	32 (37)
Male	7 (70)	47 (62)	54 (63)
Unknown	—	1	1
Tumor size (cm)			
Median (range)	5.8 (2.8-24.5)	10.0 (5.0-24.0)	10.0 (2.8-24.5)
Dedifferentiation (%)			
Median (range)	60 (3-95)	50 (5-99)	50 (3-99)
Tumor location			
Sacrococcygeal	6 (60)	53 (69)	59 (68)
Lumbar	1 (10)	4 (5)	5 (6)
Cervicothoracic spine/ mediastinum	1 (10)	4 (5)	5 (6)
Skull base	2 (20)	14 (18)	16 (18)
Mobile spine (not otherwise specified)	—	2 (3)	2 (2)
Etiology			
De novo	4 (50)	41 (58)	45 (57)
Prior radiotherapy	3 (38)	21 (30)	24 (30)
Local recurrence	1 (12)	9 (12)	10 (13)
Unknown	2	6	8
Treatment			
Surgical resection	8 (80)	72 (94)	80 (92)
Radiotherapy	5 (50)	31 (40)	36 (41)
Chemotherapy	4 (40)	13 (17)	17 (20)
Metastases (clinical-radiographic)			
All organs	6 (60)	34 (44)	40 (46)
Lungs	5 (50)	24 (31)	29 (33)
Liver	1 (10)	7 (9)	8 (9)
Brain	2 (20)	3 (4)	5 (6)
Patients with metastases sampled			
Conventional component only	1	2	3
Dedifferentiated component only	1	7	8
Both components	1	3	4
Follow-up (mo)			
Median (range)	14.7 (10.1-99.1)	12.0 (0.2-98.0)	12.0 (0.2-99.1)

RESULTS

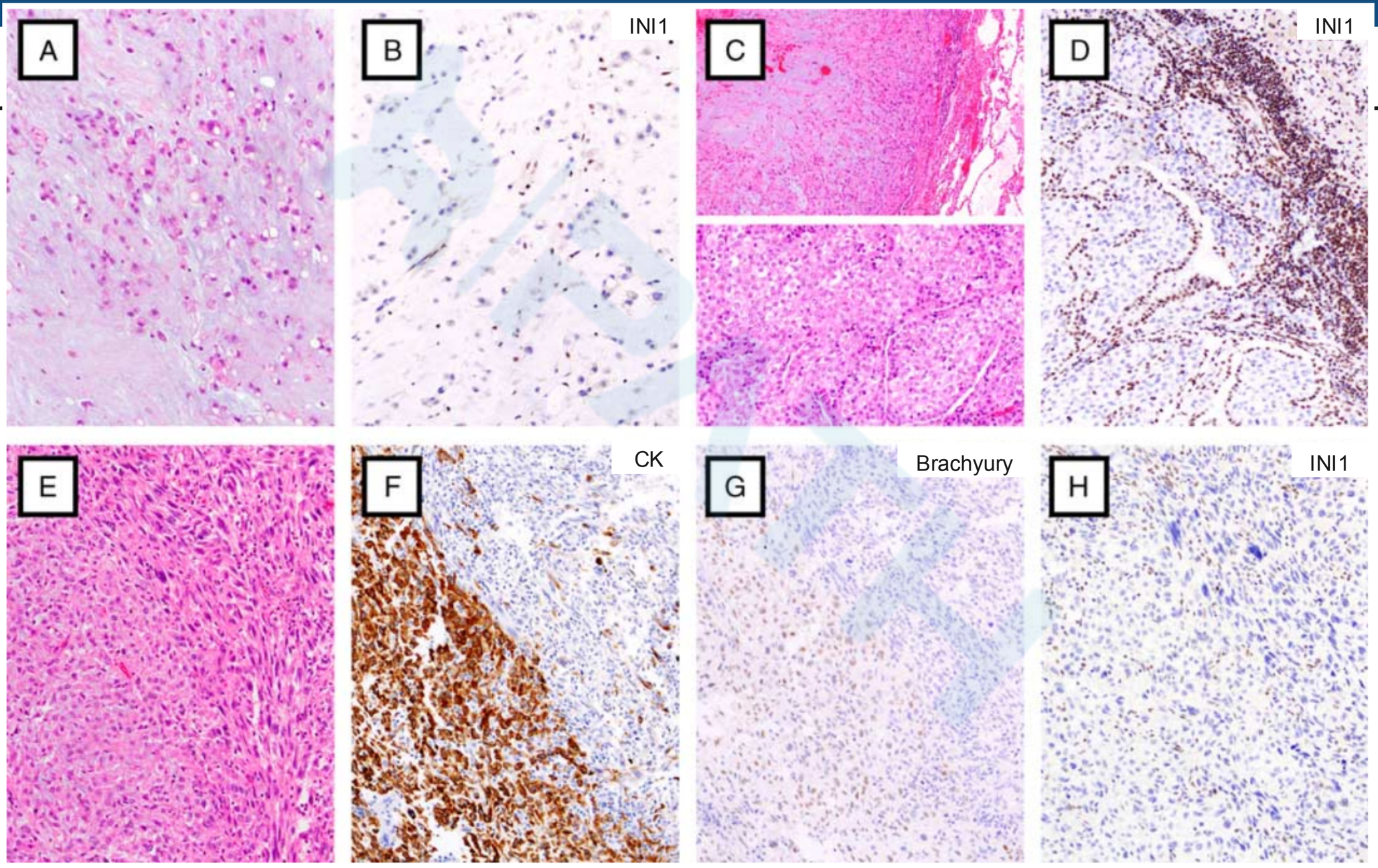


RESULTS




A
B
C
D
E
F

RESULTS



RESULTS

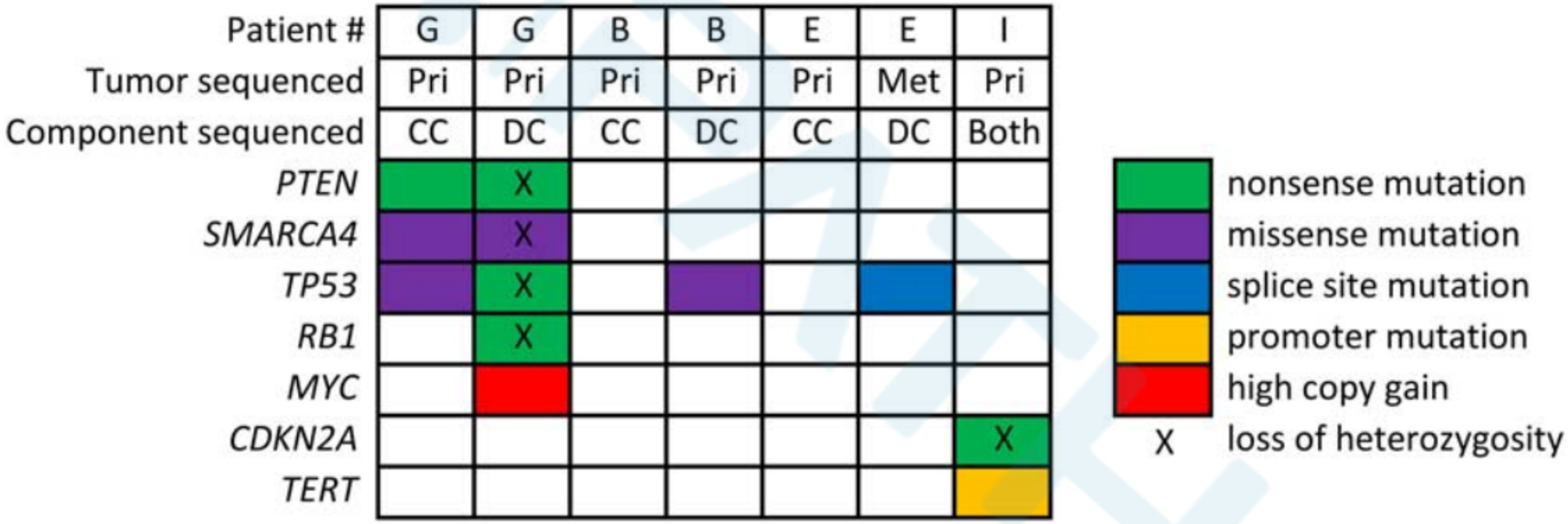


FIGURE 4. Molecular features of dedifferentiated chordomas. Heatmap showing the distribution of single nucleotide and copy number variants in 4 dedifferentiated chordomas, including each component separately in 3 tumors. CC indicates conventional component; DC, dedifferentiated component; Met, metastasis; Pri, primary.

RESULTS

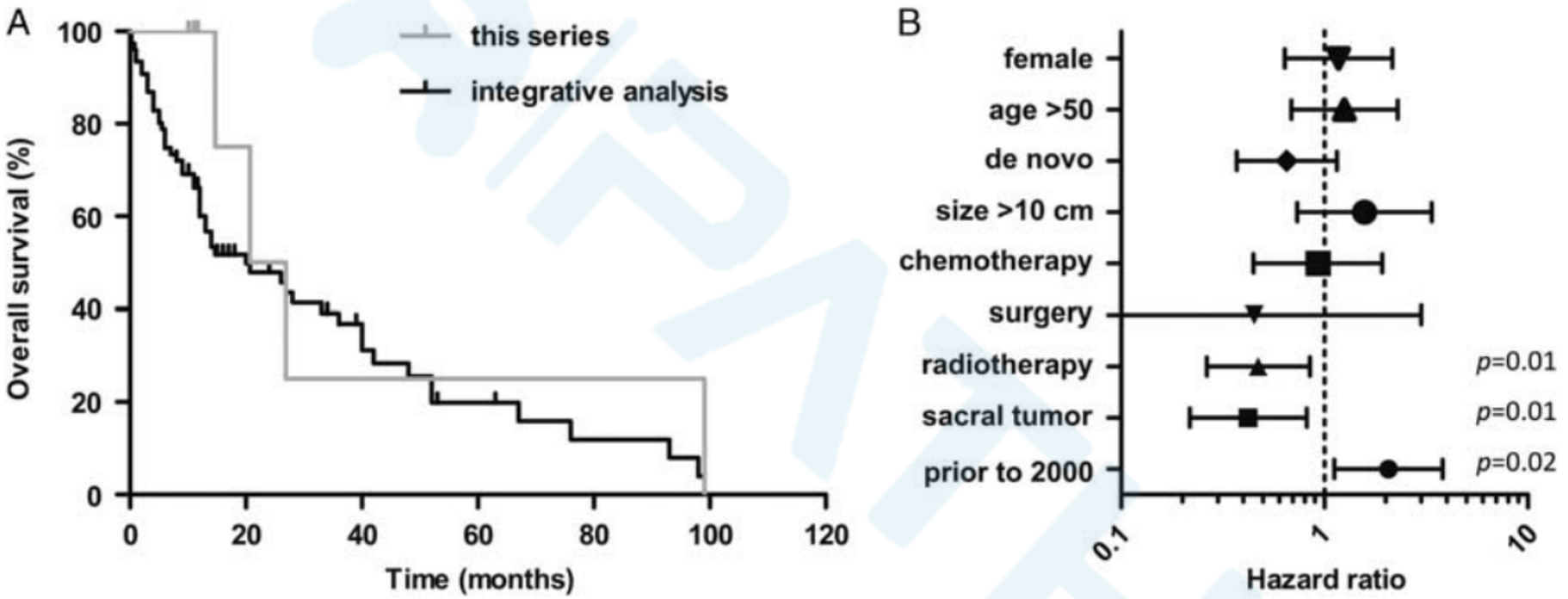
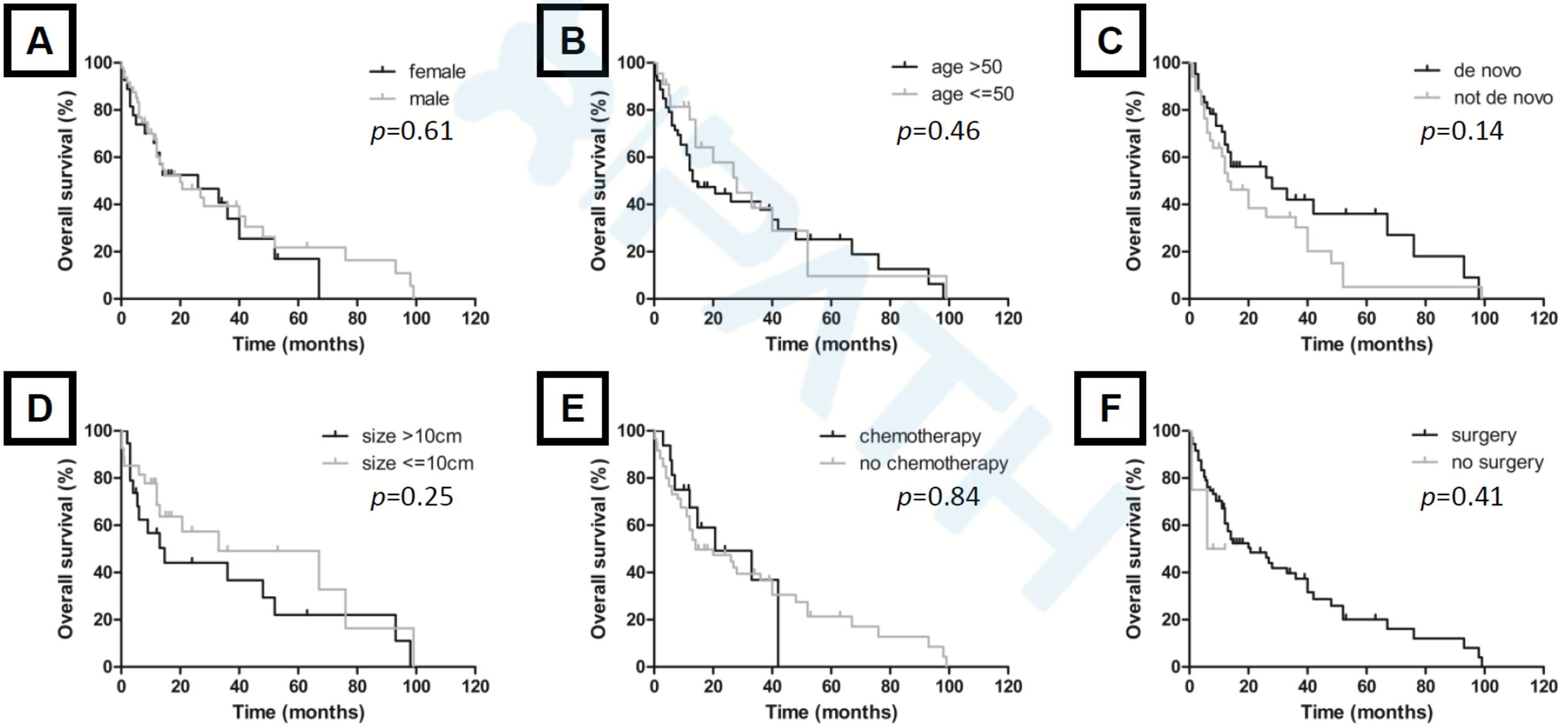
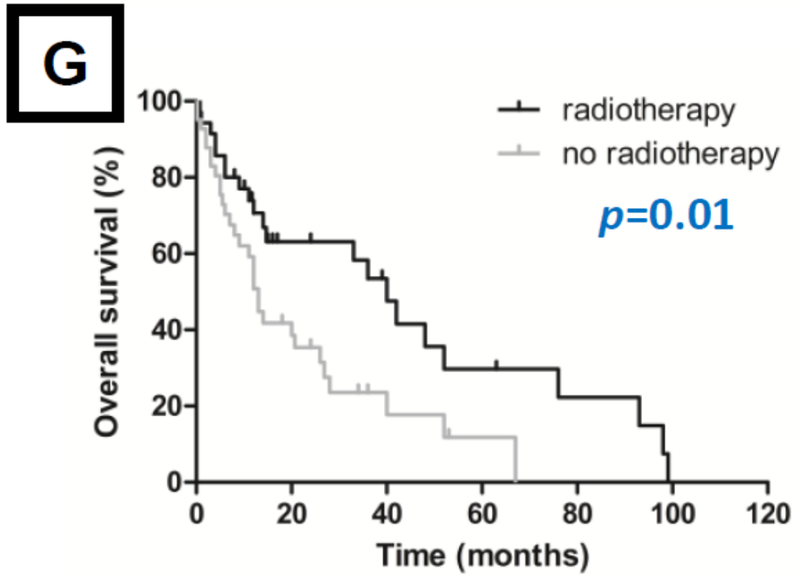


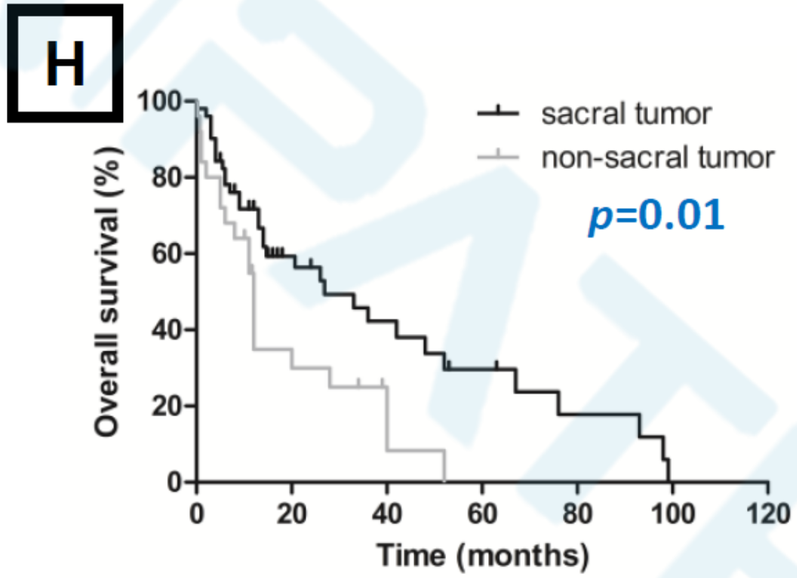
FIGURE 3. Overall survival and association with clinicopathologic factors in dedifferentiated chordomas. A, Kaplan-Meier curves of overall survival in dedifferentiated chordoma patients from this series (gray; n = 7) and the integrative analysis (black; n = 76). B, Forest plot of hazard ratios (range: 95% confidence interval) of clinicopathologic factors for dedifferentiated chordoma patients in relation to overall survival.

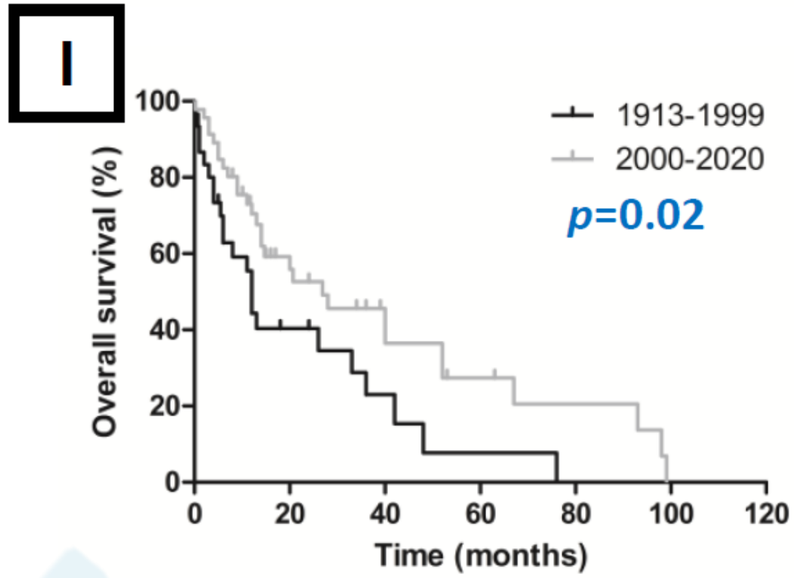
RESULTS


A
Overall survival (%)
Time (months)
female
male
p=0.61
B
age >50
age <=50
p=0.46
C
de novo
not de novo
p=0.14
D
size >10cm
size <=10cm
p=0.25
E
chemotherapy
no chemotherapy
p=0.84
F
surgery
no surgery
p=0.41

RESULTS


G
Overall survival (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
Time (months)
radiotherapy
no radiotherapy
p=0.01


H
Overall survival (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
Time (months)
sacral tumor
non-sacral tumor
p=0.01


I
Overall survival (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
Time (months)
1913-1999
2000-2020
p=0.02

DISCUSSION

DISCUSSION

- ✓ Historically, dedifferentiated chordoma was designated by various nomenclature: “anaplastic chordoma,” “sarcomatoid chordoma,” “malignant chordoma,” “malignant fibrous histiocytoma” arising in a chordoma, chordoma with “sarcomatous features (spindle cell metaplasia),” chordoma with “sarcomatous transformation,” and chordoma with “malignant spindle cell component.”
- ✓ In the 2020 (fifth edition) WHO classification, chordoma composed of high-grade sarcoma juxtaposed to a conventional or chondroid component is designated dedifferentiated chordoma.

DISCUSSION

- ✓ Dedifferentiated chordoma *vs.* Radiation-associated sarcoma：Radiation-associated sarcoma is defined as a sarcoma that arises in proximity to the radiation field, at least 6 months after radiotherapy cessation, and differs histologically from the primary malignancy.
- ✓ Dedifferentiated chordoma *vs.* other primary bone sarcomas：Other primary bone sarcomas can also mimic the dedifferentiated component of dedifferentiated chordoma. Radiologic correlation with appropriate sampling to identify the conventional component will aid the diagnosis of dedifferentiated chordoma.

DISCUSSION

- ✓ Dedifferentiated chordoma *vs.* conventional chordoma with prominent spindling:

  conventional chordoma showing gradual transition and retained cytokeratin /brachyury staining even in the spindled areas. The dedifferentiated component is overtly malignant with loss of both cytokeratin and brachyury, which would not be seen in conventional chordoma, even with prominent spindling.

DISCUSSION

Dedifferentiated chordoma *vs.* poorly differentiated chordoma

- ✓ Histologically, poorly differentiated chordoma displays epithelioid cells, lacking myxoid stroma or “physaliferous” cells as in conventional chordoma, and does not manifest the biphasic appearance with frank sarcomatous areas as in dedifferentiated chordoma.
- ✓ Immunophenotypically, poorly differentiated chordoma expresses keratin and brachyury with characteristic loss of INI1.

DISCUSSION

Brachyury

- ✓ Given that brachyury is implicated in the pathogenesis of chordoma, which commonly harbors somatic duplications with low-copy gains of *TBXT* that encodes brachyury, the consistent expression loss of brachyury in the dedifferentiated component noted herein and in the literature is intriguing.
- ✓ These findings suggest that driver gene alterations that are critical in tumor initiation and progression may not be involved in tumor dedifferentiation and high-grade transformation.

DISCUSSION

Mechanisms

- ✓ First, in cases with prior radiotherapy, the dedifferentiated component may represent radiation-induced de novo sarcoma.
- ✓ Second, dedifferentiated chordoma may represent a collision tumor of 2 genetically unrelated tumors. Nevertheless, metastases from dedifferentiated chordoma can harbor conventional, dedifferentiated, or both components, suggesting that the biphasic histology is intrinsic.

DISCUSSION

Mechanisms

- ✓ Third, the dedifferentiated component may represent *bona fide* dedifferentiation, with continual tumor evolution derived directly from the conventional component.
- ✓ Fourth, analogous to what was found in dedifferentiated chondrosarcoma, the 2 components in dedifferentiated chordoma may share a monoclonal origin with subsequent clonal divergence.

DISCUSSION

limitations

- ✓ The molecular mechanisms for INI1 expression loss in that 1 case of sacral conventional chordoma and its subsequent lung metastases remain unknown. The sequencing assay covered only portions of SMARCB1 (exons 2, 4, 5, and 9), with no copy number alterations or mutations.
- ✓ Also, we could not address the contribution of radiotherapy in the pathogenesis of dedifferentiated chordoma.

CONCLUSION

- ✓ Dedifferentiated chordoma is rare and aggressive, involves diverse sites (frequently sacrum), and presents de novo, postradiotherapy, or as recurrence/metastases months-to-years after the initial diagnosis.
- ✓ Histologically, dedifferentiated chordoma is characterized by the presence of both conventional and high-grade sarcoma components, which intermix or juxtapose to each other with abrupt to gradual transitions.

CONCLUSION

- ✓ We identified an unusual sacral conventional chordoma showing complete INI1 loss with one of the subsequent lung metastases showing dedifferentiation.
- ✓ The dedifferentiated component consistently shows loss of brachyury and cytokeratin staining and harbors recurrent TP53 mutations, which implicate dysregulation of tumor suppressors in chordoma dedifferentiation and potential therapeutic targets.

THANK YOU

感谢聆听