北京儿童医院
BEIJING CHILDREN'S HOSPITAL

儿童非霍奇金淋巴瘤的中枢神经系统侵犯及治疗对策

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关于CNS的问题

- CNS复发占NHL发病人的50%以上
- CNS侵犯的好发因素？预后怎样？
- 如何有效的预防CNS复发？
- 鞘内注射多少次合适？
- HD-MTX必须用吗？
- 需要做CNS放疗吗？
- 目前应用的靶向治疗及CAR－T等新疗法对CNS有效吗？

儿童NHL的CNS侵犯

- 儿童NHL：BL、 LBL、DLBCL、ALCL等
- 均高恶性、高侵袭性
- 初诊时CNS侵犯发生率约为4~29%，大多5~10%
- CNS侵犯发生的时间：

  初诊时21%，诱导期13%，缓解期56%

  停药后 10%

不同病理类型CNS侵犯发生率

- BL：8.8%（18.8%）
- B-LBL / B-ALL：5.4%（7.8%）
- T - LBL： 4.0% （11.4%）
- ALCL：3.3%
- DLBCL： 2.6%
- HL：低于0.5%

以BL和LBL最易发生CNS侵犯

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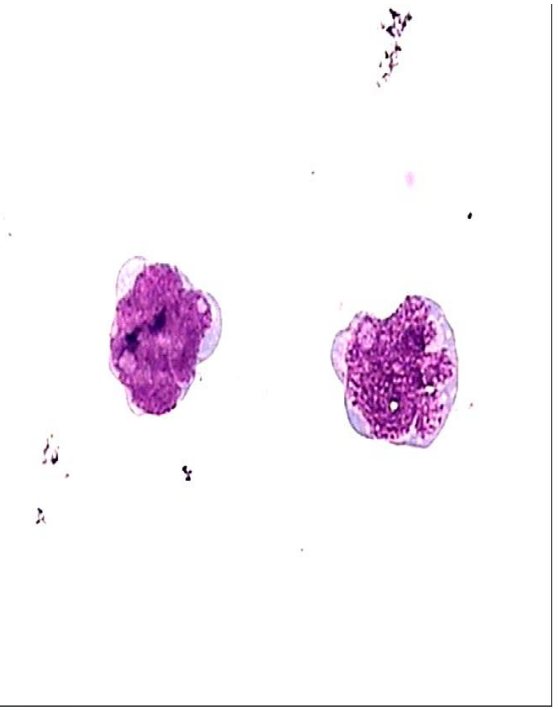
不同病理类型CNS侵犯

- BL发生CNS侵犯的危险性最大
- LBL介于BL与大细胞性淋巴瘤之间
- 大细胞性淋巴瘤CNS侵犯发生率低于5%
- BL、LBL以脑膜侵犯多见
- ALCL、DLBCL以脑实质受累多见

J Clin Oncol 25:3915-3922. © 2007

CNS侵犯的相关检查

- 常规脑脊液细胞学检查找瘤细胞是诊断CNS浸润的标准方法
- 脑膜侵犯患者脑脊液特点``
  - 脑脊液压力增高
  - 蛋白增高
  - 糖降低
  - 找到瘤细胞



CNS侵犯的相关检查

- 脑水流式细胞检测技术：免疫标志，敏感度为单纯细胞形态学检测的2-8倍以上，NCCN推荐为常规检查
- 脑水PCR检测方法：检测肿瘤细胞免疫球蛋白或是T细胞受体的基因

—可提高脑脊液肿瘤细胞的早期检出率20-30%

J Clin Transfus Lab Med, Jan. 2009, vol

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影像学检查

- 影像学检查对了解有无CNS尤其是脑实质侵犯起到了重要作用
- 检查手段：
  - CT
  - MRI（最佳检查手段）
  - PET-CT（CNS显影相对差）
  - PET—MR

Pediatr Blood Cancer 2014;61:1416–1421

Clinical Features and Early Treatment Response of Central Nervous System Involvement in Childhood Acute Lymphoblastic Leukemia

Mette Levinsen, MD,[1] Mervi Taskinen, MD, PhD,[2] Jonas Abrahamsson, MD, PhD,[3] Erik Forestier, MD, PhD,[4] Thomas L. Frandsen, MD, PhD,[1] Arja Harila-Saari, MD, PhD,[5] Mats Heyman, MD, PhD,[6] Olafur G. Jonsson, MD,[7] Päivi M. Lähteenmäki, MD, PhD,[8] Birgitte Lausen, MD, PhD,[1] Goda Vaitkevičienė, MD, PhD,[1,9] Ann Åsberg, MD, PhD,[10] and Kjeld Schmiegelow, MD, PhD,[1,11]* on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO)

Background. Central nervous system (CNS) involvement in childhood acute lymphoblastic leukemia (ALL) remains a therapeutic challenge. ***Procedure.*** To explore leukemia characteristics of patients with CNS involvement at ALL diagnosis, we analyzed clinical features and early treatment response of 744 patients on Nordic-Baltic trials. CNS status was classified as CNS1 (no CSF blasts), CNS2 (<5 leukocytes/μl CSF with blasts), CNS3 (≥5 leukocytes/μl with blasts or signs of CNS involvement), TLP+ (traumatic lumbar puncture with blasts), and TLP− (TLP with no blasts). ***Results.*** Patients with CNS involvement had higher leukocyte count compared with patients with CNS1 ($P<0.002$). Patients with CNS3 more often had T-ALL ($P<0.001$) and t(9;22)(q34;q11)[*BCR-ABL1*] ($P<0.004$) compared with patients with CNS1. Among patients with CNS involvement headache (17%) and vomiting (14%) were most common symptoms. Symptoms or clinical findings were present among 27 of 54 patients with CNS3 versus only 7 of 39 patients with CNS2 and 15 of 75 patients with TLP+ ($P<0.001$). The majority of patients with CNS involvement received additional induction therapy. The post induction bone marrow residual disease level did not differ between patients with CNS involvement and patients with CNS1 ($P>0.15$). The 12-year event-free survival for patients with leukemic mass on neuroimaging did not differ from patients with negative or no scan (0.50 vs. 0.60; $P=0.7$) or between patients with symptoms or signs suggestive of CNS leukemia and patients without such characteristics (0.50 vs. 0.61; $P=0.2$). ***Conclusion.*** CNS involvement at diagnosis is associated with adverse prognostic features but does not indicate a less chemosensitive leukemia. Pediatr Blood Cancer 2014;61:1416–1421.
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Key words: ALL; chemotherapy; minimal residual disease

具有高白细胞计数、T-ALL、Ph1染色体阳性具有CNS复发的高风险
有CNS侵犯的病人化疗敏感性并不低于CNS1病人
有CNS侵犯的病人远期EFS并不低于CNS1病人

淋巴瘤CNS侵犯的危险因素

- 临床分期III~IV期
- 病理类型：BL、LBL
- 骨髓浸润(>25%)
- T细胞表型
- 高肿瘤负荷：巨大瘤块、高白细胞、浸润器官超过4个
- 头面部侵犯（CNS2）
- 超高LDH

Table 1. Characteristics of the Included Trials

Group	Trial (Years of Recruitment)	No. of Patients	CRT		SCT	
			% of Patients	Indications	Percent of Patients	Indications
AIEOP	ALL 2000 (2000-2006)	1,999	18	CNS3*, t(4;11) T cell with WBC > 100×10^9/L, T cell and B cell with slow early response (prednisone poor response) or no CR at day 33 or high-risk MRD ($\geq 5 \times 10^{-4}$) at week 12	4	t(4;11); slow early response (prednisone poor response) and WBC > 100×10^9/L or T cell or pro-B or MRD $\geq 5 \times 10^{-3}$ at day 33; no CR at day 33; high risk MRD ($\geq 5 \times 10^{-4}$) at week 12
BFM	ALL 2000 (2000-2007)	3,582	18	CNS3*, t(4;11) T cell, B cell with slow early response (prednisone poor response) or no CR at day 33 or high risk MRD ($\geq 5 \times 10^{-4}$) at week 12	5	t(4;11); slow early response (prednisone poor-response) and WBC > 100×10^9/L or T cell or pro-B or M3 BM at day 15; no CR at day 33; high-risk MRD ($\geq 5 \times 10^{-4}$) at week 12
COALL	06-97 and 07-03 (1997-2003)	910	12	CNS3 for both protocols. For 06-97: T cell and B cell with WBC > 100×10^9/L. For 07-03: T cell with WBC > 50×10^9/L, B cell with WBC > 200×10^9/L and with WBC 100-200 $\times 10^9$/L and > 1×10^9/L blasts in the PB after prophase	4	For 06-97: no remission at day 29, t(4;11) high-risk patients and high (8 + 9) score for in vitro responsiveness to PVA. For 07-03: no remission at day 29, t(4;11)
COG	POG 9900 (B-ALL; 1999-2005)† and POG 9404 (T-ALL; 1996-2001)	3,182	15	T-ALL: all patients; CNS3	3	M3 BM at end induction or hypodiploid ALL (not included in these analyses)
DCOG	ALL9 (1997-2004)	859	0	Standard no CRT	3	*MLL* positive
JACLS	ALL02 (2002-2008)	1,246	10	CNS3, T cell with WBC > 100×10^9/L	5	Slow early response, induction failure, M3 BM at day 15 in high-risk patients, *MLL* positive, < 44 chromosomes
NOPHO	ALL 2000 (2002-2008)	1,082	14	CNS3, T cell with mediastinal mass, T cell and B cell with WBC 100-200 $\times 10^9$/L; for all, only if age > 5 years at diagnosis	6	WBC $\geq 200 \times 10^9$/L, slow response with no CR at end of induction (M3 bone marrow at day 29), *MLL* positive if ≥ 10 years, < 34 chromosomes
SJCRH	Total Therapy Study XV (2000-2007)	488	0	Standard no CRT	5	Induction failure or > 1% leukemic lymphoblasts in the bone marrow on remission date, > 0.1% leukemic lymphoblasts in the BM in week 7 of continuation treatment, re-emergence of leukemic lymphoblasts by MRD in patients previously negative for MRD
UK	ALL 2003 (2003-2011)	2,783	2	CNS3	2	t(17:19), *MLL* positive, < 44 chromosomes and M2 BM at day 28, M3 BM at day 28
DFCI	00-01 (2000-2004)	492	33	T cell and B cell with CNS3 and/or WBC > 100×10^9/L	2	Induction failure (M2 or M3 BM at end of first month of treatment)

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5-year Outcome

Table 3. Five-Year Summary Outcomes From Meta-Analyses According to Pre-emptive CRT for Subgroups Other Than CNS3 at Diagnosis

	B Cell, WBC > 100 × 10^9/L			T Cell, WBC > 100 × 10^9/L			B Cell, Slow Early Response			T Cell, Slow Early Response		
	CRT			CRT			CRT			CRT		
Outcome	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
5-year cumulative incidence, %												
Death (100% minus survival)	21.6	17.5	.49	27.2	19.0	.15	12.0	16.5	.36	36.3	24.7	.02
Any event (100% minus EFS)	37.0	27.4	.08	34.3	24.4	.08	22.0	26.0	.48	46.4	35.4	.19
BM relapse	17.4	15.6	.67	7.6	8.4	.88	13.2	14.7	.61	14.7	12.4	.65
Isolated CNS relapse	1.6	3.3	.32	5.4	6.6	.69	0.9	1.8	.40	4.5	2.8	.44
Any CNS relapse	3.8	6.0	.35	11.0	10.0	.77	1.9	3.8	.19	8.6	4.2	.25
No. of studies	3	6		7	3		2	5		4	4	
No. of patients	141	594		596	248		300	652		353	166	

NOTE. Even though it is not indicated for the subgroup overall, some patients within the subgroup received CRT for specific indications (eg, CNS3 or slow early response or minimal residual disease high-risk status in AIEOP-BFM 2000).

Abbreviations: AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster; BM, bone marrow; CNS3, overt CNS involvement; CRT, cranial radiotherapy; EFS, event-free survival.

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CNS复发的危险因素

- 白血病期首次损伤性腰穿
- 诊断时存在CNS侵犯
- 首次鞘注延迟（强调先于化疗）
- 其它基因：CCR7/CXCR4

The role of ZAP70 kinase in acute lymphoblastic leukemia infiltration into the central nervous system

- 在急性淋巴细胞白血病患儿中
  - zeta-chain-associated protein kinase 70（ZAP70），在中枢神经系统侵犯者的表达>>无中枢神经系统侵犯者
  - ZAP70通过激活细胞外传导途径，可提高CCR7/CXCR4的水平
  - 本文收集了130例B急淋及117例T急淋
  - ZAP70与B急淋中枢侵犯相关
  - CCR7/CXCR4与T急淋中枢神经系统侵犯相关
  - 多因素分析显示
    - （1）在B急淋中，中枢侵犯的危险因素中， ZAP70占第三/四位（OR=7.48）
    - （2）在T急淋中，中枢侵犯的危险因素中，CCR7占第四位（OR=11%）
  - 结论
    - 建议把ZAP70和CCR7/CXCR4作为急性淋巴瘤细胞白血病合并中枢侵犯的危险因素

Martin, HEMATOLOGY, 2017

CNS有效治疗

- 与危险度相关的有效系统化疗（包括Dex,HD－MTX及HD－Ara-C)
- 针对CNS定向治疗
  - **鞘内注射**
  - **颅脑放疗**

----儿童ALL/LBL、BL的5-EFS升至80%

CNS复发率由未预防时的30-65%降至8%以内

CNS 有效治疗

- 包含有具有良好CNS渗透性药物的系统化疗
  - Dex
  - HD-MTX
  - HD-Ara-c
  - L-ASP
- 鞘内注射
  - 三联鞘注优于单联鞘注
  - 开始化疗后鞘注时间
  - 对存在危险因素者增加鞘注次数、缩短间隔

Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead

- 儿童LBL最好的治疗方案是选择类似于ALL的方案
  - 这些方案在LSA2L2的基础上逐渐去除了CNS的放疗，而加用了HDMTX 来预防CNS的侵犯
  - 方案采用了多种化疗药物，同时追加了维持治疗，总疗程达2年
  - CNS 预防的一个重要组成部分就是HDMTX 和/或 IT
  - Pediatric Oncology Group56 and COG60 研究显示在LBL中HDMTX的重要性
  - 应用足够熟悉的IT or HDMTX 来预防CNS复发
  - HDMTX在对LBL的全身系统性治疗中的作用不及BL

Patte, Jounal of clinical oncology 2015

颅脑放疗

- 对CNS预防和治疗的疗效肯定
- 副作用
  - 近期：疲劳、血象降低、
    恶心呕吐、皮疹、皮肤剥脱、脑水肿等
  - 远期：听力障碍、学习行为障碍、多发内分泌腺体病、第二肿瘤等

----为提高生存质量，尽可能减低放疗剂量
或剔除颅脑放疗

国际多个中心已经完全取消了颅脑放疗，包括原发于CNS的淋巴瘤

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Age 18 in London with friends

Impact of Cranial Radiotherapy on Central Nervous System Prophylaxis in Children and Adolescents With Central Nervous System–Negative Stage III or IV Lymphoblastic Lymphoma

- 在NHL-BFM-95方案中，对于Ⅲ-Ⅳ期，不伴有中枢神经系统侵犯的淋巴母细胞瘤病人，去除预防性颅脑放疗的治疗，比较该方案与NHL-BFM-90/86的疗效
  - 在95方案中，共纳入156例病人，平均年龄8.6岁，平均随访时间5.1年，2年&5年的PFS分别为86 ±3% and 82 ±3%，5年DFS88 ± 3%
  - 在90/86方案中，共纳入163例病人，平均年龄8.4岁，平均随访时间10.7年， 2年&5年的PFS分别为91 ±2% and 88 ±3%， 5年DFS91 ± 2%
- 结论
  - 对于Ⅲ-Ⅳ期，不伴有中枢神经系统侵犯的淋巴母细胞瘤病人，去除预防性颅脑放疗的治疗，其疗效无明显下降

Birgit Burkhardt, JOURNAL OF CLINICAL ONCOLOGY ,2006

Influence of Cranial Radiotherapy on Outcome in Children With Acute Lymphoblastic Leukemia Treated With Contemporary Therapy

- 本文收集了从1996年-2007年全世界10个中心的16623例病人
  - 年龄1-18岁不等
  - 不同中心，颅脑预防性放疗分别占0-33%
  - 通过单臂Meta分析，比较增加颅脑放疗对于中枢复发的影响，比较其OS，CNS复发率
  - 增加颅脑放疗，仅仅能够降低病初诊断时CNS+者单纯CNS复发率(4% 颅脑放疗组vs.17% 无颅脑放疗组，P=0 .02），但该组（病初CNS+）无论是否增加放疗，发生事件率均较高（ 32% VS. 34% ，P=0.8）
  - 结论：在儿童急性细胞白血病／淋巴瘤现阶段治疗方案中，颅脑放疗并不能影响其复发率

Martin, Clinical Oncology, 2016

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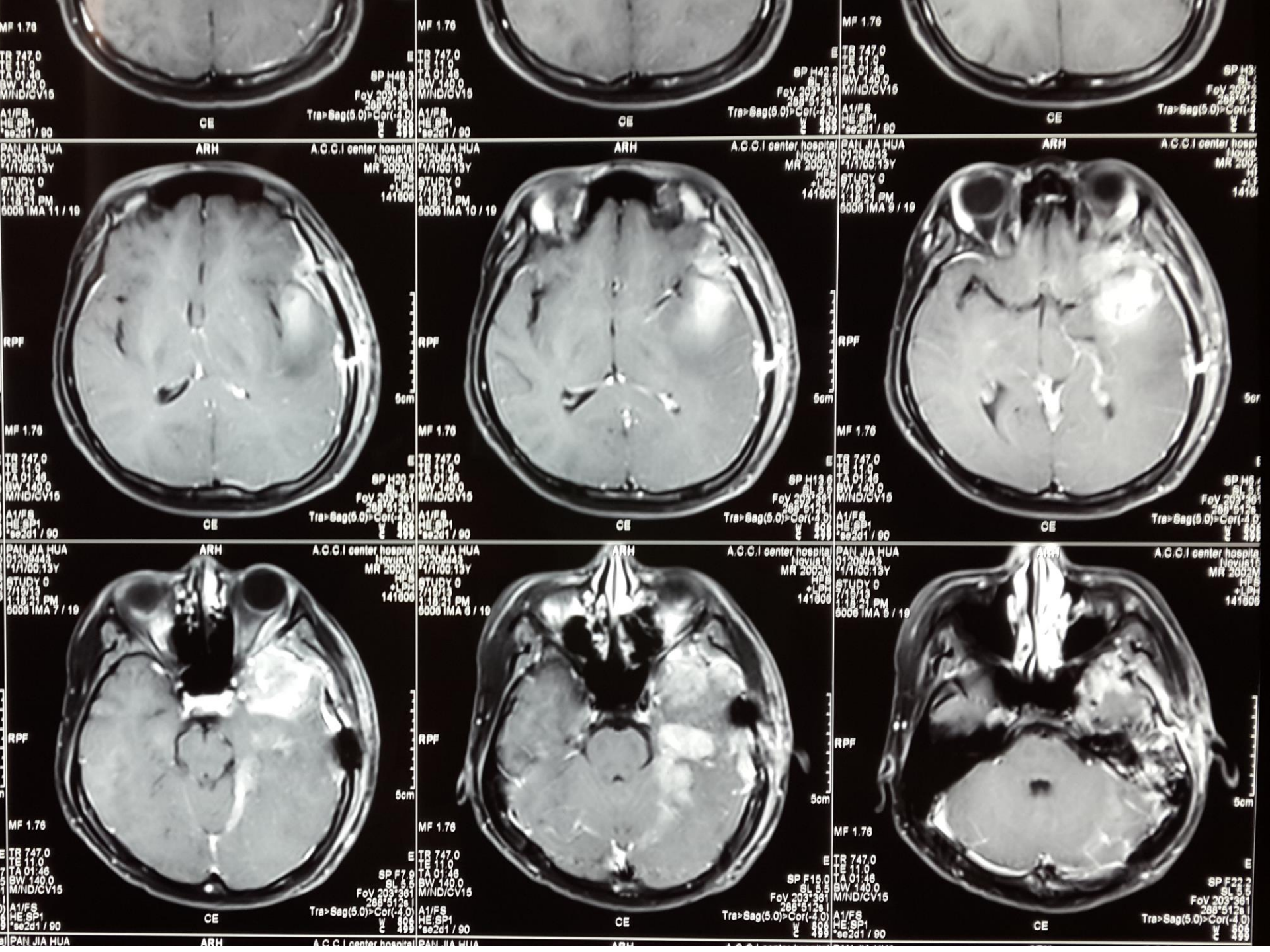
NHL侵犯及PCNSL可以取消放疗吗？

PCNSL Case Report

- XXX 男 13 岁
- 主诉：头痛3个月，进行性加重
- 当地医院行头颅MR发现占位，大小35×34×23mm
- 您如北京天坛医院
- 检查其它部位未发现占位
- 开颅手术行肿瘤切除
- 术后病理提示淋巴瘤转入医科院肿瘤医院
- 免疫组化 Ki-67(95%+) CD20,CD79a,Bcl-6,CD10阳性 Bcl-2,CD3TdT,MPO,CD56,CD99,CK,CgAEMA,GFAP,NSE,Olig-2,Vimentin均阴性
- 病理提示Burkitt转入北京儿童医院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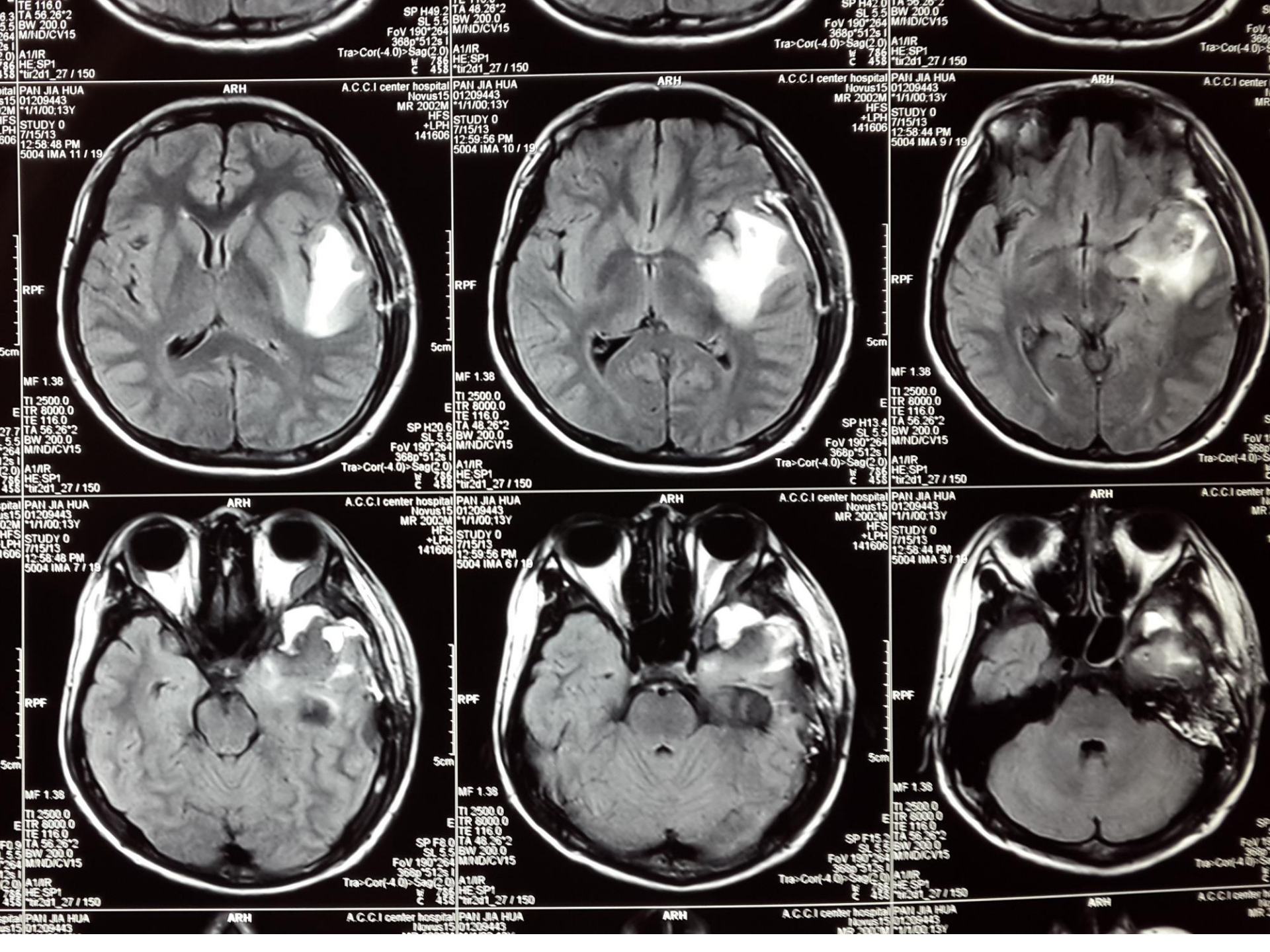
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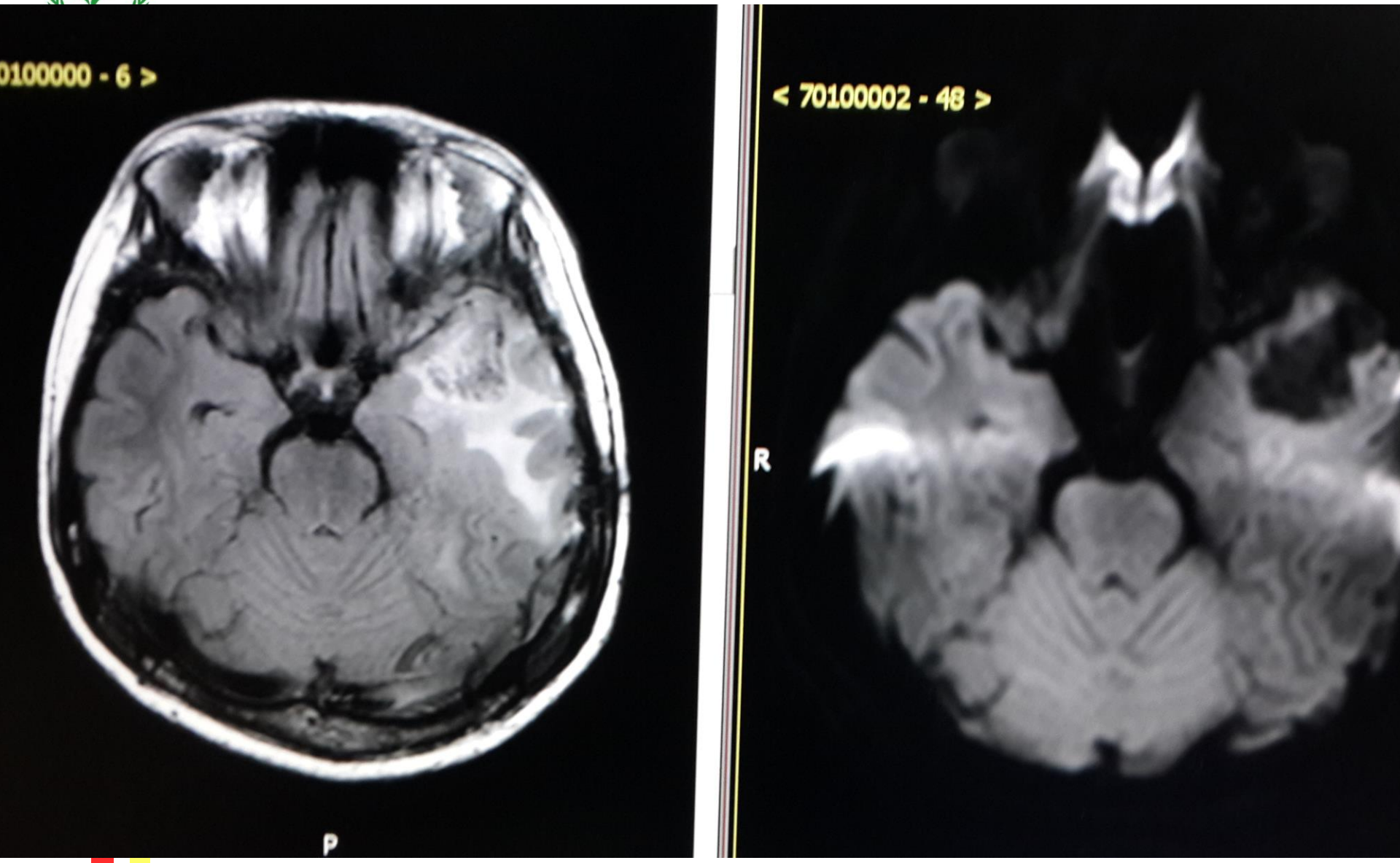
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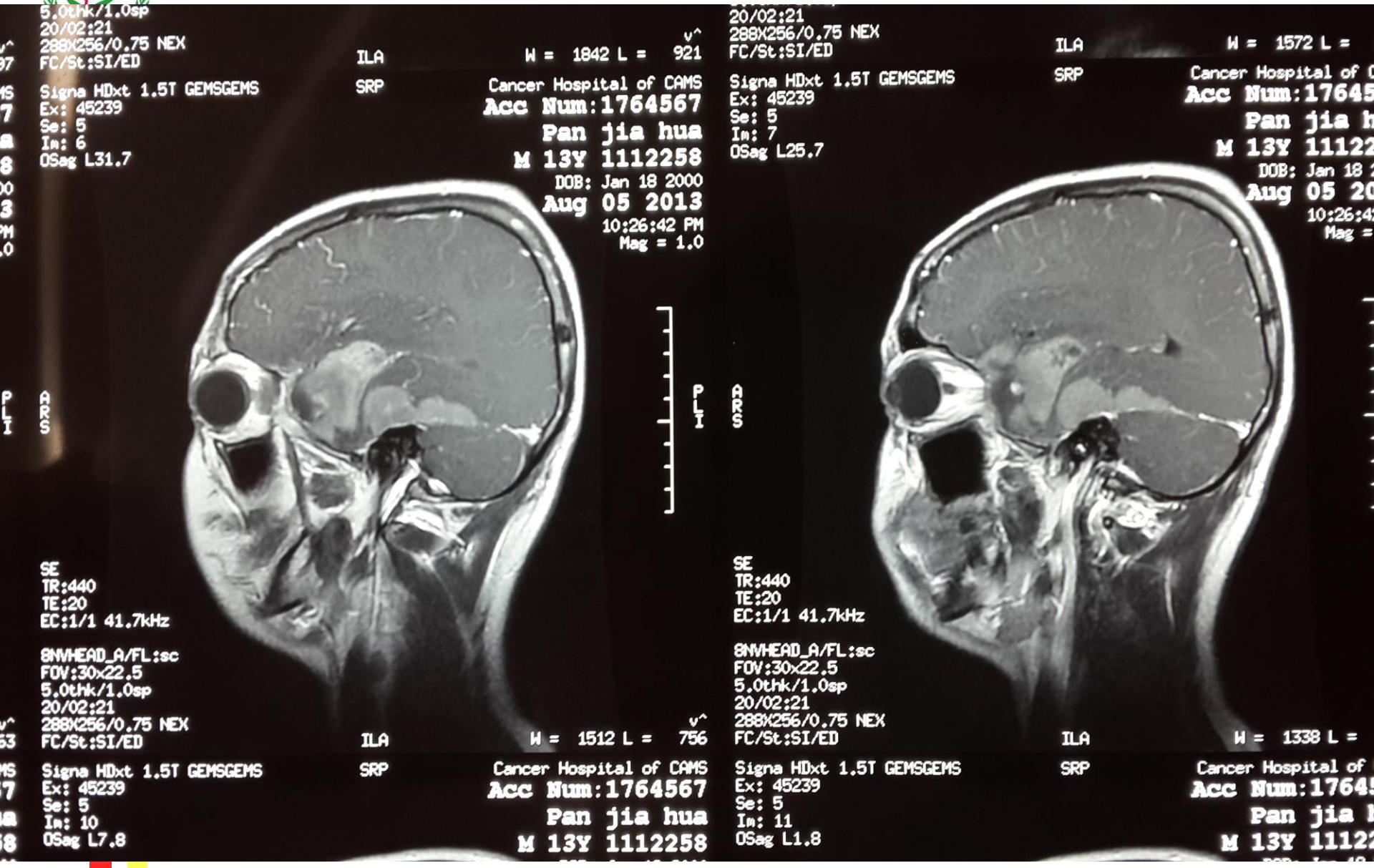
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SRP
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Acc Num:1764567
Pan jia hua
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ILA
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M 13Y 1112

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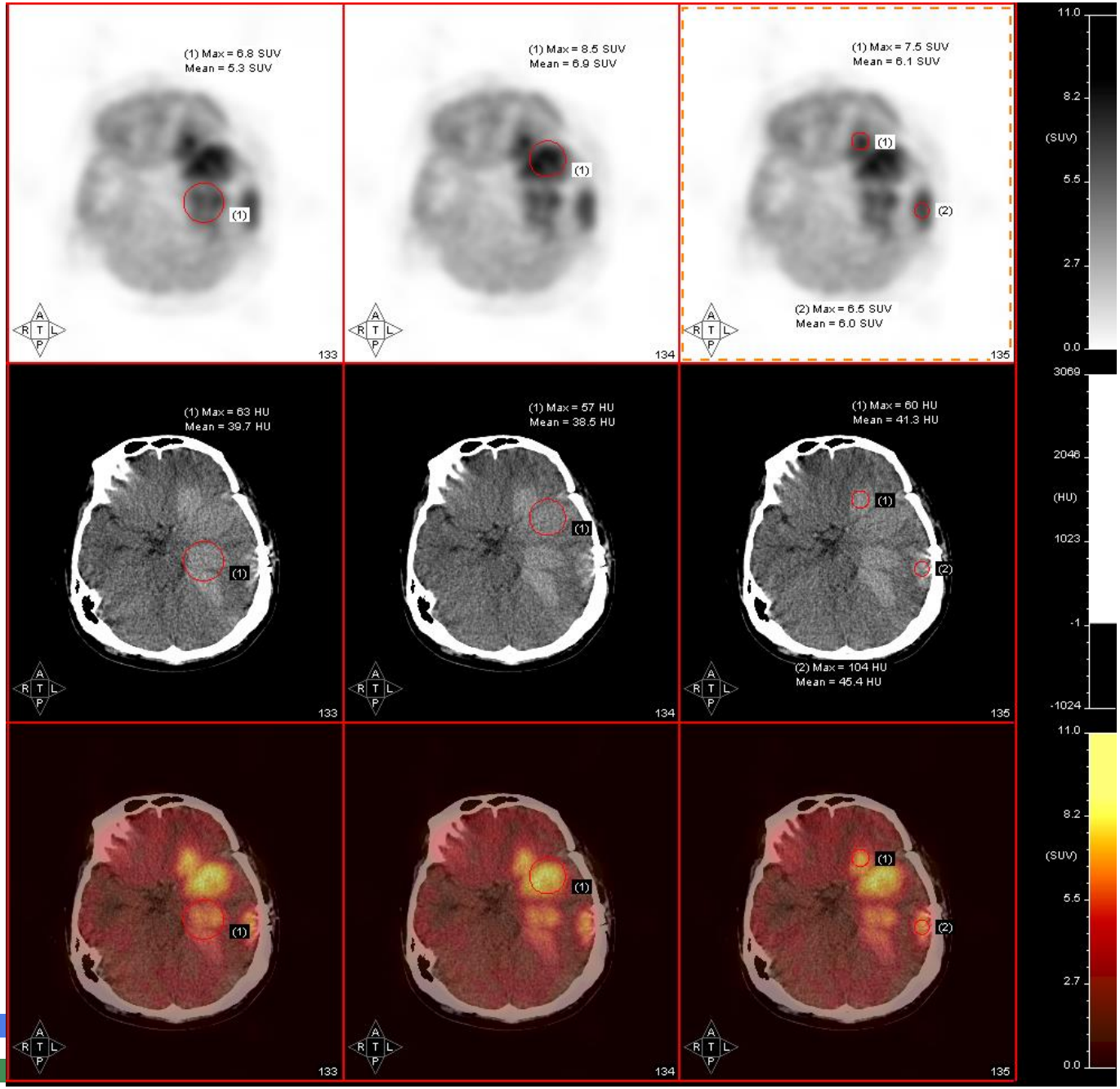

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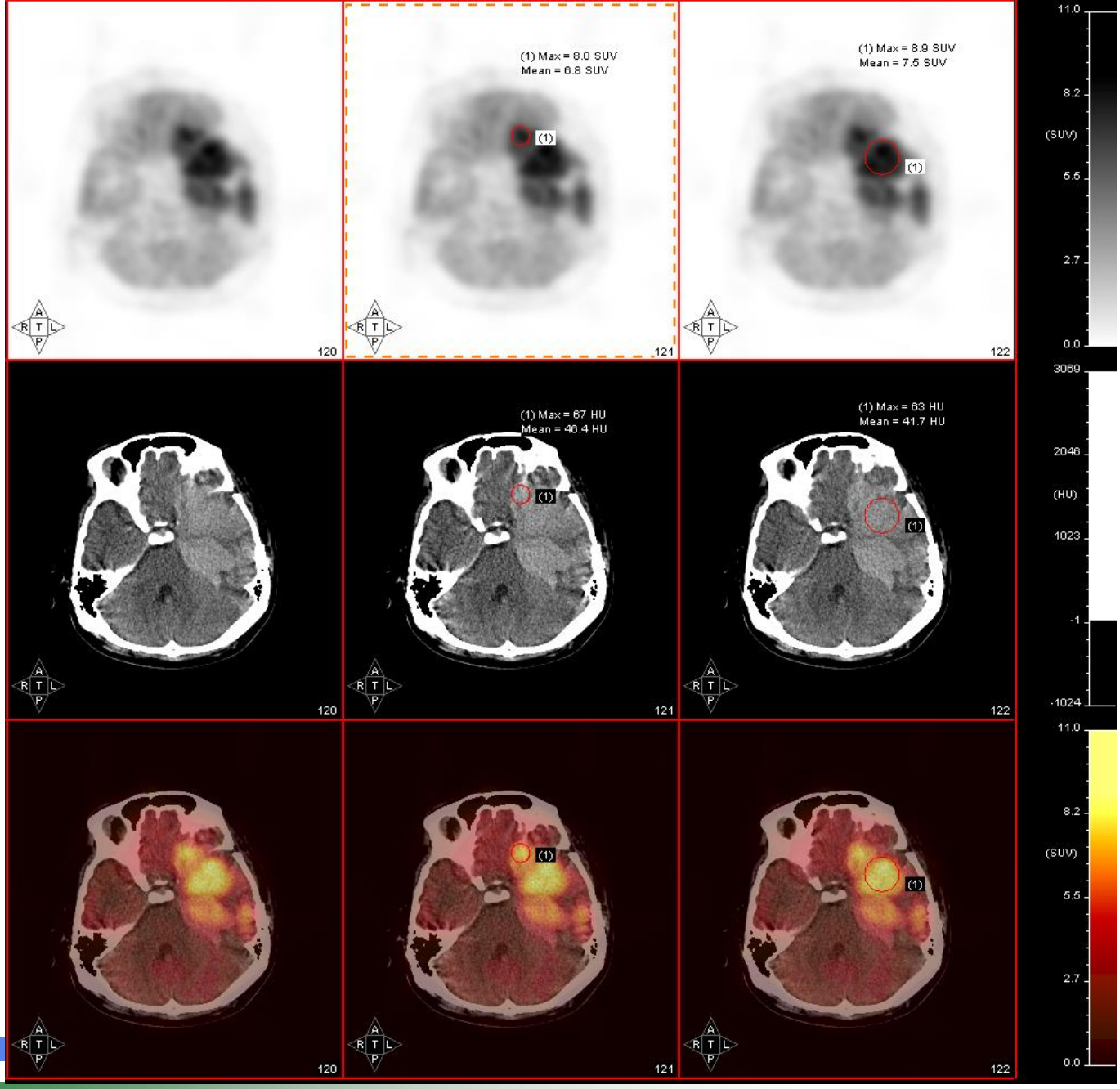

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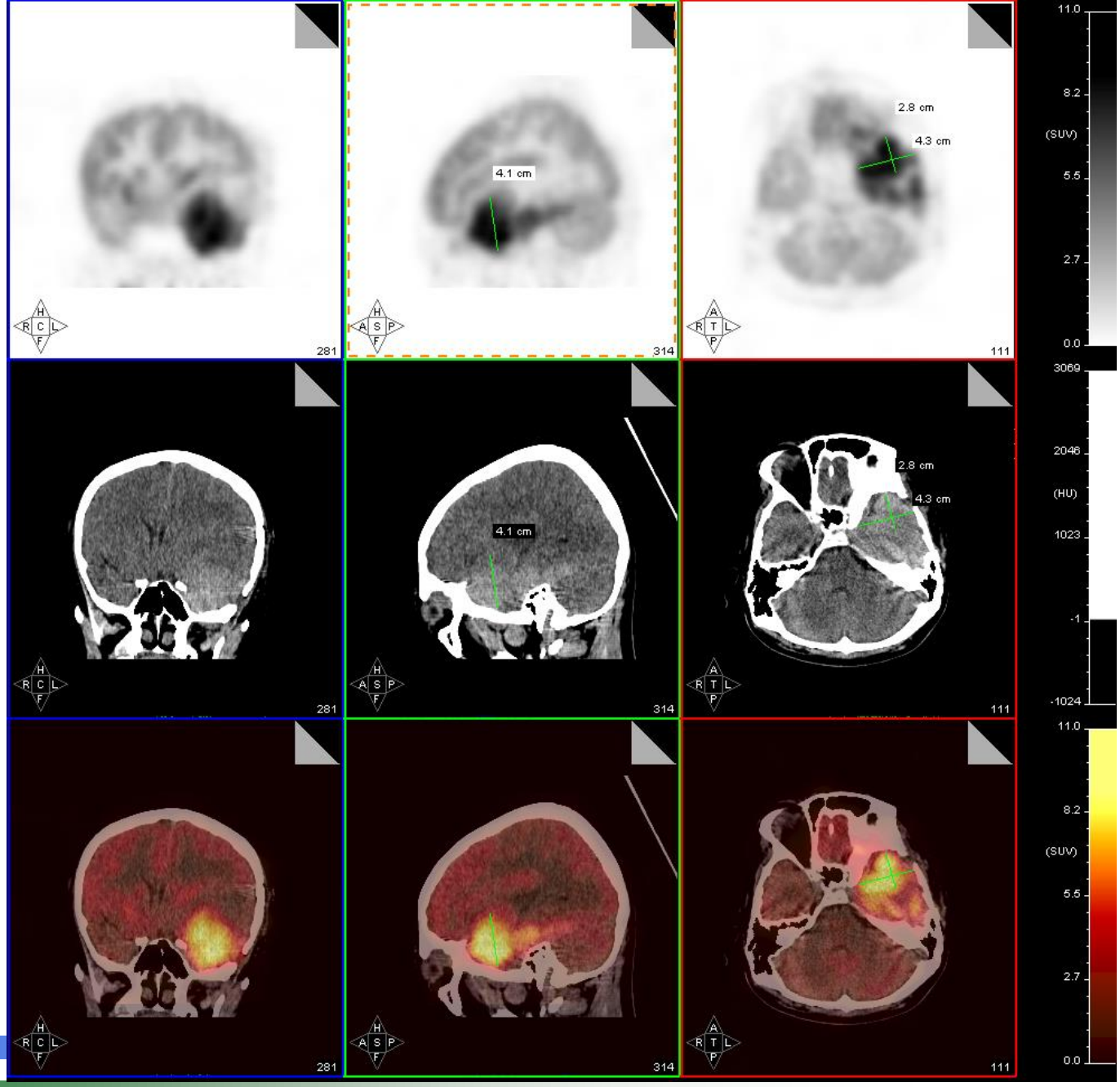

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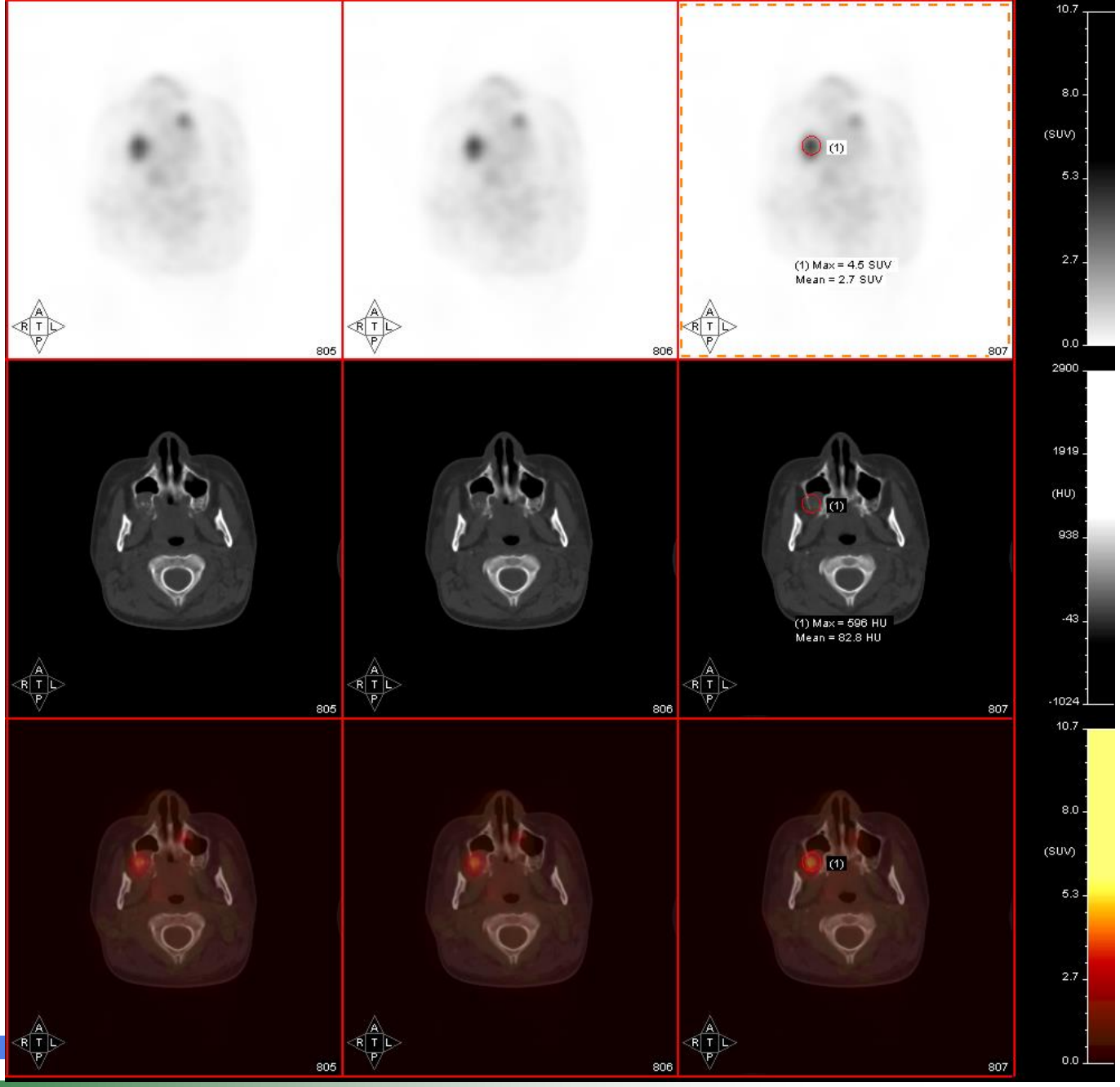

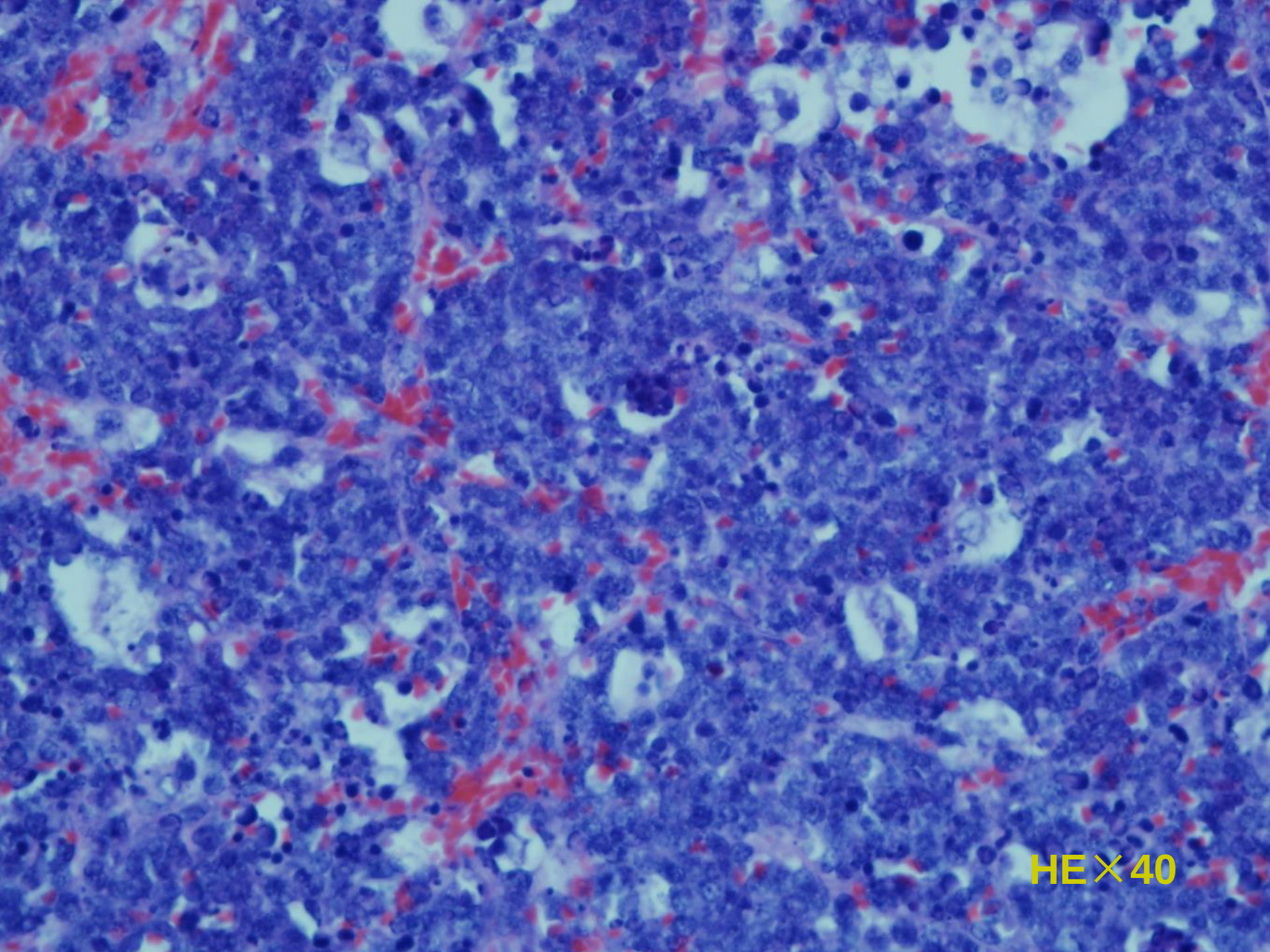
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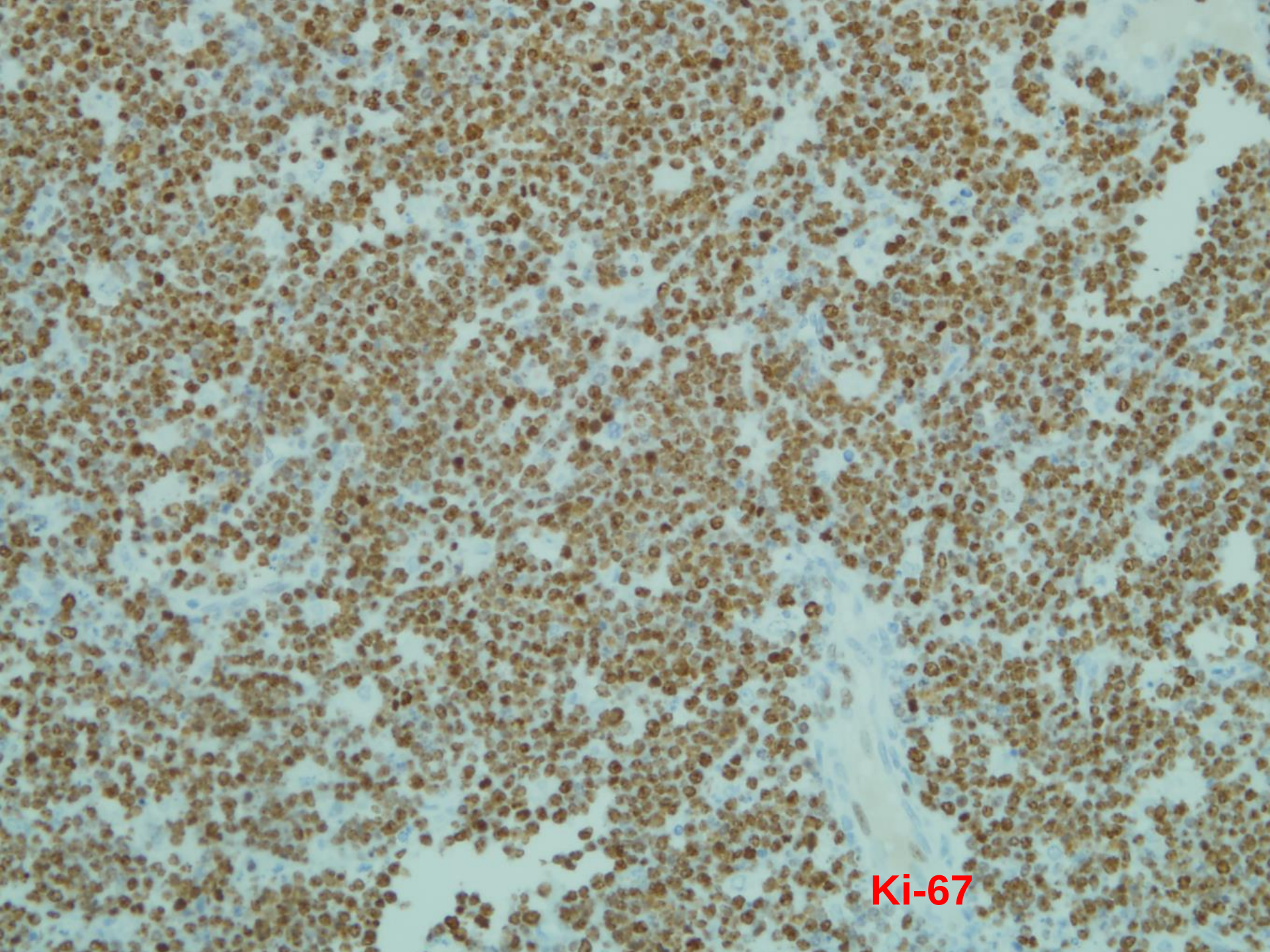
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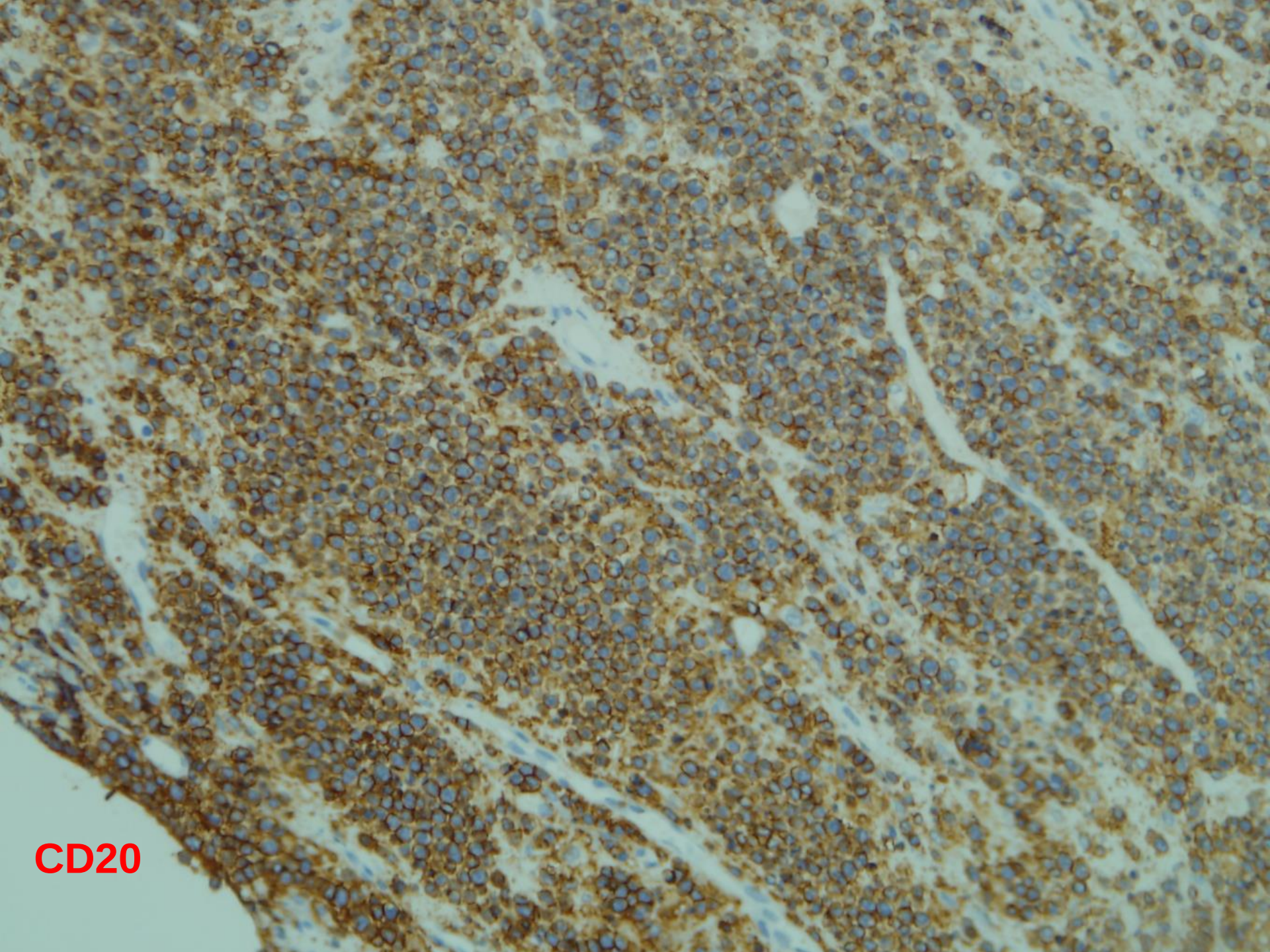
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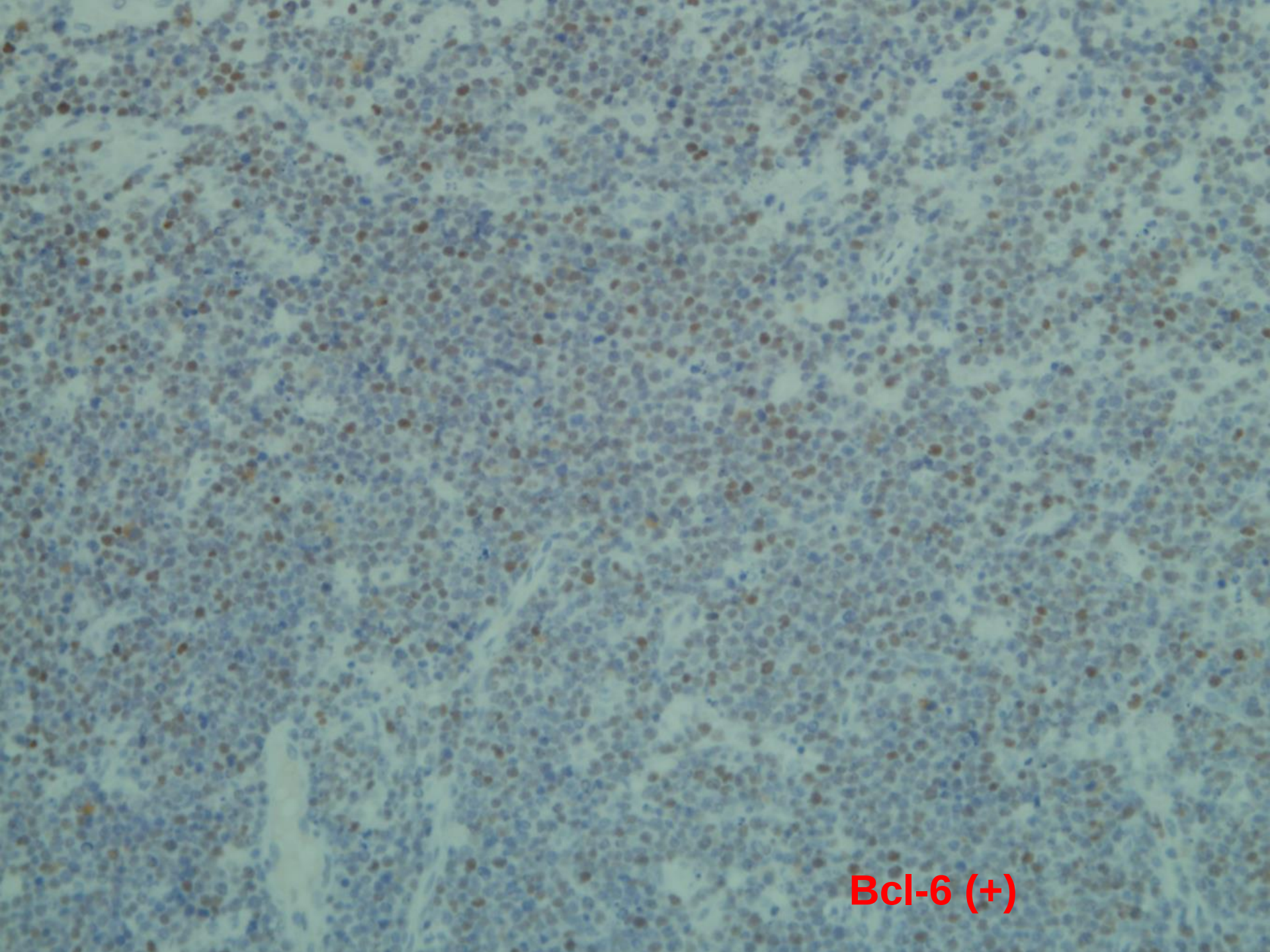
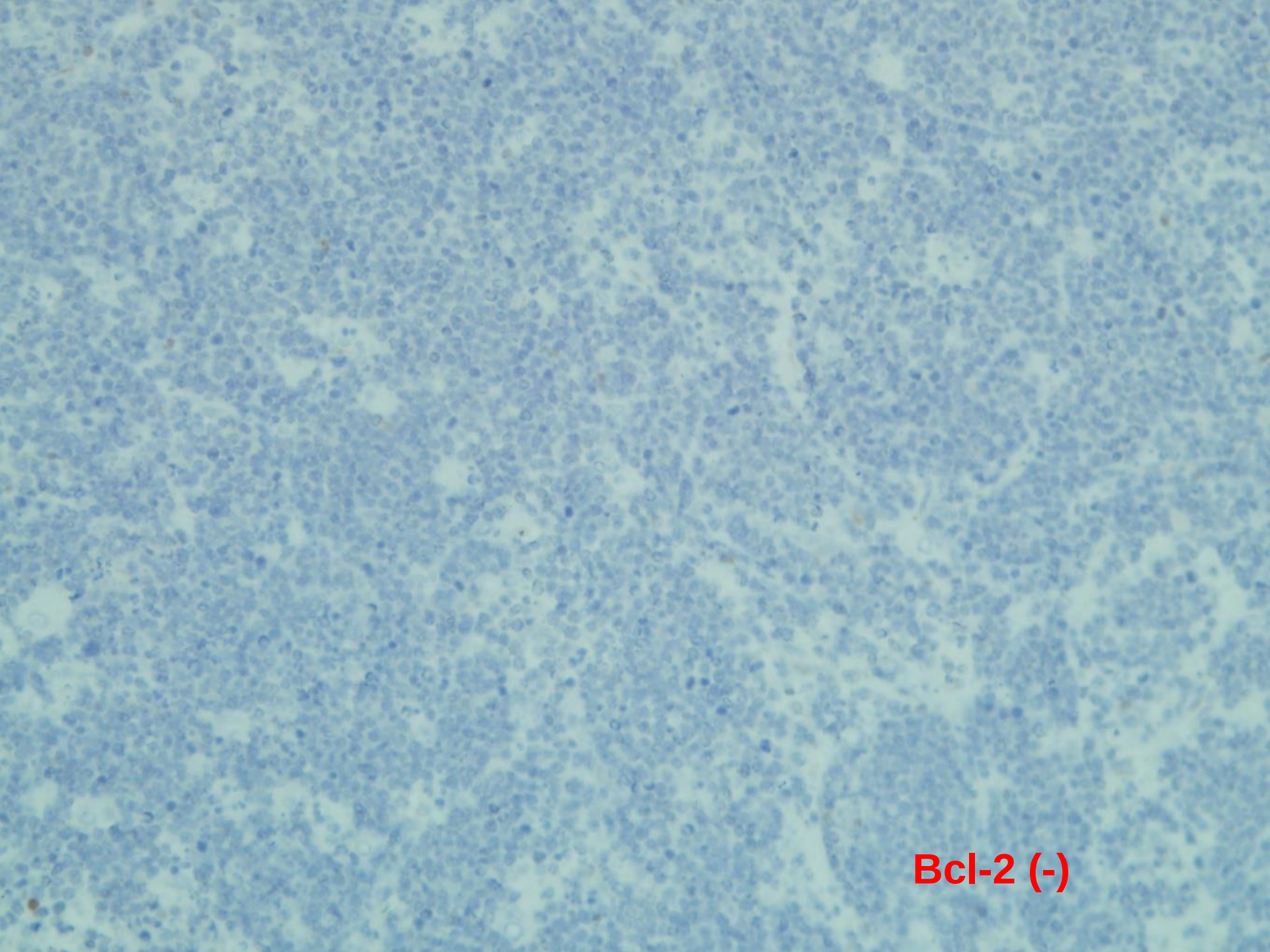

Bcl-6 (+)


Bcl-2 (-)

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其它检查

- CSF blast(+)
- Cervical nodes involves
- Kidney involves
- Bone Marrow (-)
- B symptom（-）

- FISH C-MYC(+)　(8q24)

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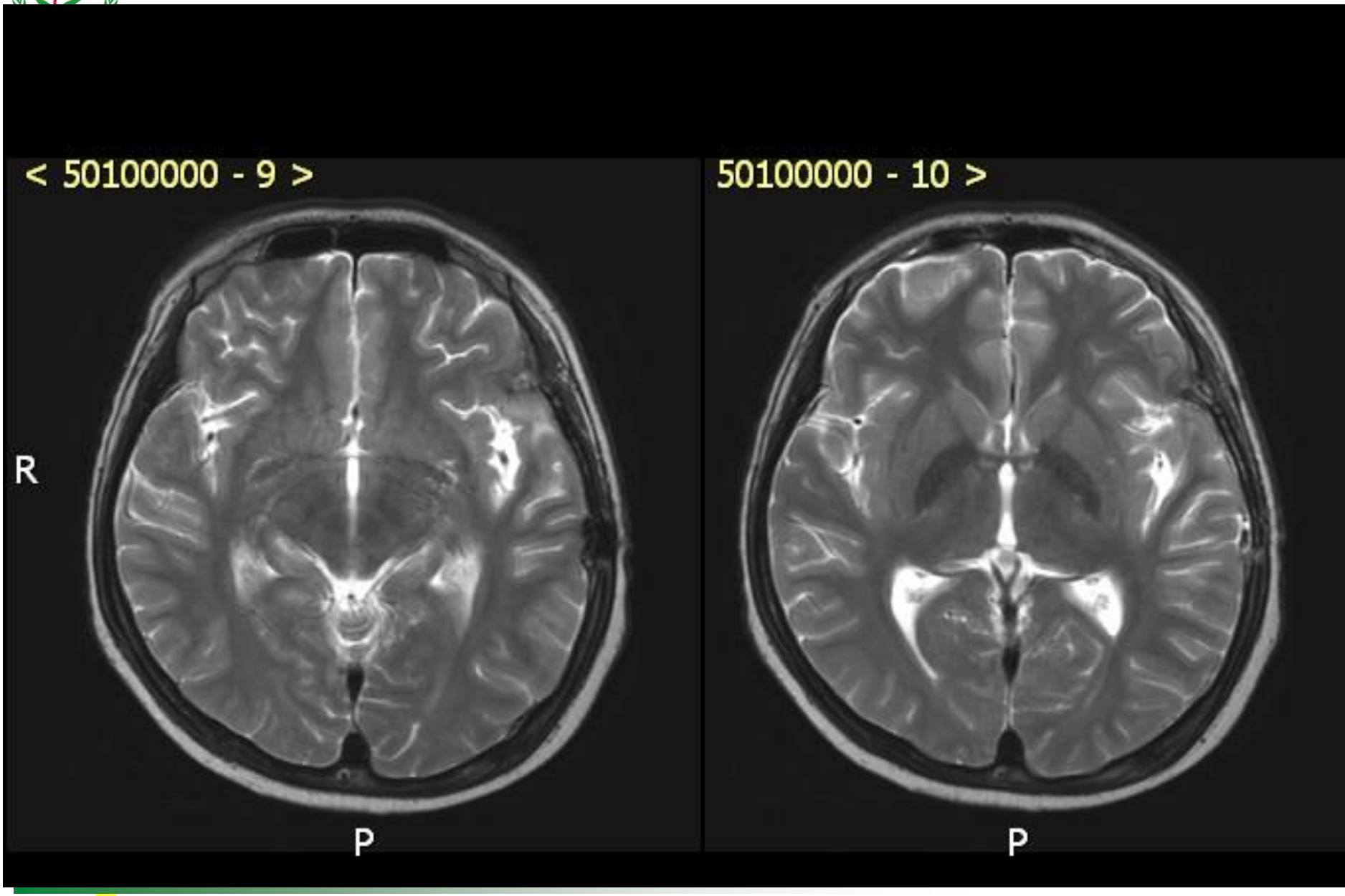
诊断与治疗

- Primary CNS Burkitt's Lymphoma

- LMB-89 Protocol

  (COP→ COPADM1→R+COPADM2→ CYVE－MTX….)

- 包含有4次HD-MTX 8g/m^2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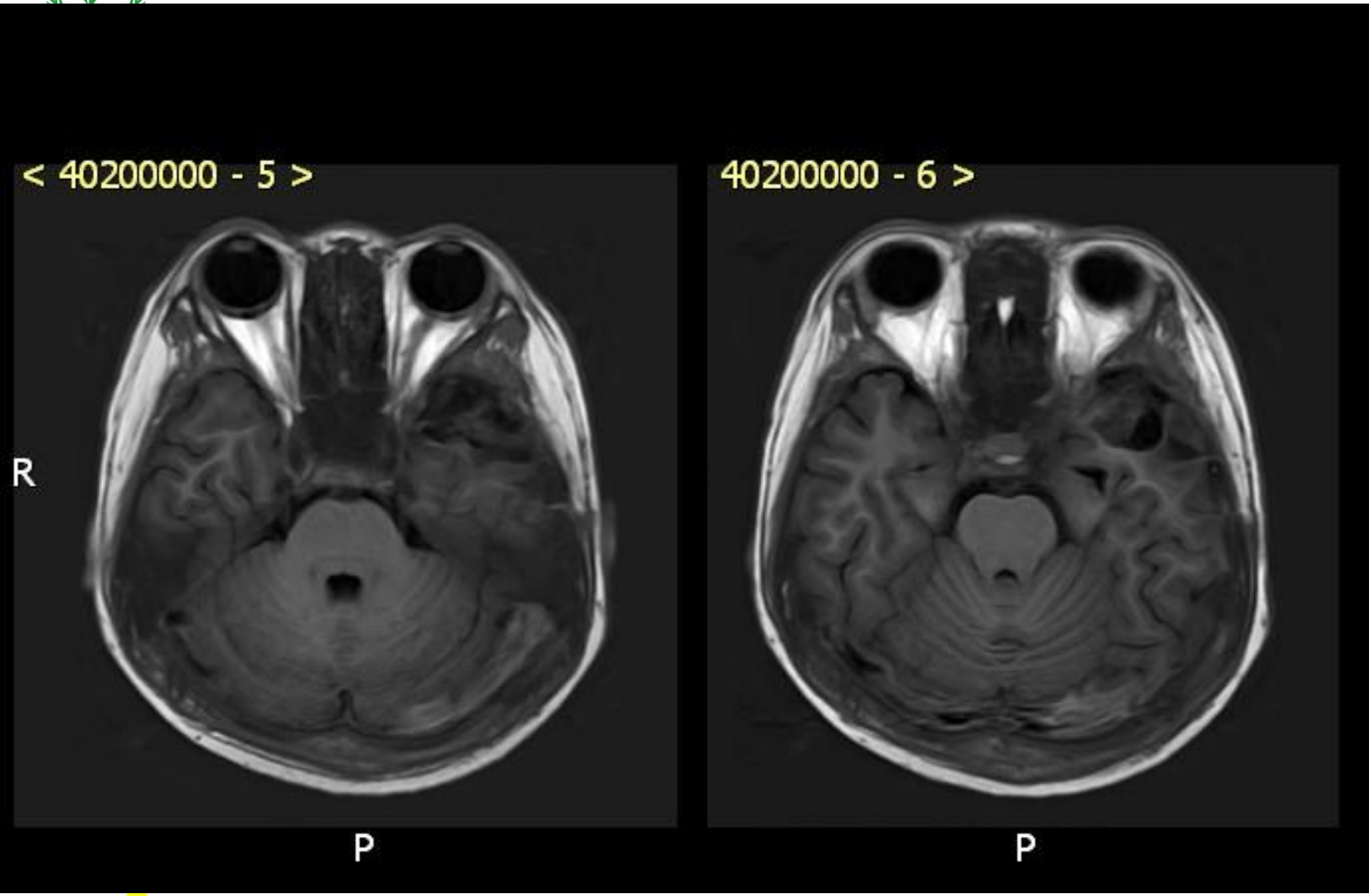
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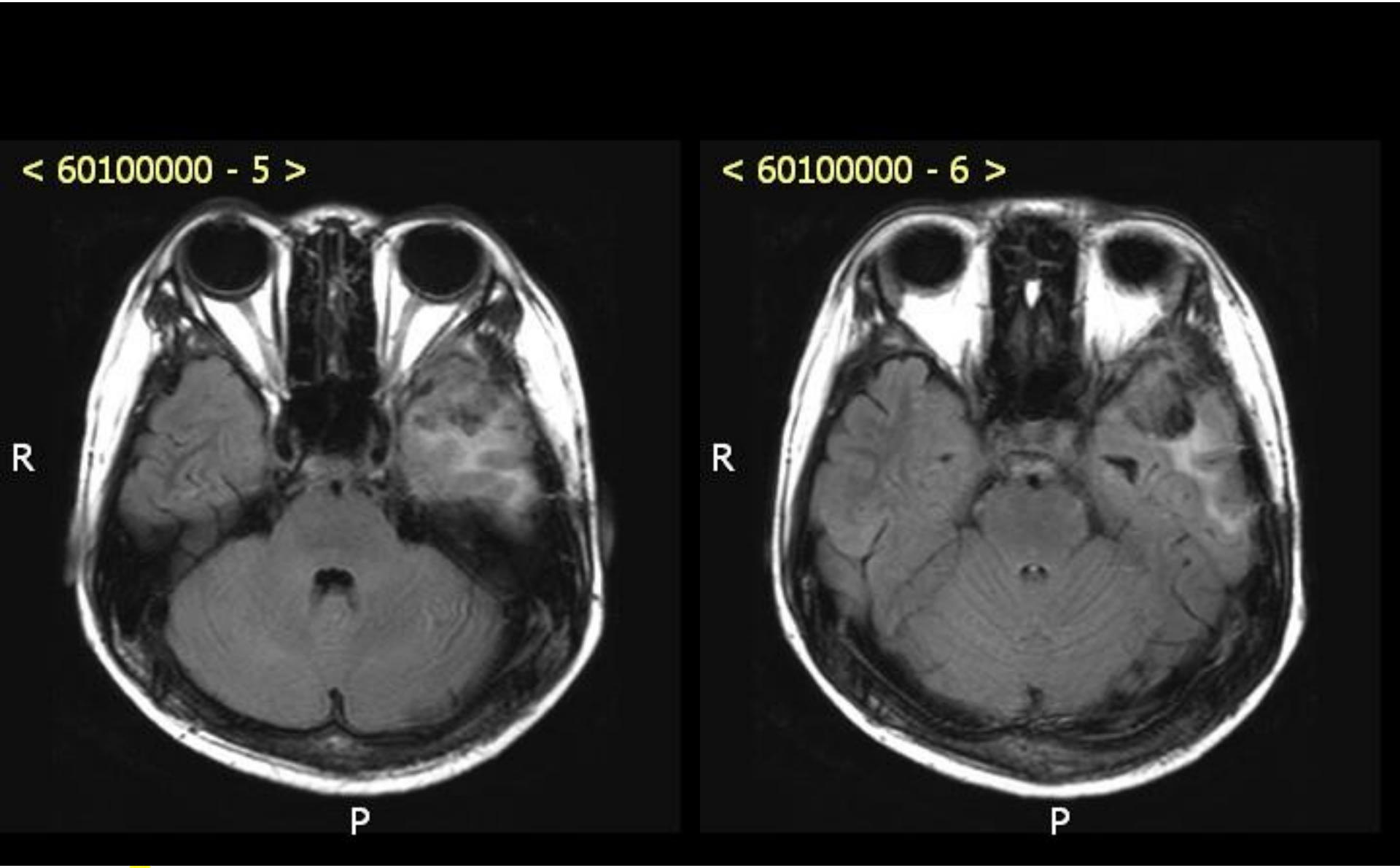
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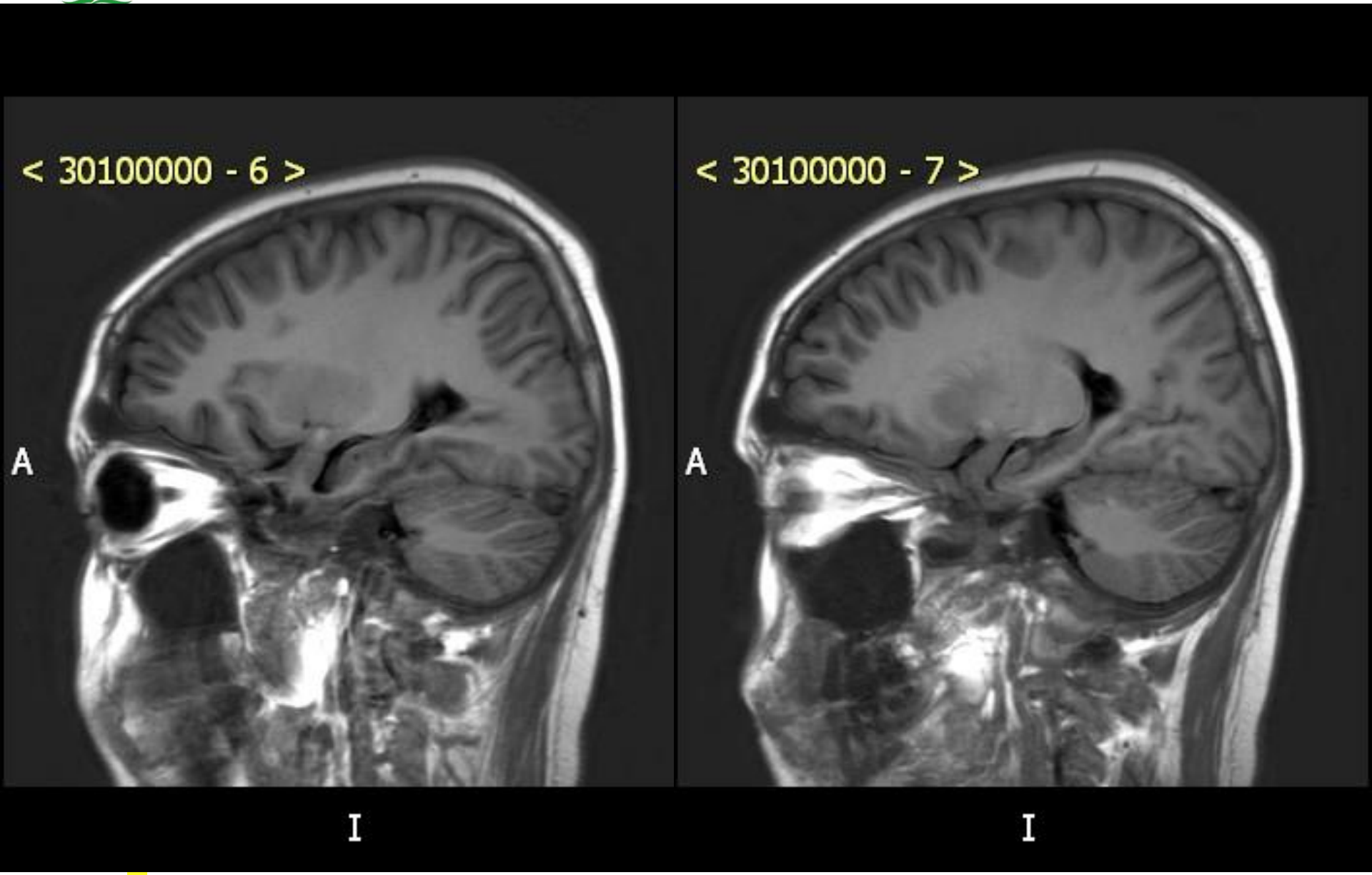
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预后

- 治疗6个月停药，未经CNS放疗
- 目前CCR5年余
- 无任何后遗症，已经上高中

伴CNS侵犯的LBL可以取消放疗吗？

- BCH总结265例LBL，21例CNS侵犯（7.8%），加强化疗并增加鞘注，
- 仅1／21例CNS侵犯（视神经）病人复发（4.7%）
- 本组6／265复发，复发率2.3%，
- 取消了颅脑放疗，CNS复发率及总体复发率均未增加

伴CNS侵犯的Burkitt可以取消放疗吗？

- 186例儿童Burkitt淋巴瘤中35例（18.8%）伴中枢神经系统侵犯
- HD-MTX5- 8g/M^2 ×次，**鞘注11次**
- **取消CNS放疗**
- 中位随访48个月，CNS复发率为零

根据CNS危险因素的分层

- CNS1：无CNS高危因素，正常化疗及巩固
  鞘注B-LBL 14-16，T-LBL： 19-22
- CNS2：有CNS高危因素，无具体CNS侵犯
  临近组织侵犯、高白细胞血症、
  首次鞘注有损伤、
  初始治疗前1周没有打鞘
  LBL鞘注增加2次，其它不变
- CNS3：有CNS侵犯（脑实质、脑膜、颅神经）
  LBL鞘注增加4次，其它治疗不变

Does the early intensification of intrathecal therapy improve outcomes in pediatric acute lymphoblastic leukemia patients with CNS2/ TLP+ status at diagnosis?

- 回顾性收集了2001年1月至2007年12月份收治的224例病人，根据其CNS状态，分为CNS1，CNS2，CNS3
  - CNS2/TLP+的病人在诱导期间增加了2次MTX鞘内注射
  - 治疗方案选择CCG1991/1961
  - 5年的无复发率分别为80.4 ± 3.0%,100%，73.5 ± 11.3%
  - 结论：诱导期间增加MTX鞘注可提高CNS2患儿的预后

Mohammed B. Abrar, Hematology,2015

bjh research paper

Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group

Amanda M. Termuhlen,[1] Lynette M. Smith,[2] Sherrie L. Perkins,[3] Mark Lones,[4] Jonathan L. Finlay,[5] Howard Weinstein,[6] Thomas G. Gross[7] and Minnie Abromowitch[8]

[1]*Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles,* [2]*Department of Biostatistics, University of Nebraska Medical Center, Omaha, NE,* [3]*Department of Pathology and ARUP Laboratories, University of Utah Health Sciences, Salt Lake City, UT,* [4]*Department of Pathology and*

Summary

The Children's Oncology Group's A5971 trial examined central nervous system (CNS) prophylaxis and early intensification in paediatric patients diagnosed with CNS-negative Stage III and IV lymphoblastic lymphoma. Using a 2 × 2 factorial design, the study randomized patients to Children's Cancer Group (CCG) modified Berlin-Frankfurt-Muenster (BFM) acute lymphoblastic leukaemia (ALL) regimen with intensified intrathecal (IT) methotrexate (MTX) (Arm A1) or an adapted non-Hodgkin lymphoma/BFM-95 therapy with high dose MTX in interim maintenance but no IT-MTX in maintenance (Arm B1). Each cohort was randomized ± intensification (cyclophosphamide/anthracycline) (Arms A2/B2). For the 254

2×2析因设计，鞘注组和MTX组及强化组疗效相当

(A)

A5971

CCG BFM = A1

Induction	Consolidation	Interim Maintenance	Delayed Intensification	Maintenance
Prednisone Vincristine day 0 Daunomycin day 0 (30 mg/m^2 x 4) L-asp day 3 (6000 u/m^2 IM x 6) IT MTX (2) IT cytarabine (1)	Cyclophosphamide Cytarabine 6-MP (60 mg/m^2) IT MTX (4)	6-MP (60mg/m^2) MTX oral IT MTX (2)	Dexamethasone Vincristine Doxorubicin L-asp (6000 u/m^2 IM x 6) Cyclophosphamide Cytarabine 6-TG IT MTX (2)	Vincristine Prednisone 6-MP (75 mg/m^2/day) MTX oral IT MTX (2 for 4 cycles, 1 per remaining cycles)

CCG-BFM = A2 (Intensified)

Prednisone Vincristine day 0 L-asp day 3 (6000 u/m^2 IM x 6) IT MTX (2) IT cytarabine (1) **Daunomycin day 0** **(60 mg/m^2/day)** **infusion for 48 h** **Cyclophosphamide** **(1 g/m^2) day 2**	Same as above	Same as above	Dexamethasone Vincristine L-asp (6000 u/m^2 IM x 6) 6-TG IT MTX (2) **Daunomycin** **(60 mg/m^2/day)** **infusion for 48 h** **Cyclophosphamide** **(1 g/m^2)**	Same as above

(B)

A5971

CCG modified NHL BFM = B1

Induction	Consolidation	Interim Maintenance	Delayed Intensification	Maintenance
Prednisone Vincristine day 0 Daunomycin day 0 (30 mg/m^2 x 4) L-asp day 3 (6000 u/m^2 IM x 6) IT MTX (2) IT cytarabine (1)	Cyclophosphamide Cytarabine 6-MP (60 mg/m^2) IT MTX (4)	6-MP (25 mg/m^2) MTX IV (5 g/m^2 x 4) IT MTX (4)	Dexamethasone Vincristine Doxorubicin L-asp (6000 u/m^2 IM x 6) Cyclophosphamide Cytarabine 6-TG IT MTX (2)	Vincristine Prednisone 6-MP (75 mg/m^2/d) MTX oral No IT MTX

CCG modified NHL BFM = B2 (Intensified)

Prednisone Vincristine day 0 L-asp day 3 (6000 u/m^2 IM x 6) IT MTX (2) IT cytarabine (1 **Daunomycin day 0** **(60 mg/m^2/day)** **infusion for 48 h** **Cyclophosphamide** **(1 g/m^2) day 2**	Same as above	Same as above	Dexamethasone Vincristine L-asp (6000 u/m^2 IM x 6) 6-TG IT MTX (2) **Daunomycin** **(60 mg/m^2/day)** **infusion for 48 h** Cyclophosphamide (1 g/m^2)	Same as above

COG A5971: 基于NHL-BFM 95方案

24 mts

设计	诱导	M	再诱导	6-MP/MTX
NHL- BFM		iv 4x5g/m² MTX 4x IT		ca. 18x VCR + 5d Pred no MTX IT
intensified	CPM + 蒽环类 均为 d1	iv 4x5g/m² MTX 4x IT	CPM + 蒽环类	ca. 18x VCR + 5d Pred no MTX IT
CCG BFM		po 4x15mg/m² MTX 2x IT		ca. 18x VCR + 5d Pred ca. 10x MTX IT
CCG BFM intensified	CPM + 蒽环类 均为 d1	po 4x15mg/m² MTX 2x IT	CPM + 蒽环类	ca. 18x VCR + 5d Pred ca. 10x MTX IT

Abromowitch et al. 2008 [Abstract 3rd Internatl Sympos Childh NHL Frankfurt 2009]

COG A5971: III/IV期-CNS阴性LBL

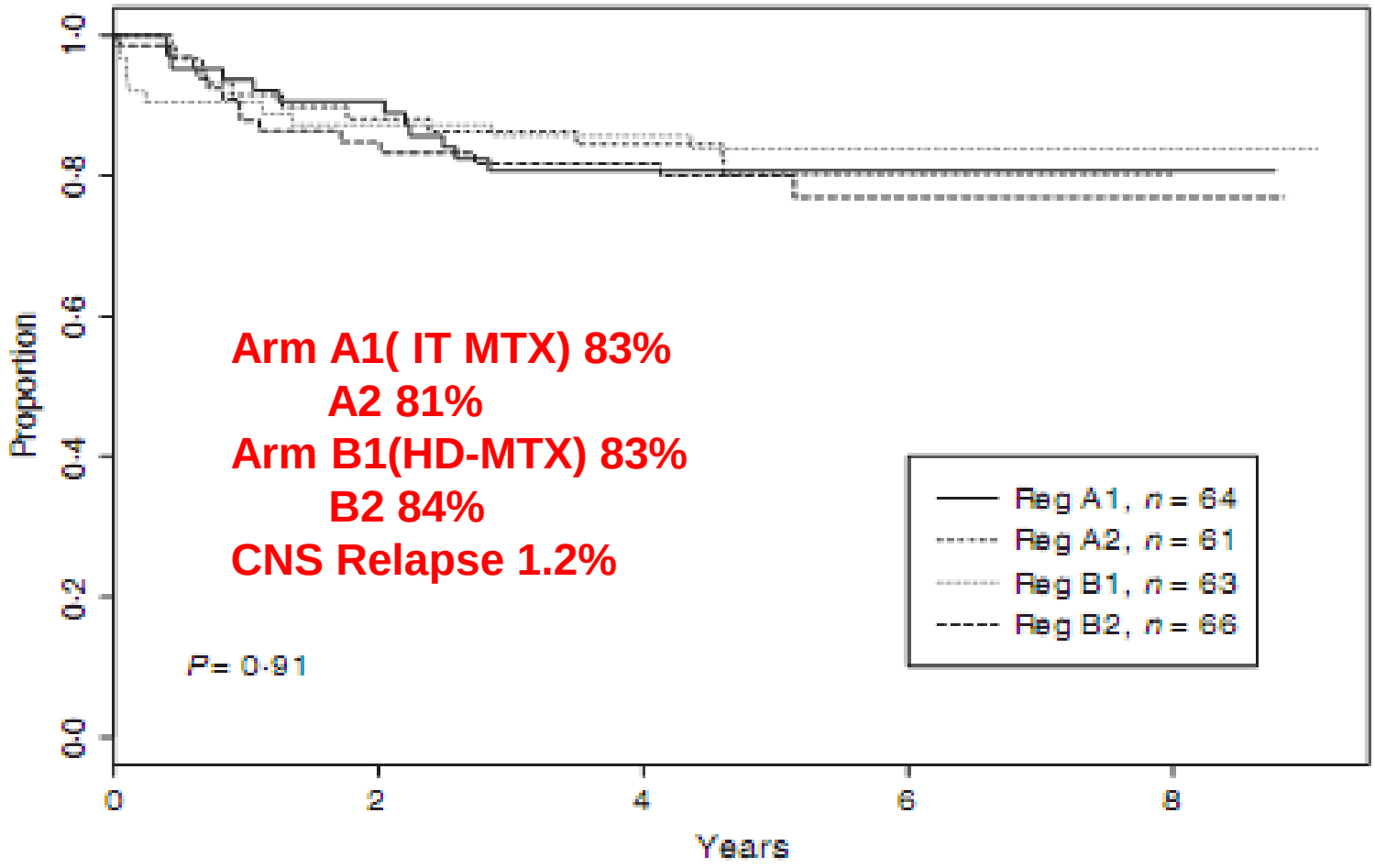
结果 (N=257 pts)

Abromowitch et al. 2008 [Abstract 3rd Internatl Sympos Childh NHL Frankfurt 2009]

治疗	pEFS
BFM95 withHD MTX	84±3%
w/o HDMTX	83±4%
with早期强化	83±4%
w/o早期强化	83±4%

COG A5971结果

Outcomes for disseminated paediatric lymphoblastic lymphoma



Arm A1(IT MTX) 83%

A2 81%

Arm B1(HD-MTX) 83%

B2 84%

CNS Relapse 1.2%

各治疗组鞘注次数表（单位：次）

类别	普通组 CNS1	具有CNS复发危险因素组			
		CNS2		CNS3	
		鞘注组	MTX组	鞘注组	MTX组
T-LBL	23	27	23	29	25
B-LBL	17	23	19	25	21

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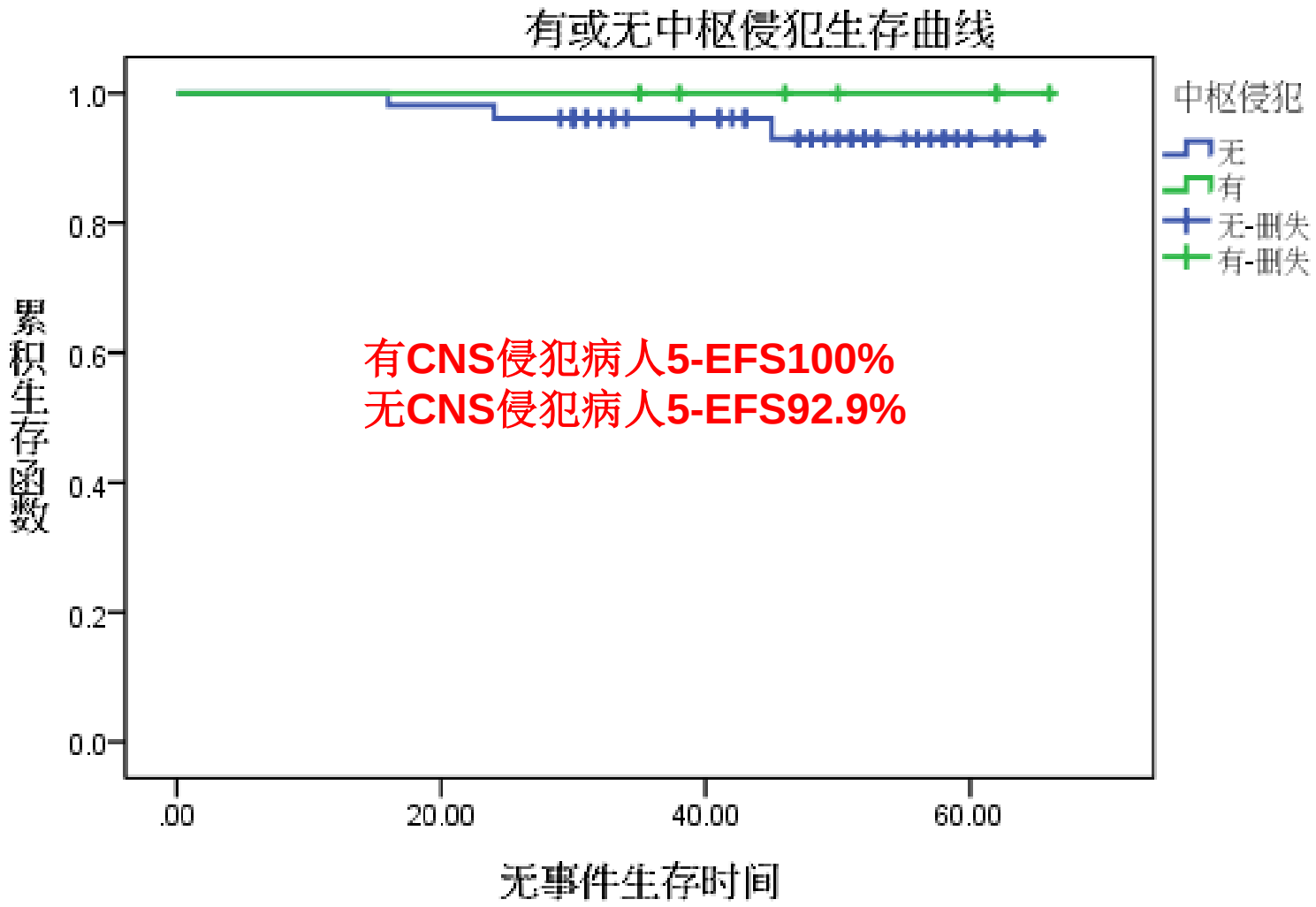
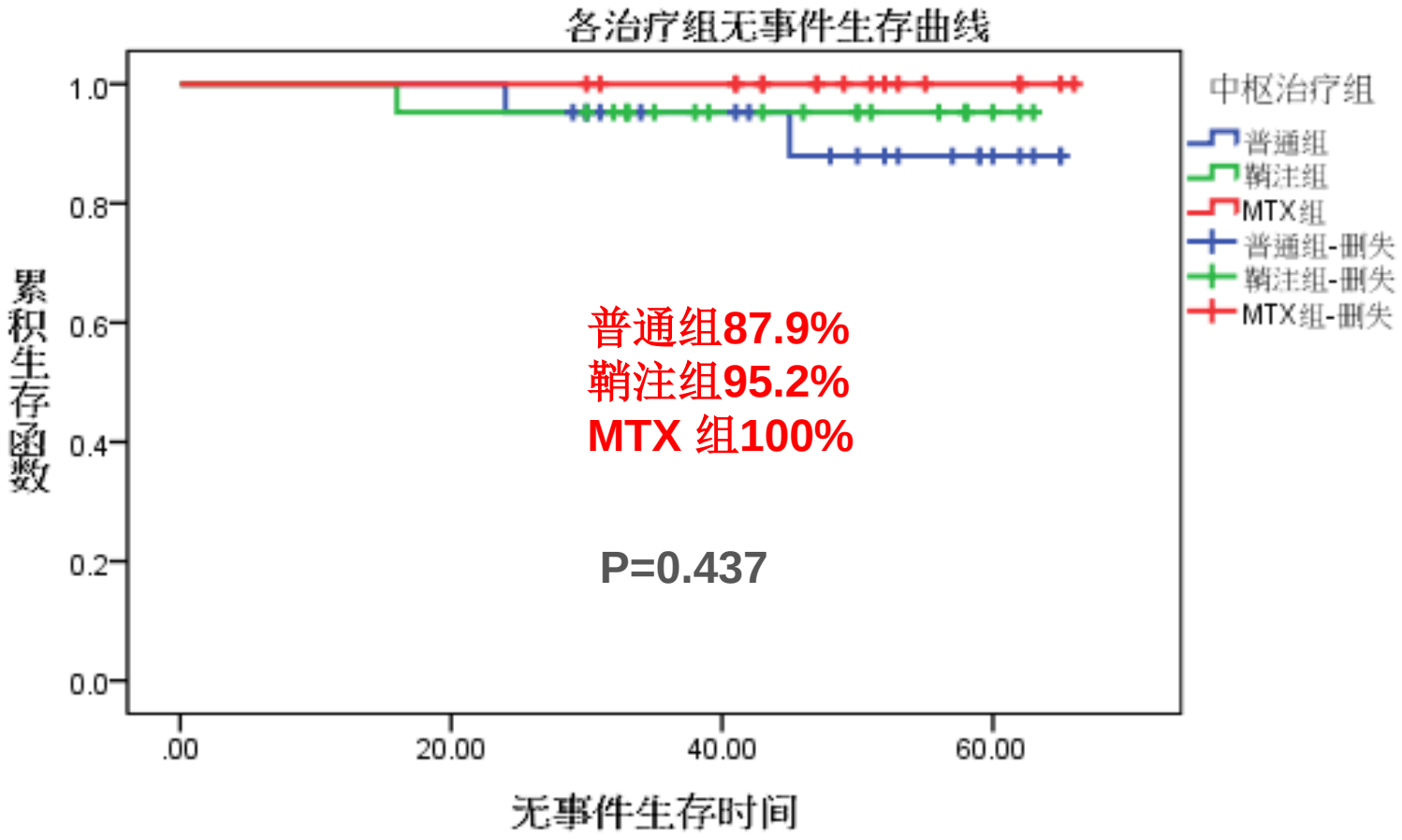
结果



有CNS侵犯病人5-EFS100%
无CNS侵犯病人5-EFS92.9%

我院应用不同CNS预防方案疗效



CNS复发

- 复发时间多在诊断后5-24月
- 大多表现为脑膜病变，部分为孤立的脑实质病变，或二者均有
- 约50%为单纯CNS复发，另一半为伴随全身疾病进展复发
- 单纯CNS复发挽救治疗成功率高于其他部位复发

CNS复发的治疗

- 早期加强鞘注配合系统化疗
- Ommaya囊脑室内注药
- 应用二线药物：
  - 脂质体Ara-c 鞘注
- ASCT
- 颅脑放疗？
- 免疫靶向治疗？

Analysis of the role of intratecal liposomal cytarabine in the prophylaxis and treatment of central nervous system lymphomatosis: The Balearic Lymphoma Group experience

- 回顾性总结了从2005年至 2015年 (n = 58)应用脂质体阿糖胞苷鞘内注射的病人
  - 33% 头痛, 20% 神经系统损伤, 11% 恶性, 9% 眩晕, 4% 呕吐, 4% 高热, 2% 一过性失明
  - 在预防组(n = 26)，平均随访时间55个月 (17±81)，只有3个 CNS复发 (11%)
  - 在治疗组(n = 32), CSF 完全缓解者77%.OS=6 months (0±16) 死亡原因为淋巴瘤进展 (19例), 治疗毒性(2例)
  - 在预防组CNS复发的病人数与之前报道的HDMTX相似，
  - 脂质体阿糖胞苷鞘注的次数，与脑脊液肿瘤细胞清除率，PFS，低复发率均呈正相关

Antonio GutieÂrrez, PLOS ONE,2017

靶向药物治疗CNS淋巴瘤

- nivolumab对难治复发的原发CNS的淋巴瘤有效
- 原发CNS的淋巴瘤多数有9p24表达，也就是PD-L1水平高，因此本药有效。
- 只要肿瘤有PD-L1高表达，使用PD-1抑制剂就会有效。
- Nivolumab加强了T细胞的杀伤功能，增加了机体正常的免疫监控功能，对CNS的的肿瘤细胞同样有作用
- CD20需要直接进入CNS才能起作用
- 有行美罗华脑室化疗囊注射治疗CNS淋巴瘤的报告

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Brief Report

blood

CLINICAL TRIALS AND OBSERVATIONS

PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma

Lakshmi Nayak,[1,2] Fabio M. Iwamoto,[3] Ann LaCasce,[1,2] Srinivasan Mukundan,[1,2] Margaretha G. M. Roemer,[1] Bjoern Chapuy,[1] Philippe Armand,[1,2] Scott J. Rodig,[1,2] and Margaret A. Shipp[1,2]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; and [3]New York Presbyterian Hospital, New York, NY

Key Points

- Genetic analysis reveals frequent 9p24.1/PD-L1/PD-L2 copy-number alterations and increased expression of the PD-1 ligands in PCNSL and PTL.
- PD-1 blockade with nivolumab demonstrated activity in patients with relapsed/refractory PCNSL and PTL.

Primary central nervous system (CNS) lymphoma (PCNSL) and primary testicular lymphoma (PTL) are rare extranodal large B-cell lymphomas with similar genetic signatures. There are no standard-of-care treatment options for patients with relapsed and refractory PCNSL and PTL, and the overall prognosis is poor. PCNSLs and PTLs exhibit frequent 9p24.1 copy-number alterations and infrequent translocations of 9p24.1 and associated increased expression of the programmed cell death protein 1 (PD-1) ligands PD-L1 and PD-L2. The activity of PD-1 blockade in other lymphomas with 9p24.1 alterations prompted us to test the efficacy of the anti–PD1 antibody, nivolumab, in 4 patients with relapsed/refractory PCNSL and 1 patient with CNS relapse of PTL. All 5 patients had clinical and radiographic responses to PD-1 blockade, and 3 patients remain progression-free at 13^{+} to 17^{+} months. Our data suggest that nivolumab is active in relapsed/refractory PCNSL and PTL and support further investigation of PD-1 blockade in these diseases. (*Blood*. 2017;129(23):3071-3073)

Introduction

nivolumab对难治复发及原发CNS淋巴瘤有效

原发CNS的淋巴瘤多数有9p24表达，也就是PD-L1水平高，因此本药有效。

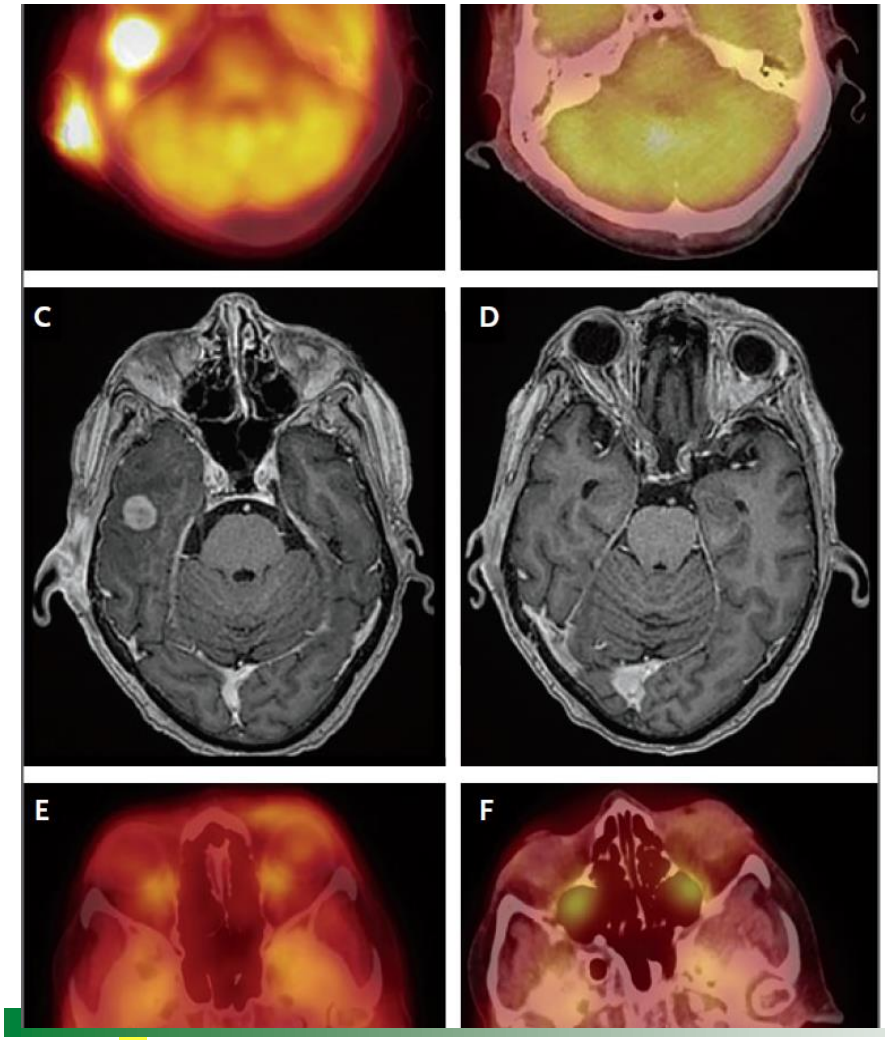
4例复发的PCNSL，1例PTL伴CNS复发，5例治疗后临床及影像提示有效

其中3例持续缓解13-17个月

CAR-T治疗CNS淋巴瘤

- CAR-T对CNS淋巴瘤有效，
- 因为没有很好的控制中枢CRS的有效措，目前用于治疗CNS淋巴瘤比较谨慎
- 这种免疫反应可以是致死性的
- 目前还没有把它做为儿童CNS淋巴瘤的治疗手段

Anti-CD19 CAR T Cells in CNS Diffuse Large-B-Cell Lymphoma，



- 1名难治的68岁老年女性DLBCL患者，伴有BCL-2重排及MYC,BCL6多拷贝，在经历了DA-EPOCH方案、四线化疗方案、自体干细胞移植等治疗后出现CNS复发（PET/CT显示了右侧颞叶复发）
- 入组了JCAR017临床试验（CD19 CAR T），1月后达CR，CSF中可以检测到CAR T细胞，认为其可透过血脑屏障，
- 随访的12个月中，一直处于CR状态。

eremy S. et,al, 2017.8,(377):8. DOI: 10.1056/NEJMc1704610

应用靶向治疗是否还需要做CNS预防性治疗？

- 应用**vinblastine, crizotinib, or brentuximab vedotin**治疗ALK阳性的ALCL（CNS阴性）
- 5例病人出现CNS转移
- 应用靶向治疗同时不应忽视CNS的预防性治疗

Ruf S[1] et,al. Pediatr Blood Cancer. 2018 Mar 7. doi: 10.1002/pbc.27003.

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小结

- 脑膜侵犯为LBL最常见CNS侵犯部位，BL及ALCL则以脑实质为主。
- ALL/LBL的CNSL危险因素：高白细胞、T细胞表型、Ph1染色体阳性及ZAP70、CCR7/CXCR4基因
- 其它NHL－CNS侵犯的危险因素：临床进展期、骨髓浸润、高肿瘤负荷、头面部侵犯、多发结外侵犯
- 针对危险因素，调整CNS定向分层治疗，以增加鞘注、加强系统化疗逐渐替代颅脑放疗是可行方案
- 新的治疗方法：靶向药物及CAR－T对CNS有治疗作用，远期疗效有待探讨

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谢谢聆听！