2014 北京淋巴瘤国际研讨会

# $^{18}$F-FDG PET/CT在淋巴瘤中的应用：共识及争议

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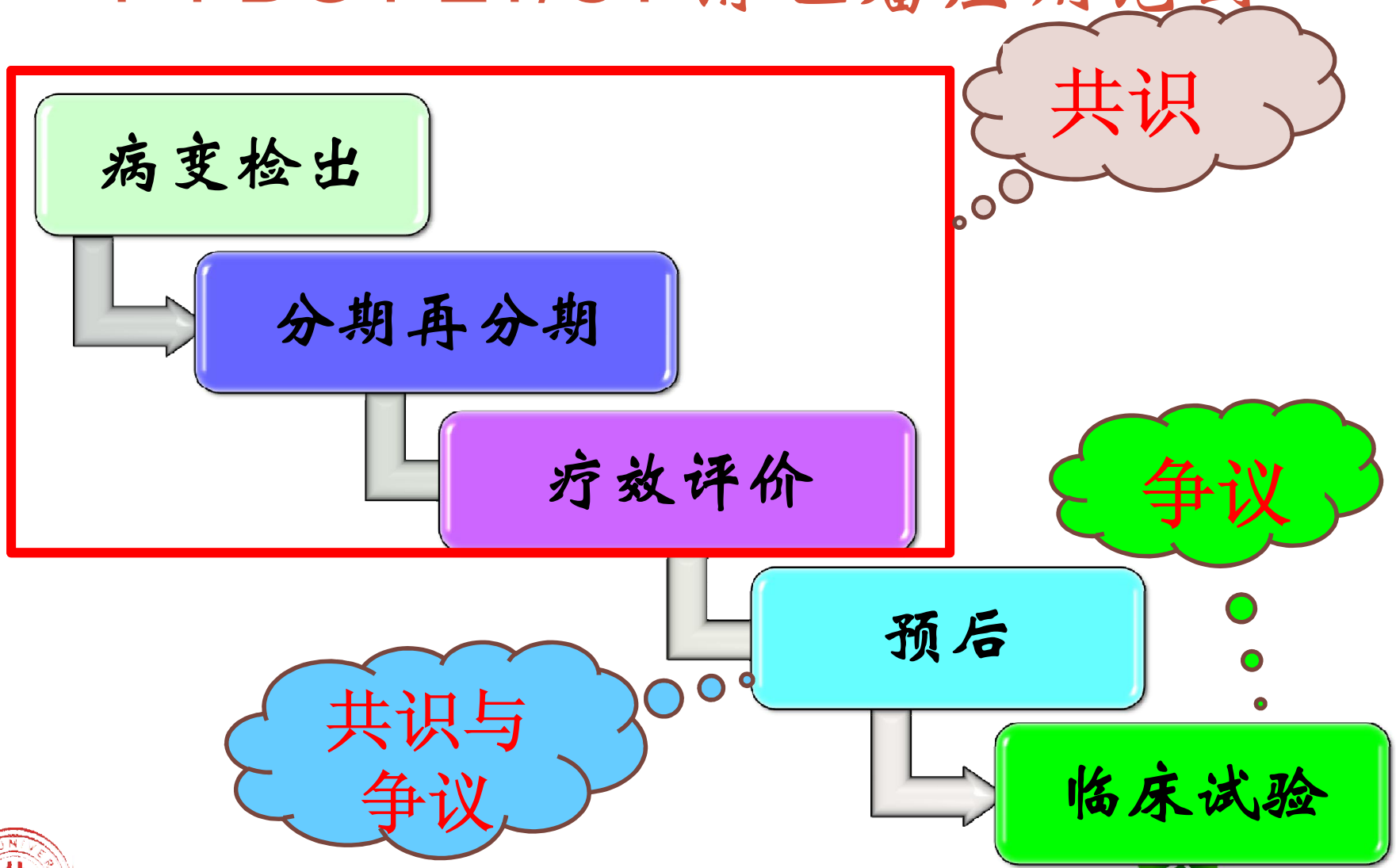
北京大学肿瘤医院 BEIJING CANCER HOSPITAL

# 病 例

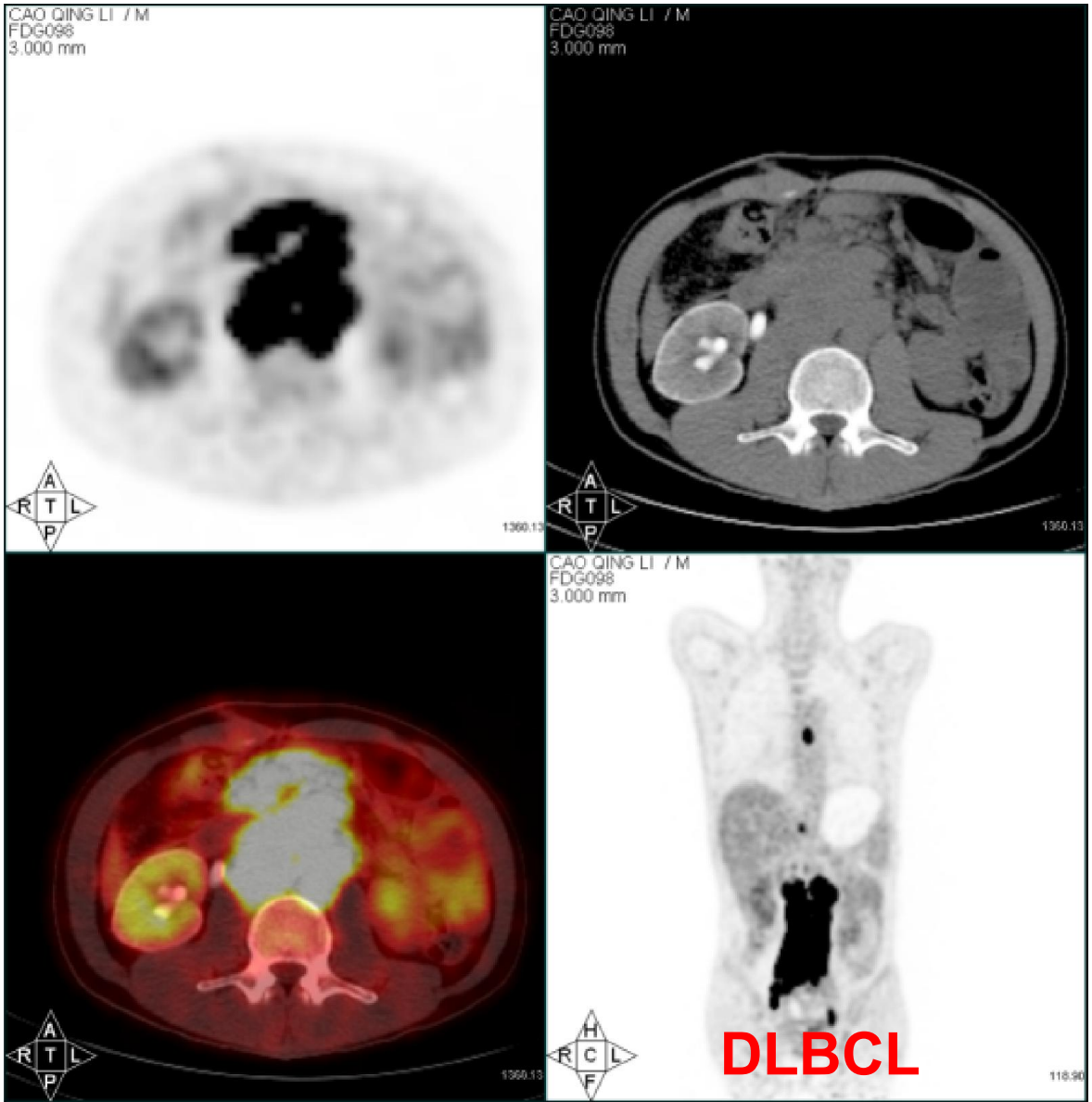
- 患者，18岁，无明显诱因出现右手指肌无力，进行性加重；大小鱼际肌肉萎缩；右上肢肿胀。后右侧眉骨上方出现质软、无压痛肿物，并逐渐增大至右侧头皮、额部、眼睑部、颧骨上方。
- 化验：WBC 1.6-2.1*$10^9$/L，微量蛋白尿，骨髓细胞学示WBC减少症。CSF常规无异常。
- 肌电图示右侧桡神经不全受损。
- 眼眶MRI、CT示局部软组织肿胀，炎性改变？
- 抗炎治疗（罗红霉素、贝他米松、氯化钠局部冲洗）无效。

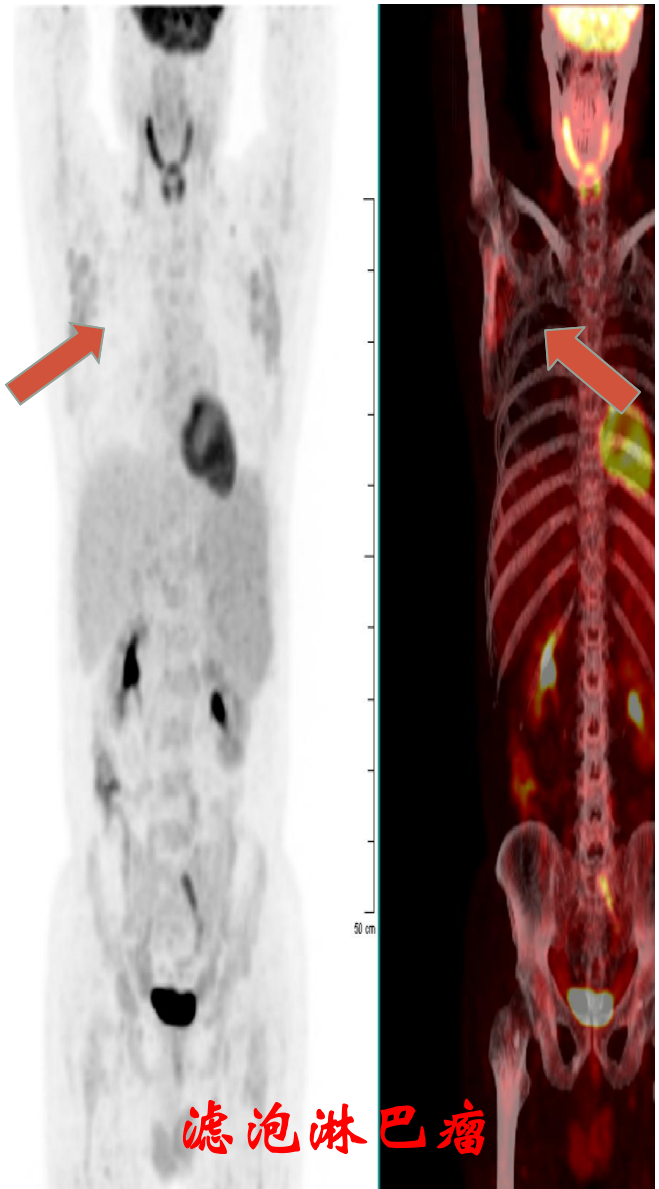

# 外周T细胞淋巴瘤

# $^{18}$F-FDG PET/CT 淋巴瘤应用范围



# 共识一：淋巴瘤PET表现取决于病理类型



# 推荐PET用于高代谢淋巴瘤的诊断及分期

| Histology | Percent avid |
|---|---|
| HL | 97-100 |
| DLBCL | 97-100 |
| FL | 95-98 |
| MCL | 100 |
| Nodal MZL | 67-100 |
| Non-gastric Extranodal MZL | ~70+ |
| Gastric MALT | 0-40 |
| CLL/SLL | 47-83 |
| PTCL nos | 90-100 |
| AITL | 100 |
| ALCL | 100 |
| MF/SS | 13-90 |

Cheson BD. 12th ICML, abstract 128

# 2013 NCCN 指南

- PET用于HL, DLBCL, AIDS相关性B细胞淋巴瘤等FDG-avid淋巴瘤，病变高代谢能较好地鉴别良恶性、发现小病灶/易忽略病灶、指导活检
- 辅助诊断（A useful test）：FL, MZL等
- 不建议应用于CLL/SLL
- 国内大多数医院CT是淋巴瘤分期的主要手段，对于大于1cm的淋巴结和大块肿物具有较好的诊断价值

# 共识二：提高分期准确性

| Authors (ref) | No. pa | Upstage (%) | Downstage (%) | Change in therapy (%) |
|---|---|---|---|---|
| HL | | | | |
| Buchman et al. | 25 | 8 | 0 | 8 |
| Wirth et al. | 31 | 14 | 0 | 18 |
| Pelosi et al. | 35 | 11.4 | 0 | 9 |
| Naumann et al. | 88 | 14.7 | 8 | 18 |
| NHL | | | | |
| Bangerter et al. | 44 | 12 | 2 | 14 |
| Partridge et al. | 44 | 40.9 | <10 | 25 |
| Jerusalem et al. | 33 | 1 | 1 | 1 |
| Weiharauch et al. | 22 | 18 | 0 | 5 |
| Munker et al. | 73 | 29 | 3 | <1 |
| Hutchings et al. | 99 | 17 | 5 | 7 |
| Rigacci et al. | 186 | 14 | 1 | 7 |

# 新进展：PET可代替部分患者的骨髓活检

- PET可以代替HL患者的骨髓活检（90%）
- DLBCL PET骨髓阳性（敏感性75%）

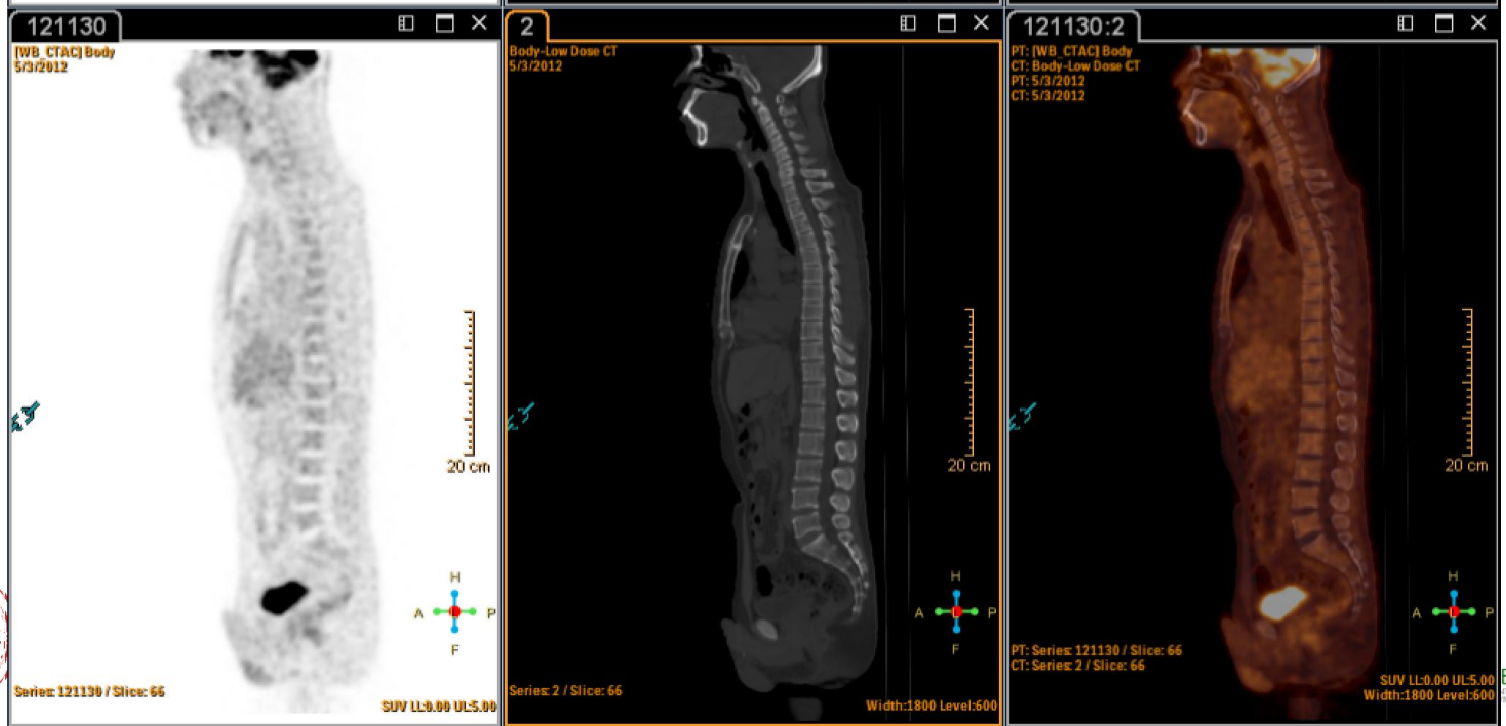
  可以确定为进展期，不需骨髓活检
- DLBCL PET骨髓阴性，考虑骨髓活检

  活检结果可能会是不同病理类型

  骨髓活检可以发现PET不能发现的微小病灶
- 其他病理类型仍需进行骨髓活检（敏感性50%）

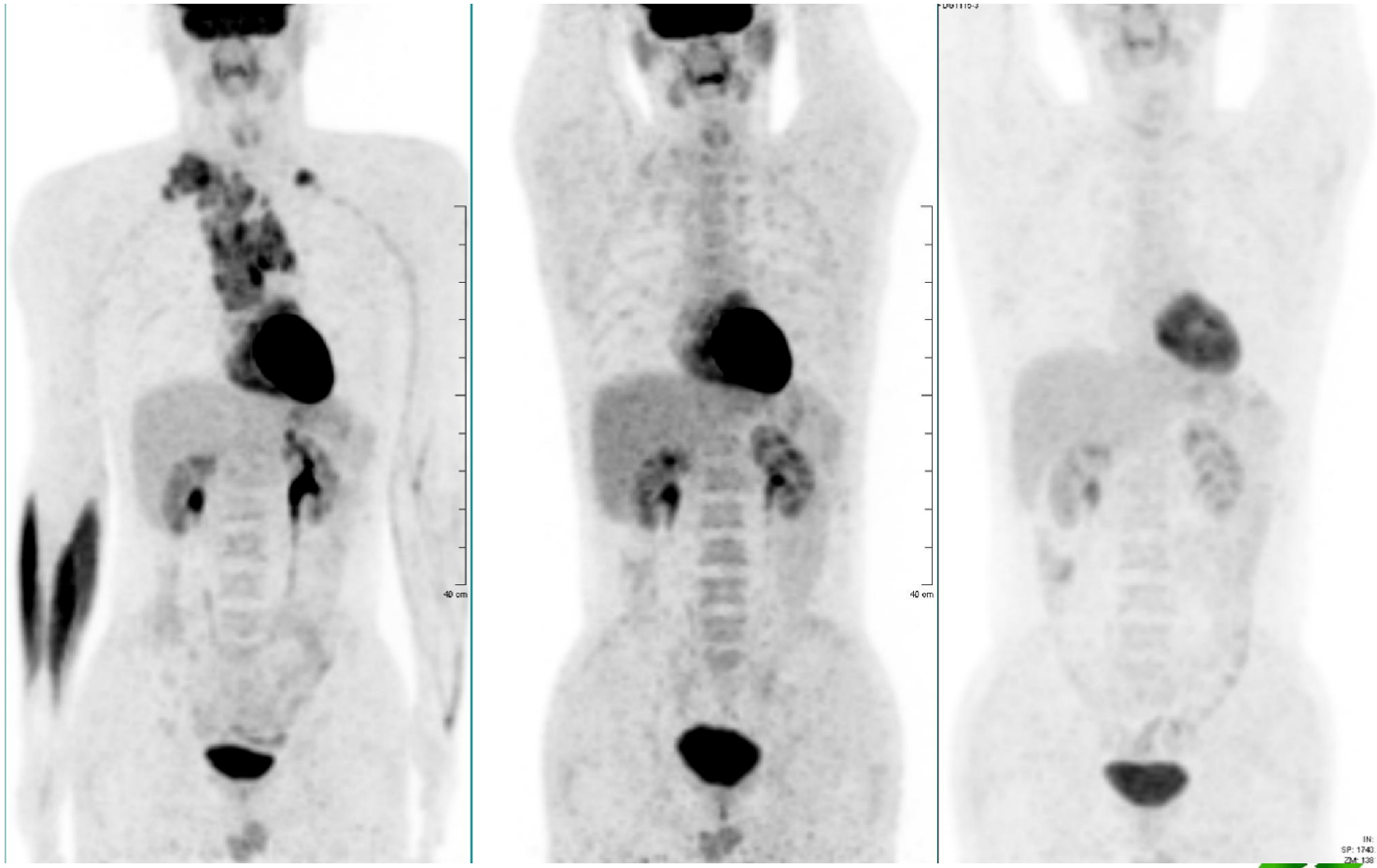
Cheson BD. 12th ICML, abstract 128

霍奇金淋巴瘤

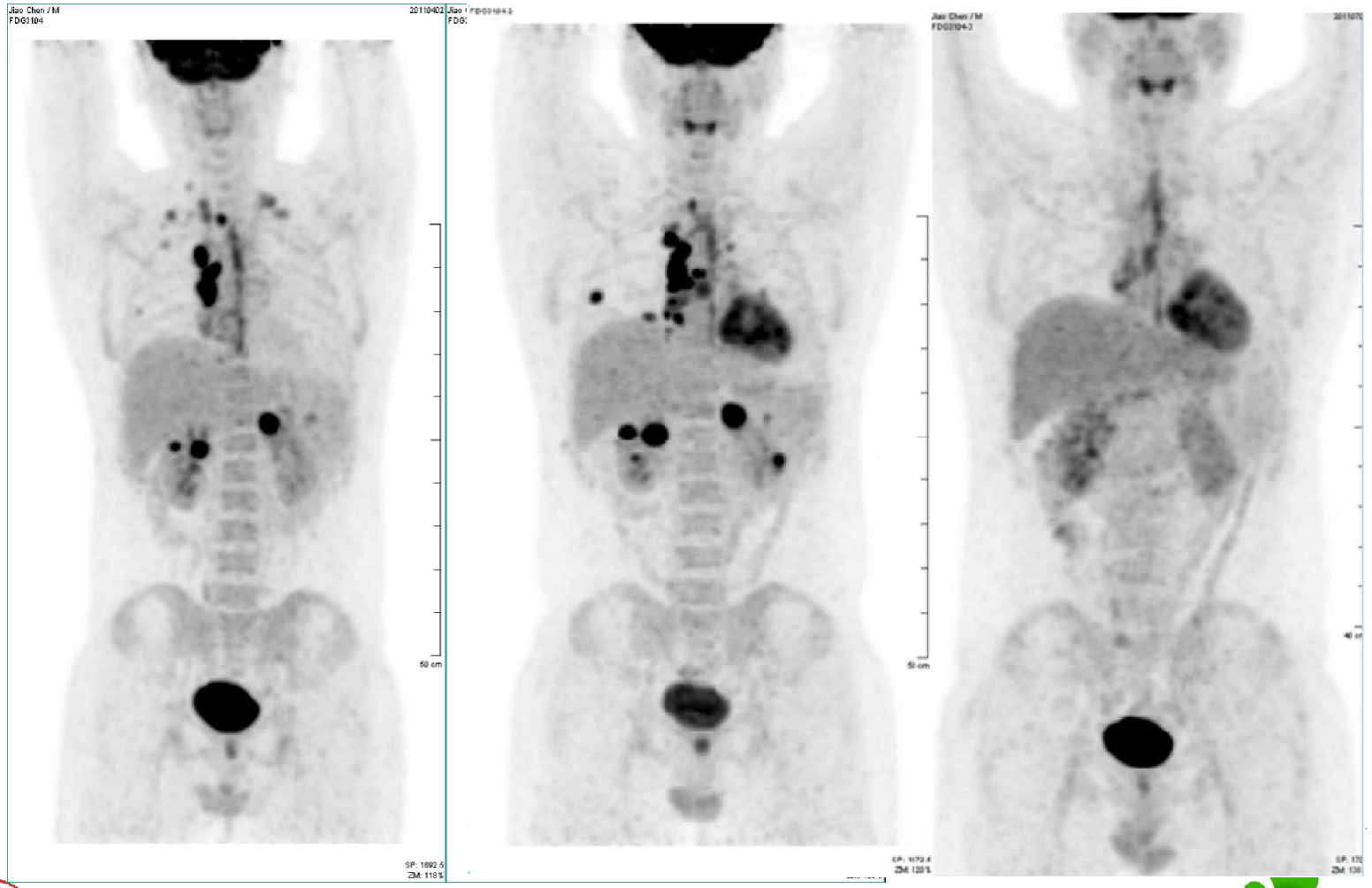
# 共识三：疗效评价

标准化治疗后，7天即可见FDG摄取明显下降　新药试验



化疗前　化疗2周期　化疗6周期

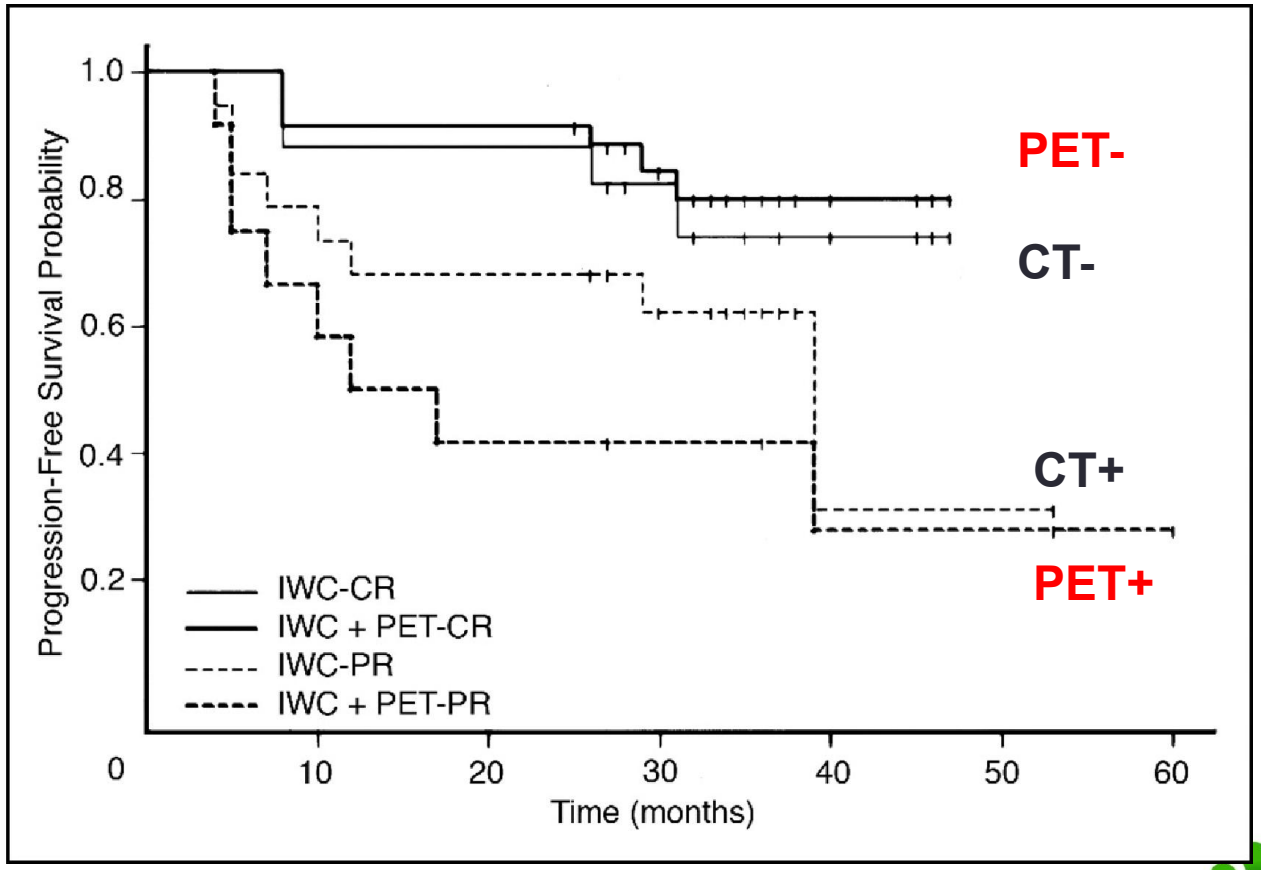
# 疗效评价——调整治疗方案



（前纵隔）DLBCL合并经典HL → HL结节硬化型伴DLBCL

# 共识四：疗后PET/CT对预后的预测

## DLBCL (n=54)



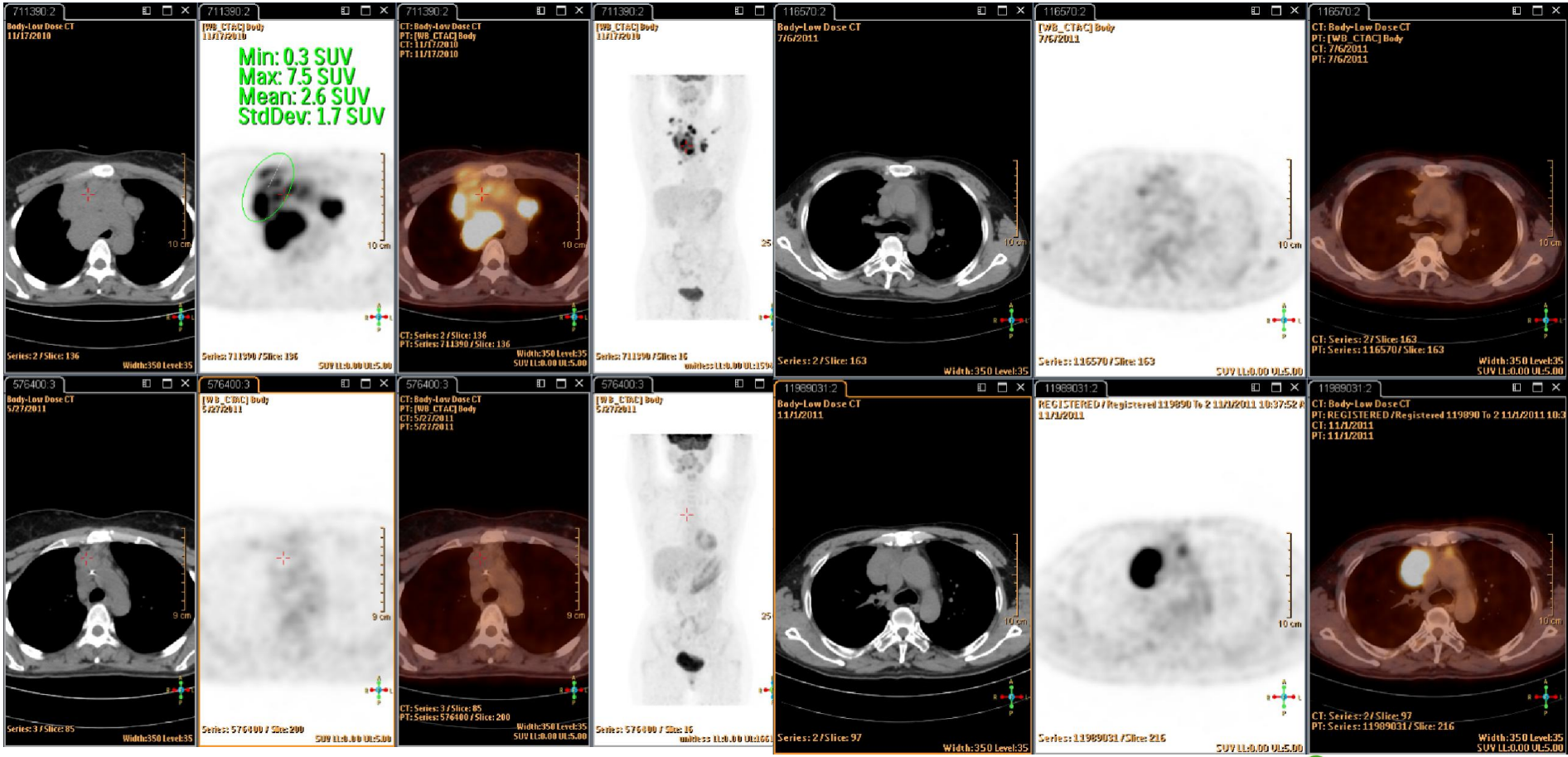

**progression-free survival (PFS)**

Juweid M E et al. JCO 2005;23:4652-4661

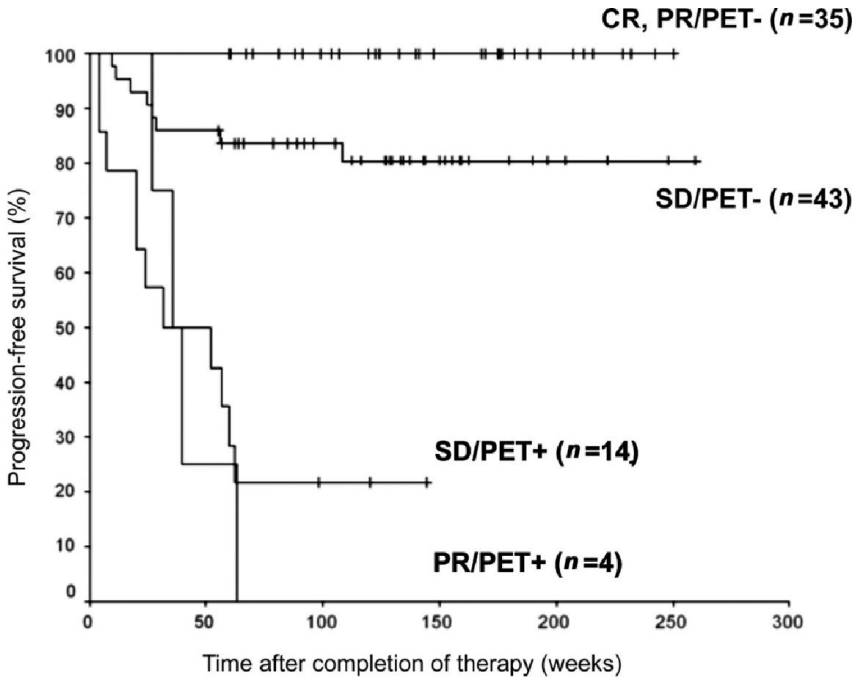
# 疗后PET重点：残存病灶判断

- 淋巴瘤治疗后病灶因纤维化坏死常导致残留肿块，病灶活性与其大小改变无必然联系
- 2/3的HL有残留病灶，约20%的病灶最终复发；50%的侵袭性NHL治疗后有残存灶，约25%复发
- PET灵敏度和特异性分别为71%~100% 和69%~100%，CT特异性只有4%~31%

# 残存病灶判断



# 残存病灶及预后




- PET(-)残存病灶大小和预后正相关。
- 病灶越大，DFS值越低
- Cut-off值为：4cm

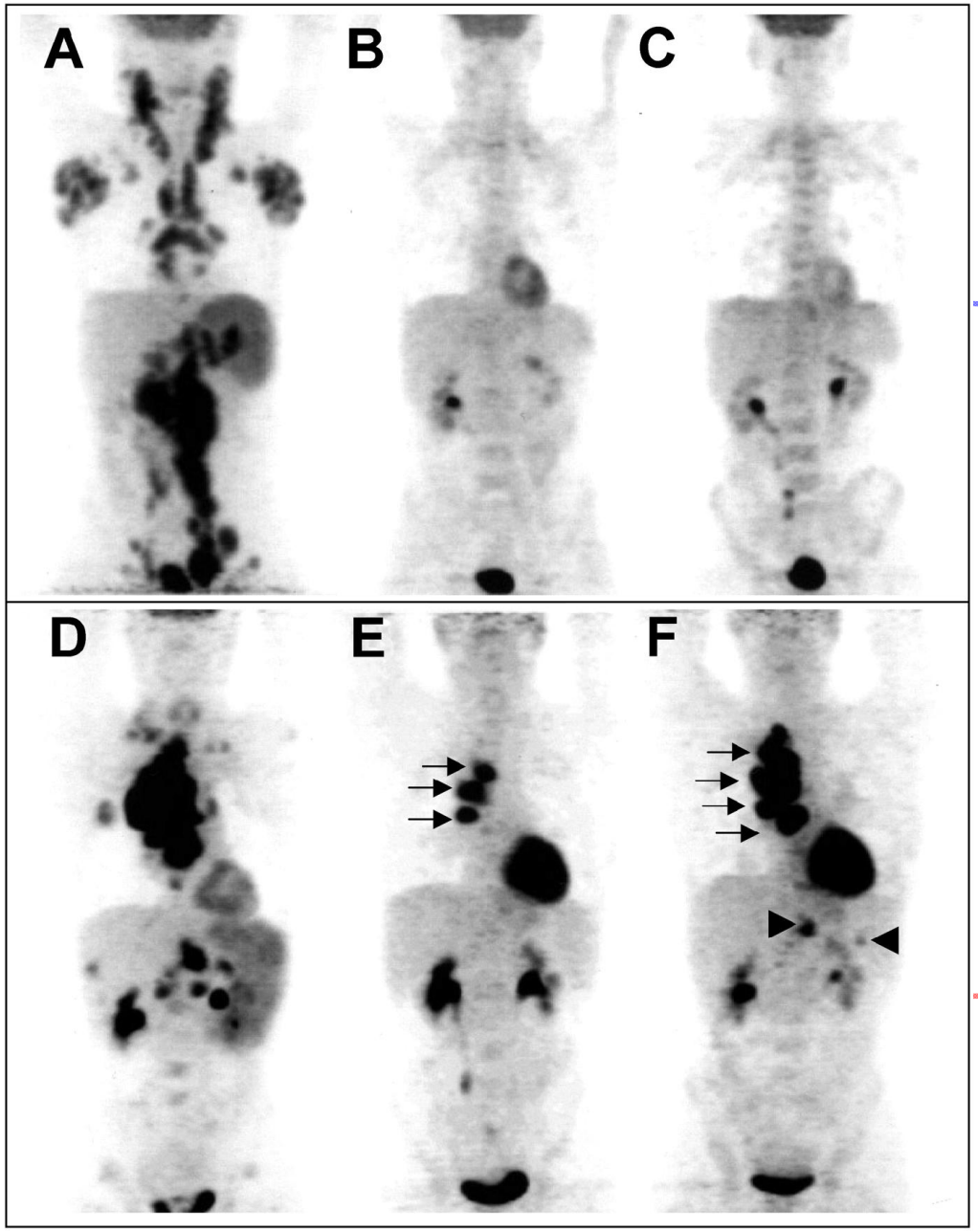
| | | % 5-yr DFS | p | Therapy |
|---|---|---|---|---|
| Residual size | < 4 cm | 77 | 0.0029 | ABVD (34)<br>VEBEP (40)<br>2-nd line (21) |
| | ≥ 4 cm | 52 | | |

Reinhardt M J et al. Ann Oncol 2005

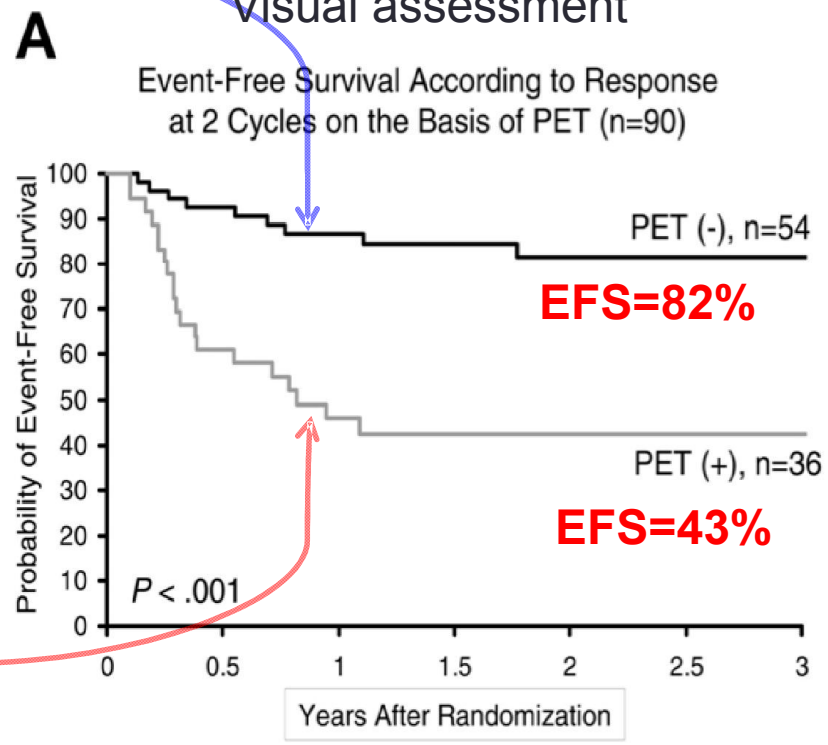
# 共识&争议：

中期PET/CT

# 中期PET




**NHL** 90 pts (2000-2004)
PET0, PET2, PET4
Visual assessment




**2 years median follow-up**

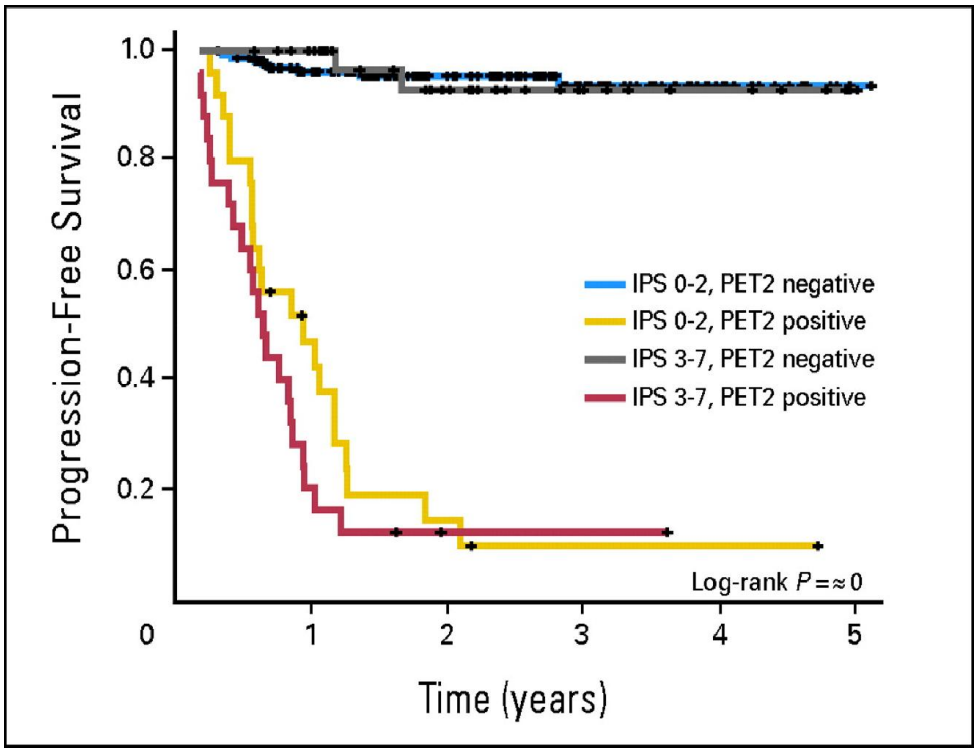
Haioun C et al. Blood 2005;106:1376-1381

# 中期PET/CT：HL

PET2 (-) ≈95%

2 yr PFS

PET2 (+) ≈12%



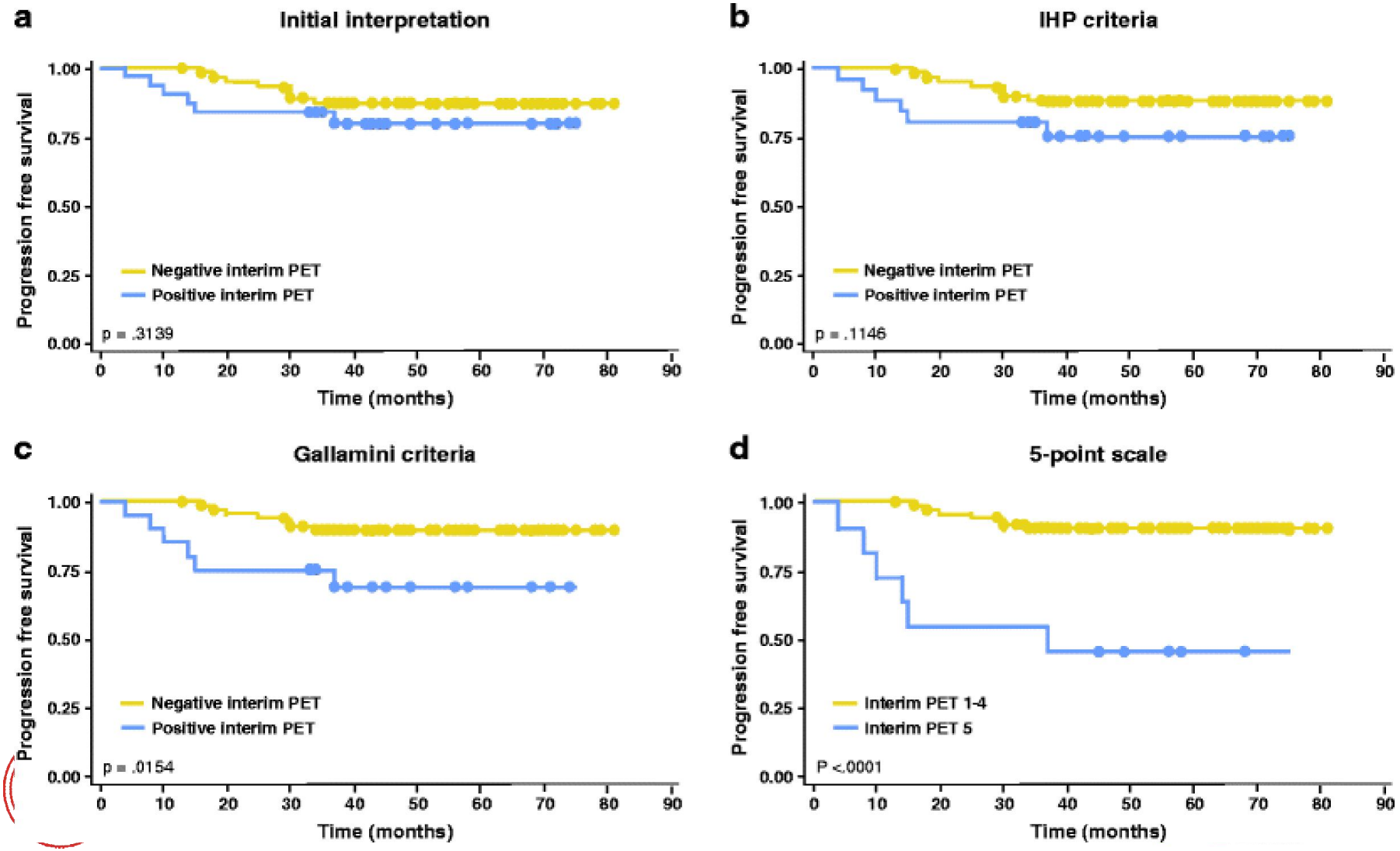

**Negative:** No pathologic FDG uptake at any site.

**Positive:** Focal FDG concentration outside the physiological uptake areas, with clearly increased activity relative to the background

Gallamini A et al. JCO 2007;25:3746-3752

| Authors (ref) | Patient No. | Cycles | PET negative | PFS (%) | PET positive | PFS (%) |
|---|---|---|---|---|---|---|
| HL | | | | | | |
| Kostakoglu et al. | 23 | 1 | 74 | 100 | 26 | 12.5 |
| Hutchings et al. | 85 | 2–3 | 72 | 94 | 13 | 38 |
| Hutchings et al. | 77 | 2 | 79 | 95 | 21 | 31 |
| Zinzani et al. | 40 | 2 | 80 | 97 | 20 | 12 |
| Gallamini et al. | 260 | 2 | 81 | 95 | 19 | 14 |
| Markova et al. | 50 | 4 | 72 | 100 | 28 | 86 |
| NHL | | | | | | |
| Kostakoglu et al. | 24 | 1 | 58 | 100 | 42 | |
| Jerusalem et al. | 28 | 2–3 | 82 | 100 | 18 | 30 |
| Spaepen et al. | 47 | 3–4 | 47 | 84 | 53 | 0 |
| Haioun et al. | 90 | 2 | 60 | 82 | 40 | 43 |
| Mikhaeel et al. | 121 | 2–3 | 41.7 | 93 | 43 | 30 |
| Zinzani et al. | 91 | | 61.5 | 89 | 38.5 | 17 |
| Cashen et al. | 50 | 2–3 | 30 | 85 | 30 | 75 |

# 判读标准


a
Initial interpretation
Progression free survival
1.00
0.75
0.50
0.25
0.00
Negative interim PET
Positive interim PET
p = .3139
0 10 20 30 40 50 60 70 80 90
Time (months)
b
IHP criteria
Progression free survival
1.00
0.75
0.50
0.25
0.00
Negative interim PET
Positive interim PET
p = .1146
0 10 20 30 40 50 60 70 80 90
Time (months)
c
Gallamini criteria
Progression free survival
1.00
0.75
0.50
0.25
0.00
Negative interim PET
Positive interim PET
p = .0154
0 10 20 30 40 50 60 70 80 90
Time (months)
d
5-point scale
Progression free survival
1.00
0.75
0.50
0.25
0.00
Interim PET 1-4
Interim PET 5
P <.0001
0 10 20 30 40 50 60 70 80 90
Time (months)

Deauville 2009

Menton 2010

Menton 2011

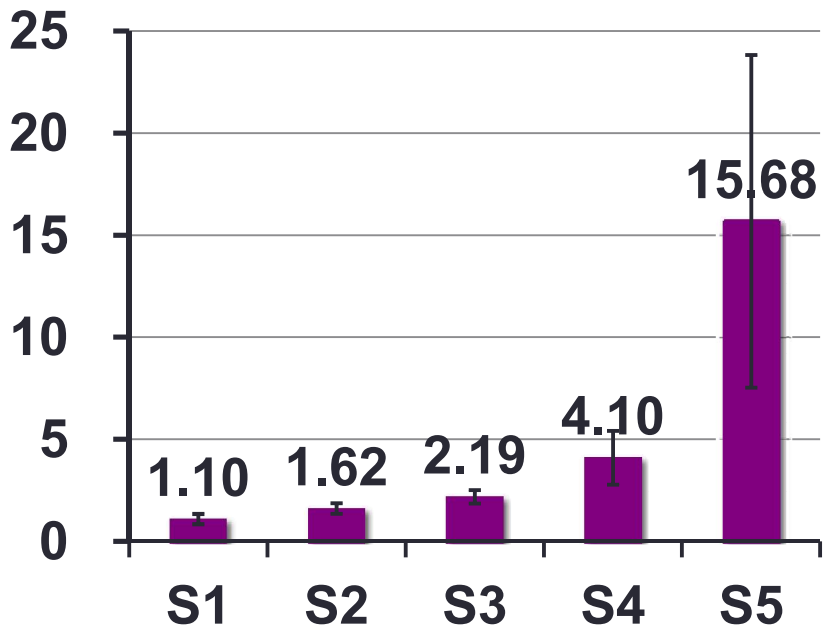
Menton 2012

# Deauville scale

1. No uptake
2. Uptake <= mediastinum
3. Uptake >mediastinum but <= liver
4. Uptake > liver at any site
5. Uptake >> liver and/ or new sites of disease

Barrington SF, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. 2010 EJNMMI

# 5-PS 评分 vs. $SUV_{max}$ 值



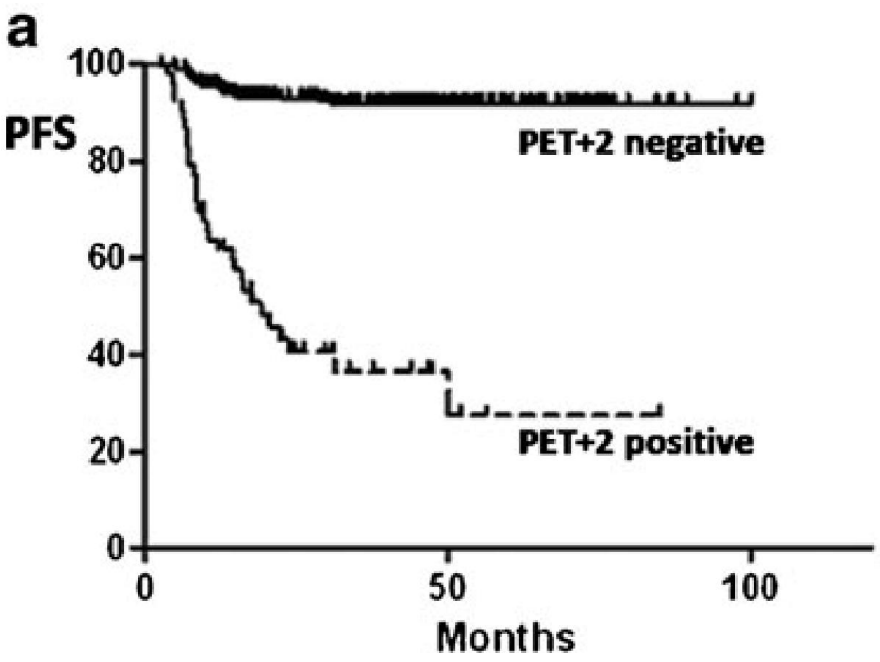

| Score | $SUV_{max}$ |
|---|---|
| S1 | 0.8-1.5 |
| S2 | 1.3-2.3 |
| S3 | 1.8-2.7 |
| S4 | 2.4-5.9 |
| S5 | 5.6-32.4 |

| | 肝脏 | 纵膈 |
|---|---|---|
| 范围 | 2.0-4.0 | 1.0-2.8 |
| 均值 | 2.7±0.4 | 1.9±0.3 |

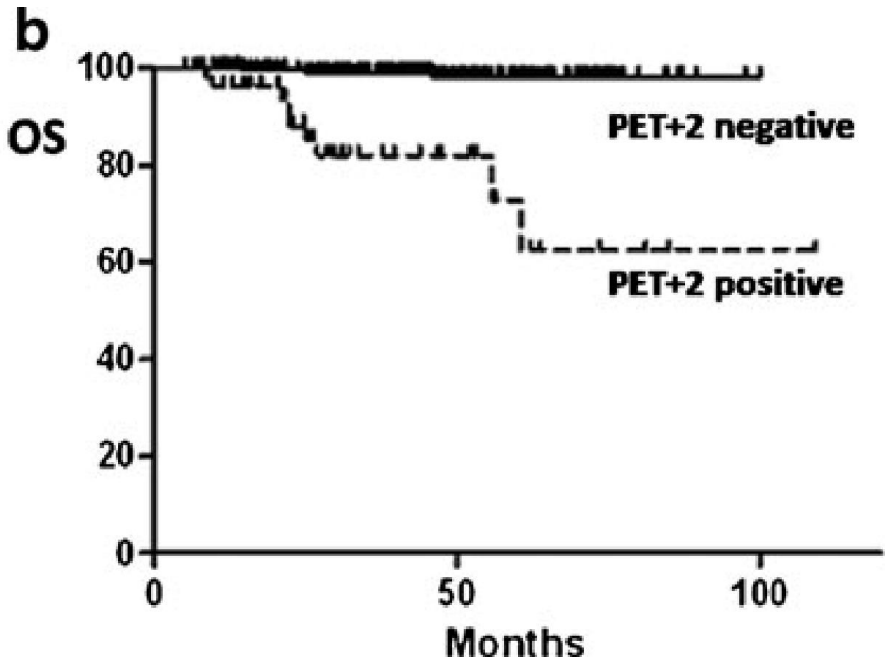
# 共识五：2013 NCCN指南---HL中期PET

- Deauville（五分法）：中期PET评估标准
- 建议在ABVD /递增剂量BEACOPP 2-4 周期后行中期PET
- 对于接受Stanford V 方案患者，通常在化疗后8 和12 周后行中期疗效评估
- 专家组同样承认，基于中期PET 结果指导下的治疗属科研性质，在临床试验环境之外并不推荐使用

# 霍奇金淋巴瘤：化疗后2周期，304名患者




PFS




OS

Zinzazi et. al. EJNMMI. 2012 Jan;39(1):4-12.

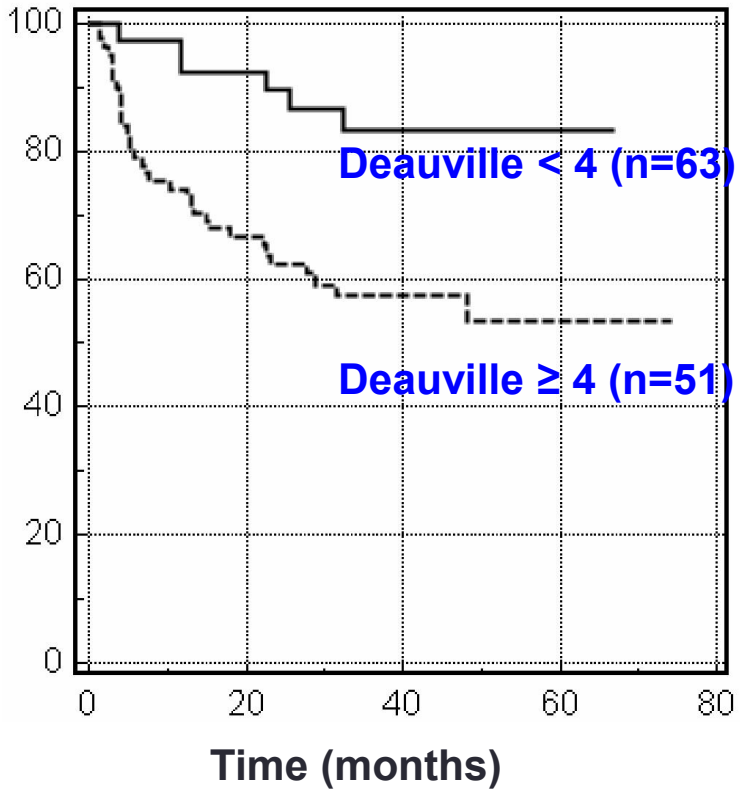
# 争议：弥漫大B淋巴瘤--判读标准

$$\Delta SUV_{max}\text{值}(\%)=\frac{(SUV_{max\text{-治疗前}}-SUV_{max\text{-中期}})\times 100\%}{SUV_{max\text{-治疗前}}}$$

**争论点：Cutoff值**

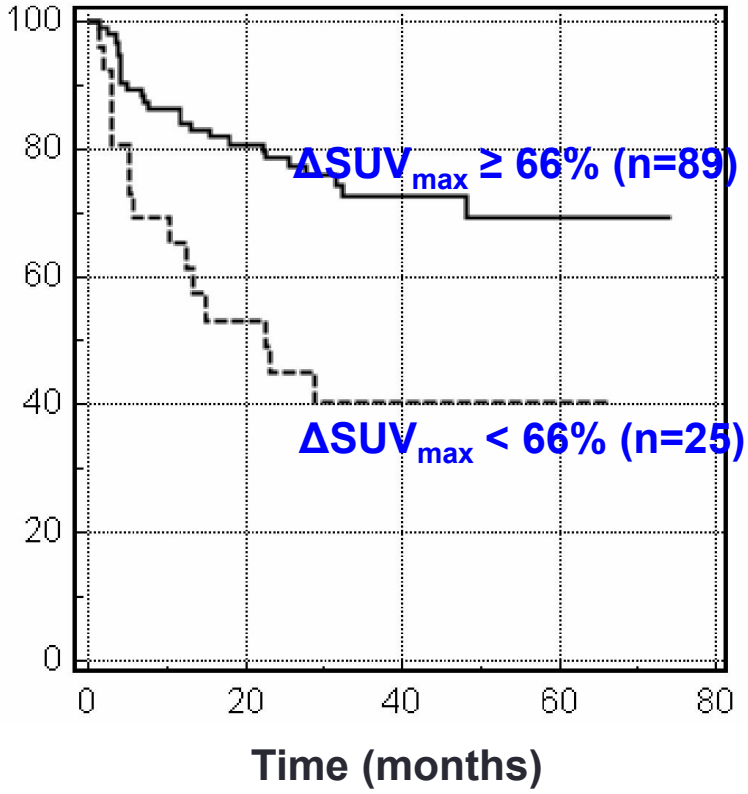
# 视觉法 *vs.* $\Delta SUV_{max}$ 值

**5-point scale (Cut-off ≥ 4)**




**3-y PFS: 81% vs 59%**

**$\Delta SUV_{max}$ (Cut-of ≥ 66%)**



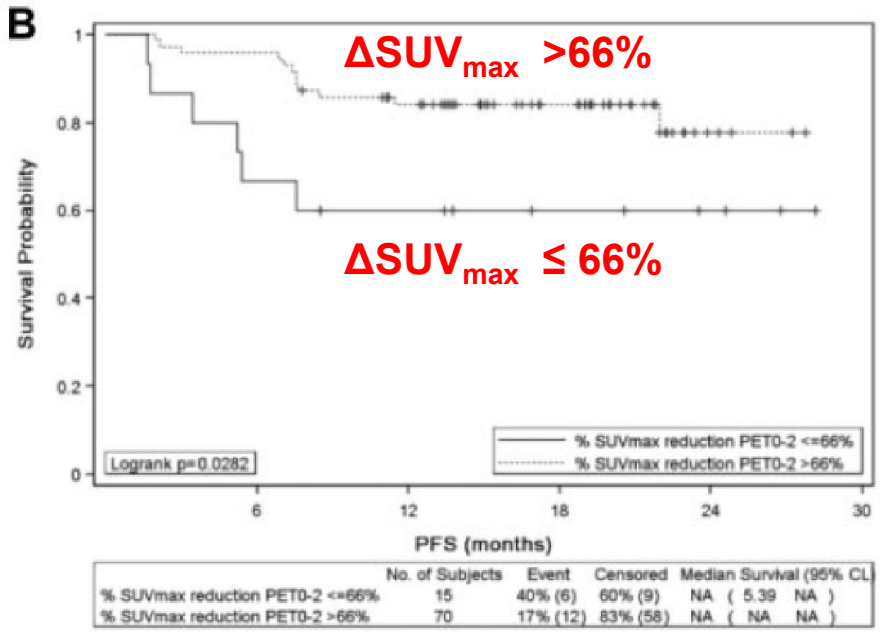

**3-y PFS: 79% vs 44%**

Itti, Menton 2012

# Cutoff值的探索

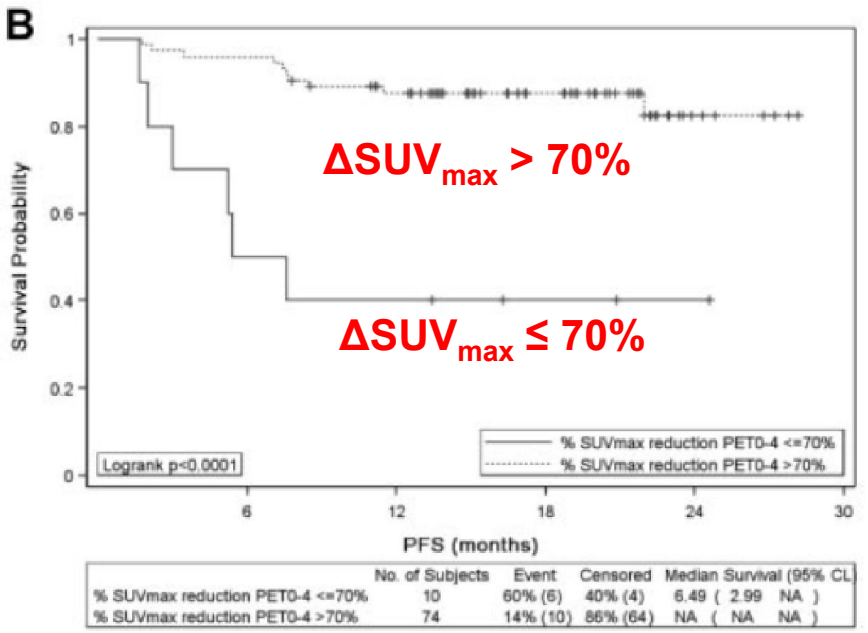
**85 patients, DLBCL, aaIPI2-3, randomized R-ACVBP/ROCHOP 14 interim analyss of LNH073B trial, PET 2/4 driven strategy**

$SUV_{max}$ reduction (>66 % versus ≤ 66%)




| | No. of Subjects | Event | Censored | Median Survival (95% CL) |
|---|---|---|---|---|
| % SUVmax reduction PET0-2 <=66% | 15 | 40% (6) | 60% (9) | NA ( 5.39 NA ) |
| % SUVmax reduction PET0-2 >66% | 70 | 17% (12) | 83% (58) | NA ( NA NA ) |

$SUV_{max}$ reduction (> 70 % versus ≤ 70%)



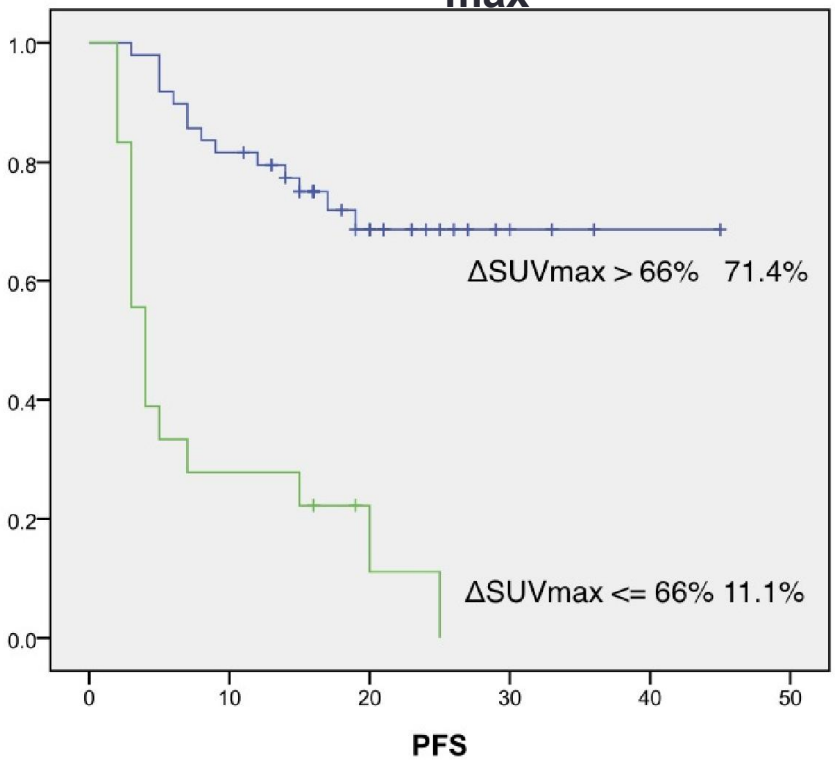

| | No. of Subjects | Event | Censored | Median Survival (95% CL) |
|---|---|---|---|---|
| % SUVmax reduction PET0-4 <=70% | 10 | 60% (6) | 40% (4) | 6.49 ( 2.99 NA ) |
| % SUVmax reduction PET0-4 >70% | 74 | 14% (10) | 86% (64) | NA ( NA NA ) |

Casasnovas R et al. Blood 2011;118:37-43

# 中期PET/CT评估患者预后

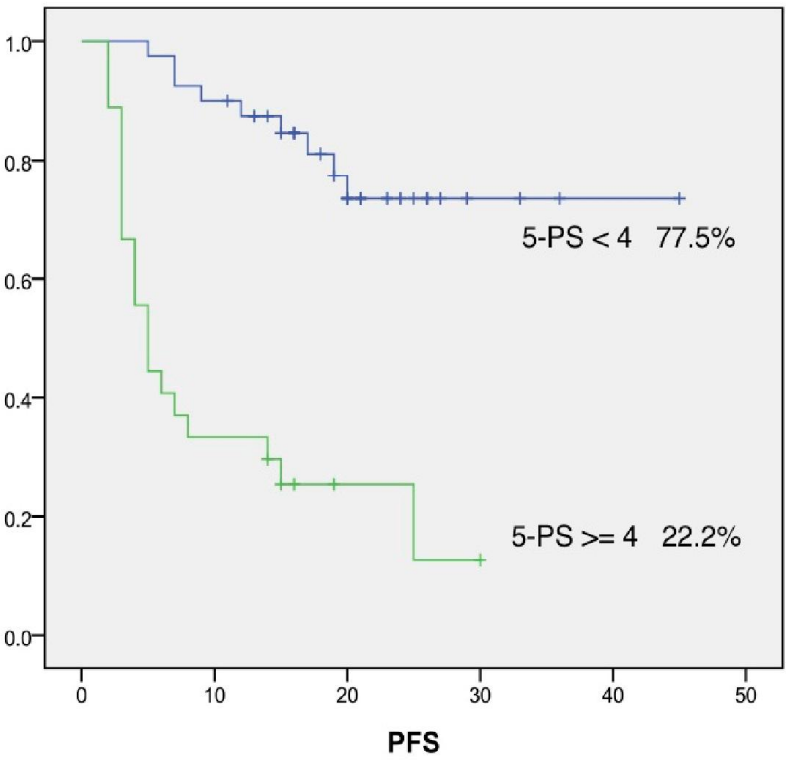
## DLCBL, 65名患者 R-CHOP, 4周期

### $\Delta SUV_{max}$ 法




2-y PFS: 71.4% vs 11.1%

### 五分法




2-y PFS: 78% vs 22%

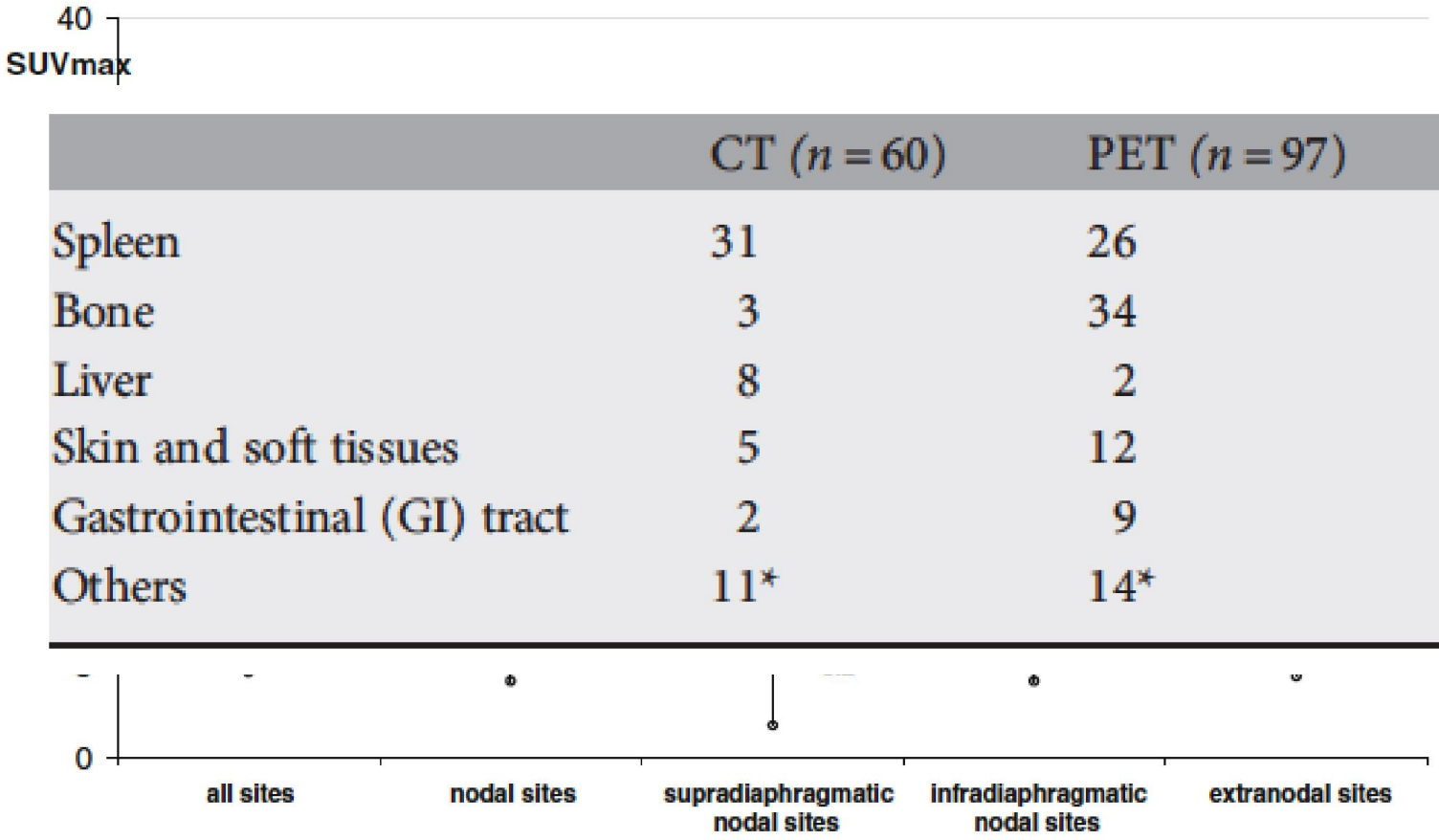
Itti, Menton 2012

# 评估指标比较

| 标准 | PFS | 差值 | OS | 差值 |
|---|---|---|---|---|
| 5-PS | 78% vs 22% | 56% | 93% vs 44% | 49% |
| ΔSUVmax | 71% vs 11% | 60% | 89% vs 33% | 56% |
| SUVmax | 84% vs 20% | 64% | 92% vs 50% | 42% |

# 争议&困惑

# 争议&困惑：滤泡淋巴瘤

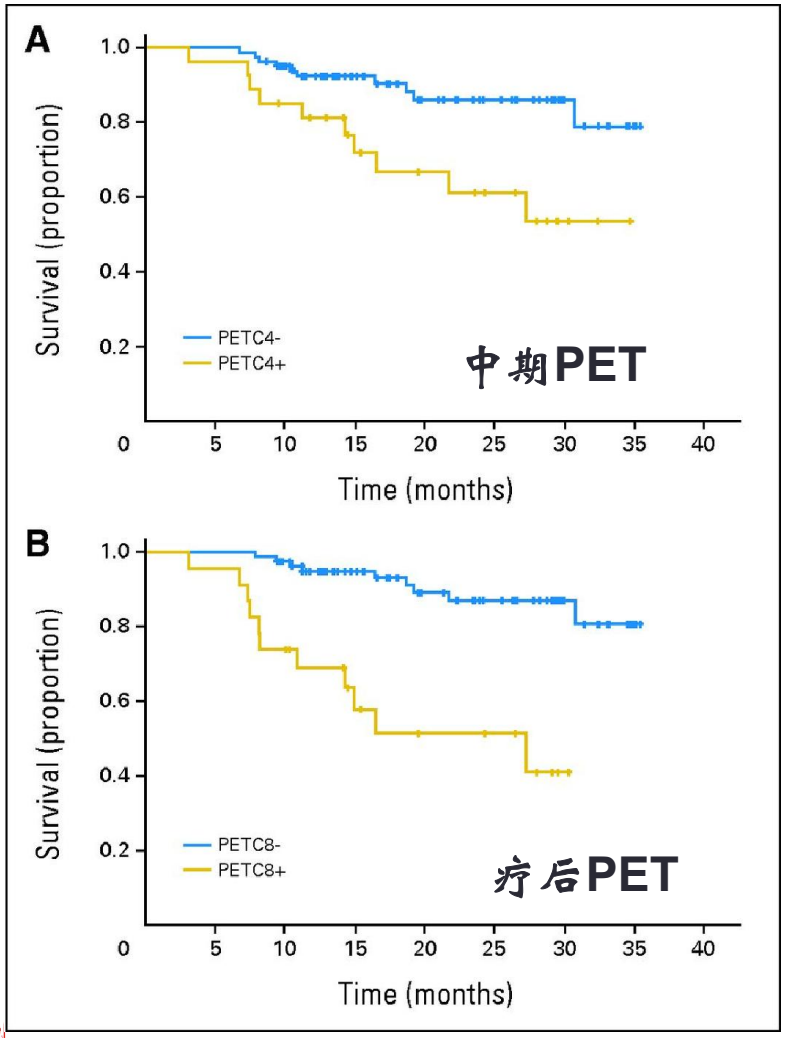



| | CT ($n=60$) | PET ($n=97$) | $\kappa$ |
|---|---|---|---|
| Spleen | 31 | 26 | 0.49 |
| Bone | 3 | 34 | 0.07 |
| Liver | 8 | 2 | 0.18 |
| Skin and soft tissues | 5 | 12 | 0.44 |
| Gastrointestinal (GI) tract | 2 | 9 | 0.35 |
| Others | 11* | 14* | NA |

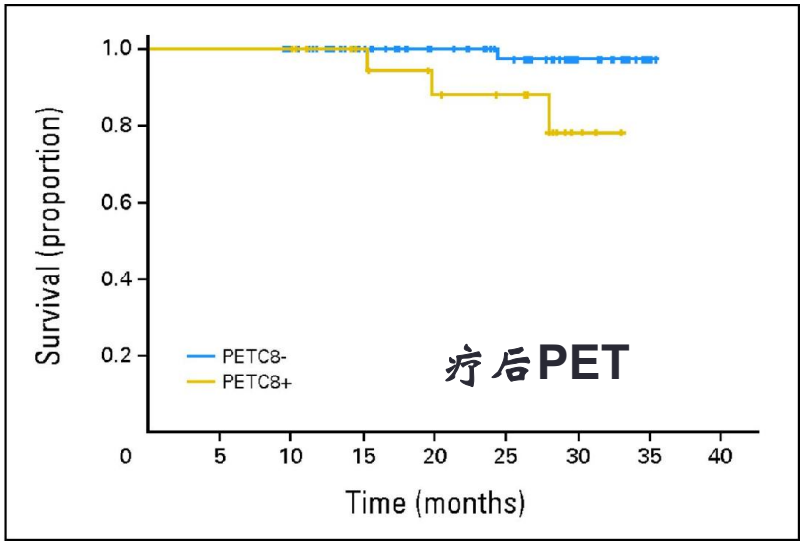
Tychyj-Pinel et al EJNMMI 2014 （PRIMA study）
Luminari Annals of oncology 2013

# 争议&困惑：滤泡淋巴瘤

PFS



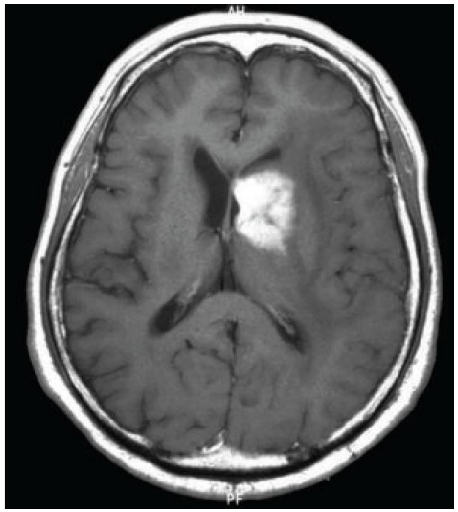

OS

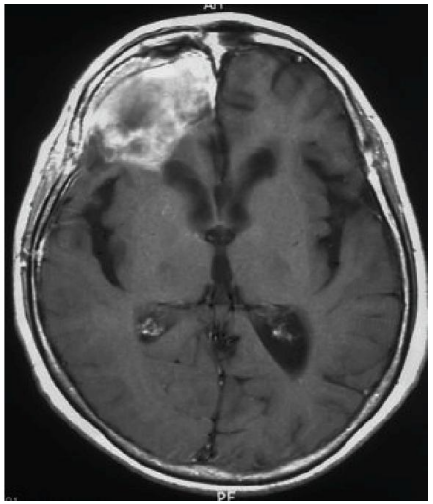
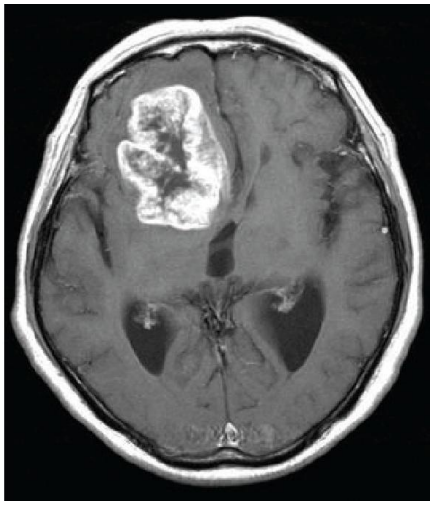
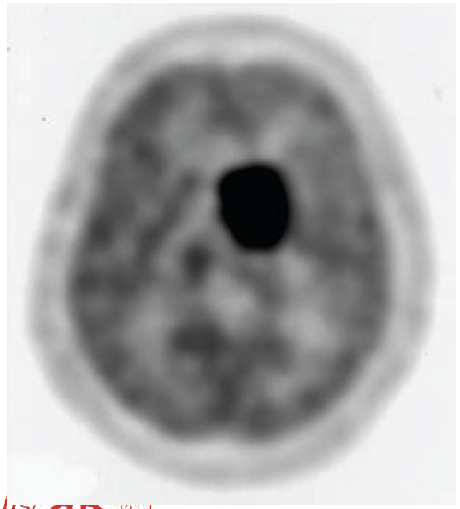
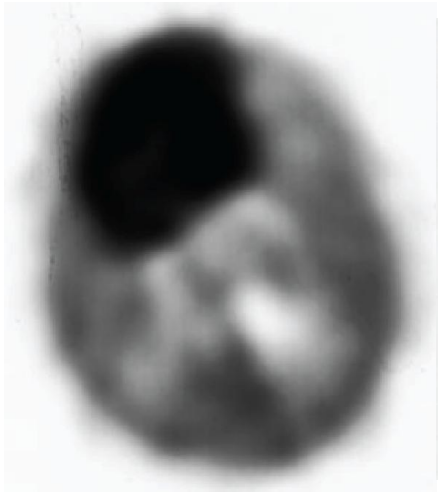
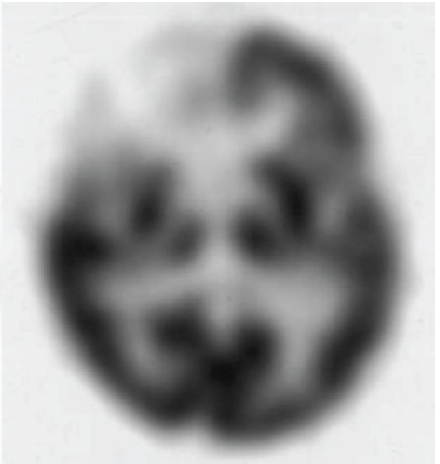
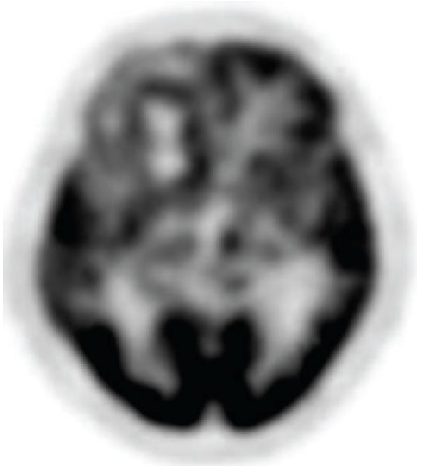



**GOELAMS:**
**119 FL patients,**
**R-CHOP×4+R-CHOP/Rituximab**

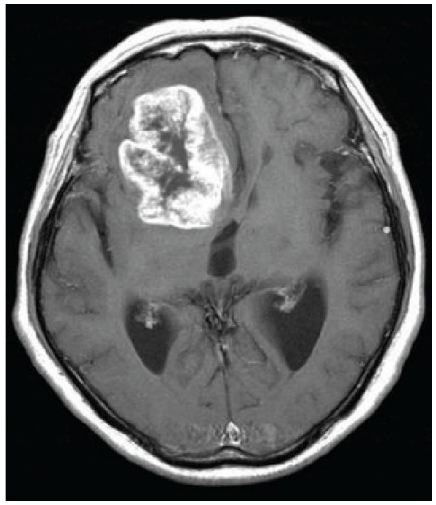
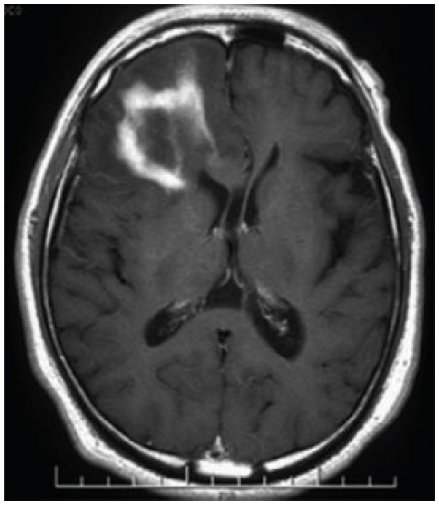
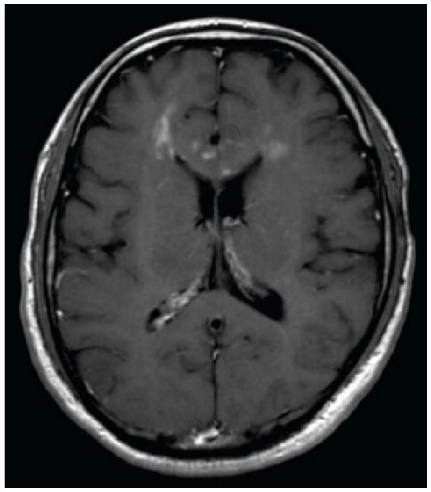
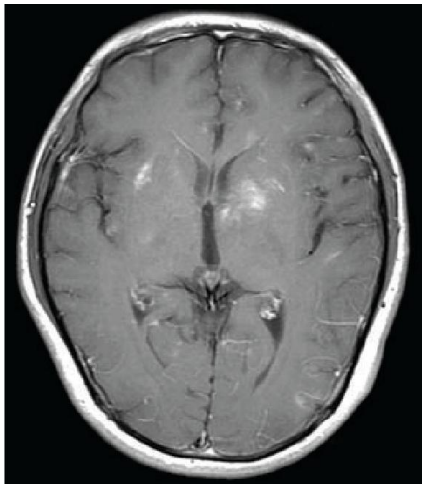
Dupuis J et al. JCO 2012;30:4317-4322

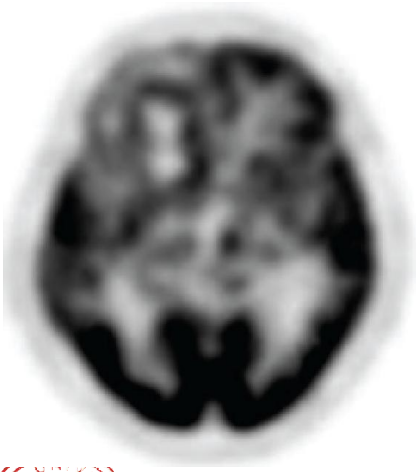
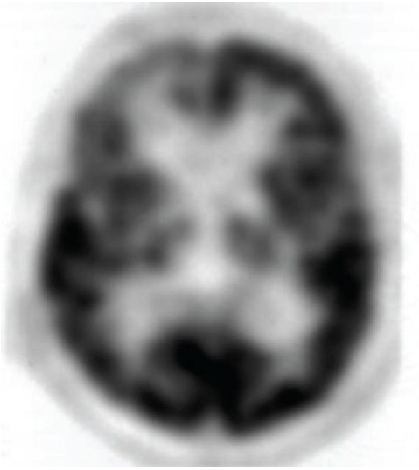
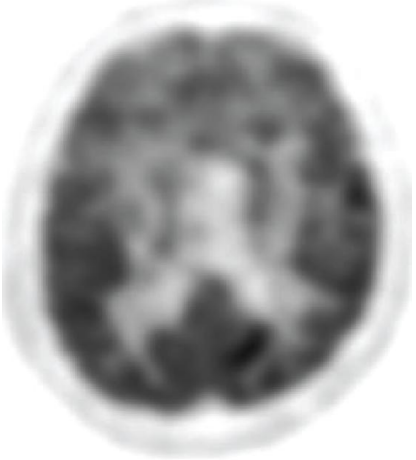
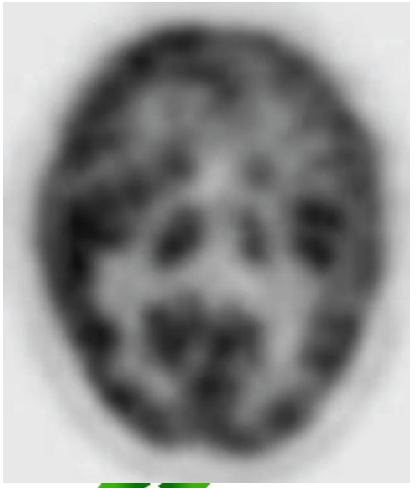
# 争议&困惑：神经系统淋巴瘤



# 争议&困惑：神经系统淋巴瘤

胶质瘤　　不典型淋巴瘤　　不典型淋巴瘤　　弓形虫感染

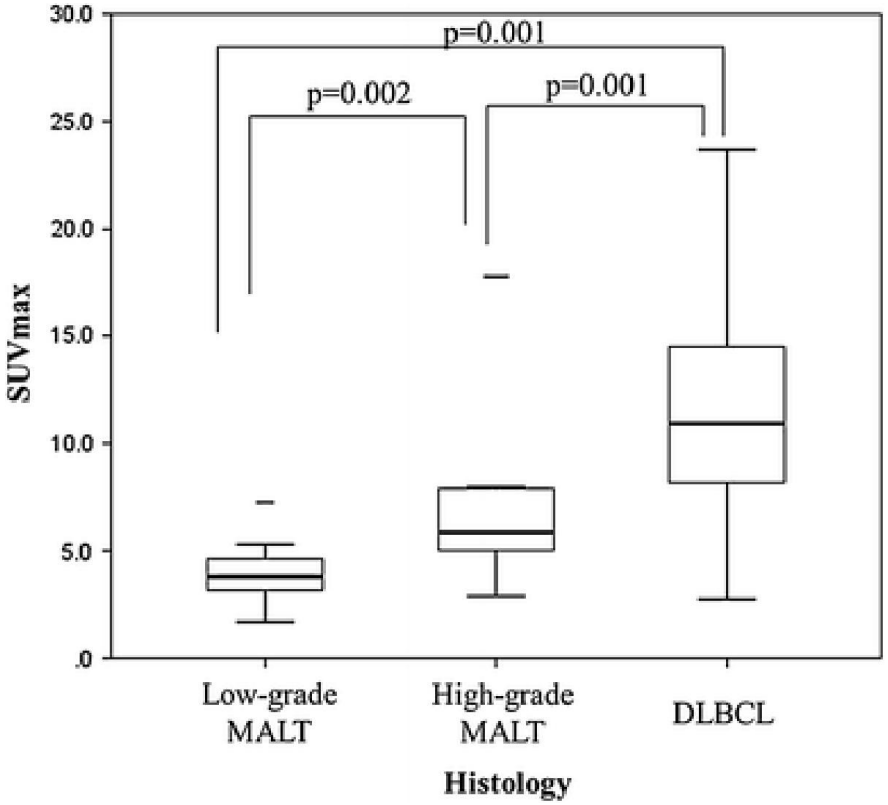
# 争议&困惑：神经系统淋巴瘤

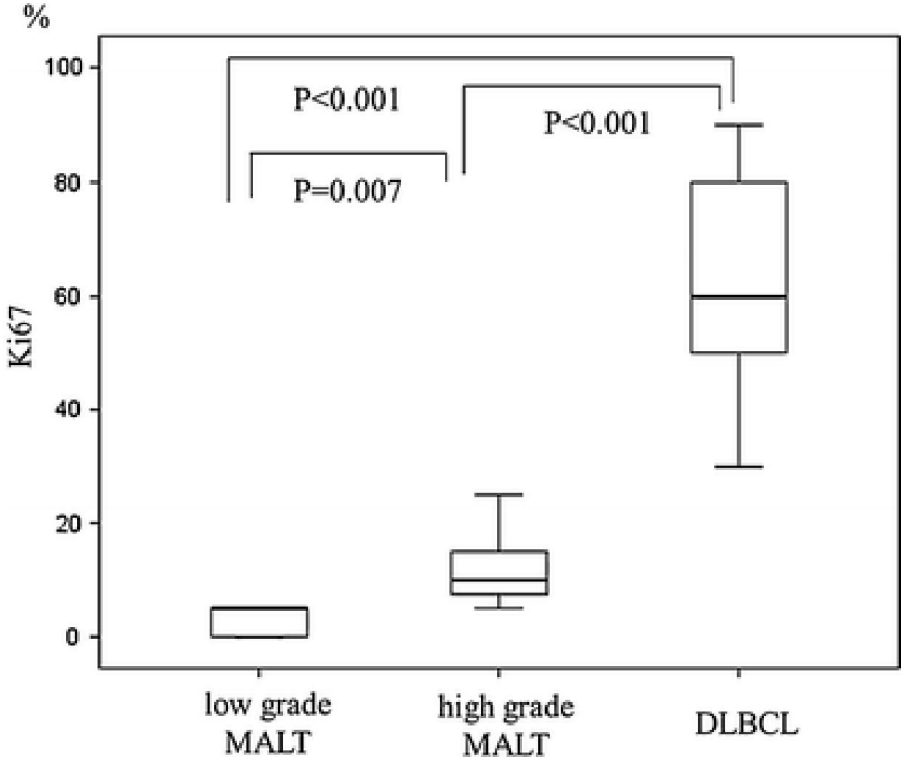
- $^{18}$F-FDG PET/CT能检出典型神经系统淋巴瘤，表现为极高放射性摄取（$SUV_{max}$8~22），比脑灰质$SUV_{max}$高2.5倍，亦高于其他恶性肿瘤（胶质瘤及转移瘤）放射性摄取
- 淋巴瘤$SUV_{max}$大于12预后不良
- 在治疗早期，$^{18}$F-FDG PET/CT能评估典型淋巴瘤治疗效果。
- 类固醇治疗患者能显著减少淋巴瘤的放射性摄取，从而增高假阴性率
- 头颅$^{18}$F-FDG PET/CT阴性，仍需做脑脊液检测

# Ki67 vs. $^{18}$F-FDG vs. $^{18}$F-FLT

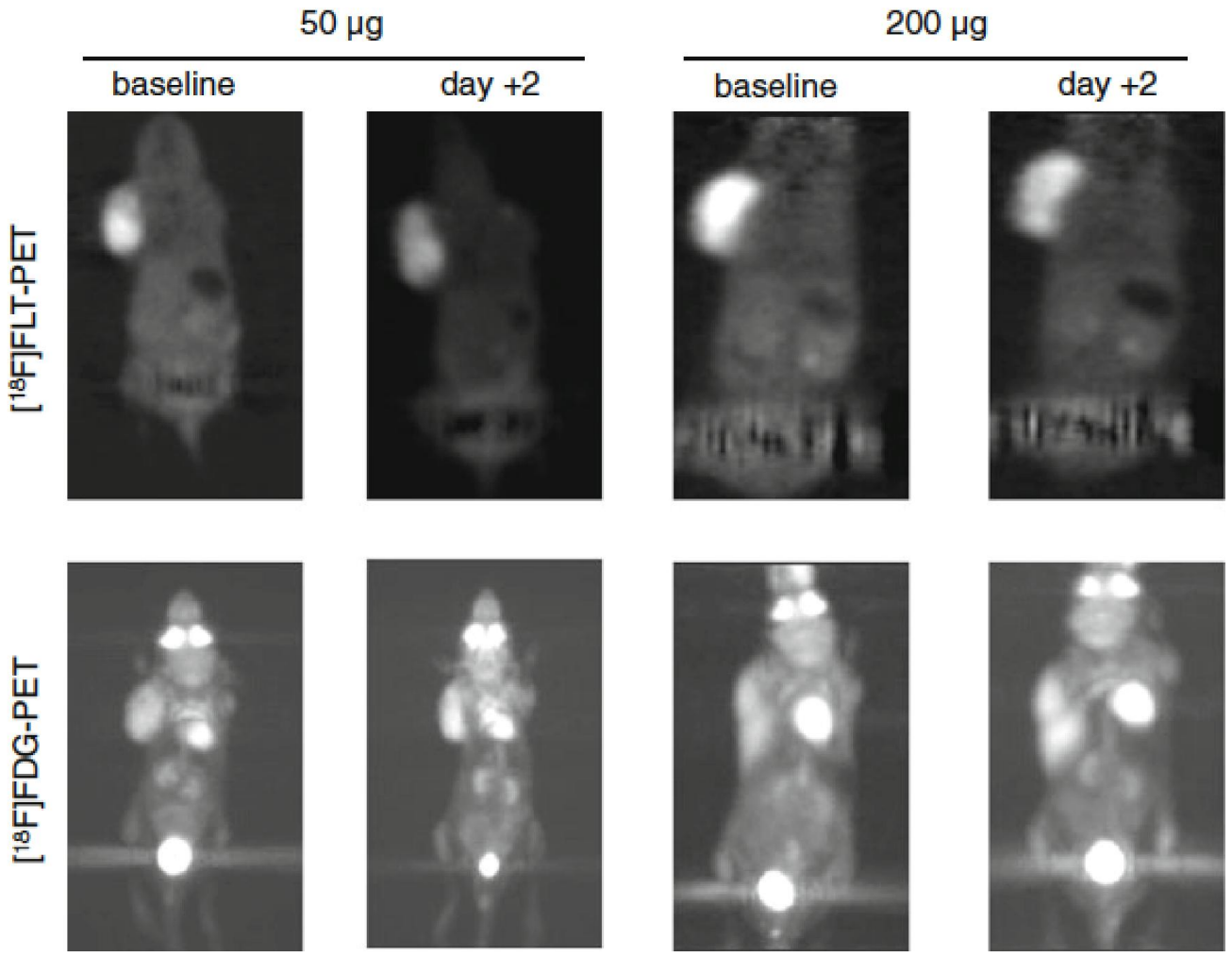
- 通常意义上的PET为$^{18}$F-FDG PET。FDG（2-$^{18}$F-2-脱氧-D-葡萄糖）为葡萄糖类似物，代表细胞糖代谢水平。
- Ki67是一种增殖细胞相关的核抗原,其功能与有丝分裂密切相关
- FLT（3'-脱氧-3'-$^{18}$F-胸腺嘧啶）为胸腺嘧啶类似物，代谢细胞增殖水平
- 最大SUV值（$SUV_{max}$）代表细胞摄取放射性示踪剂的剂量

# Ki67 vs. $^{18}$F-FDG PET



# $^{18}$F-FLT较$^{18}$F-FDG更能反映细胞增殖



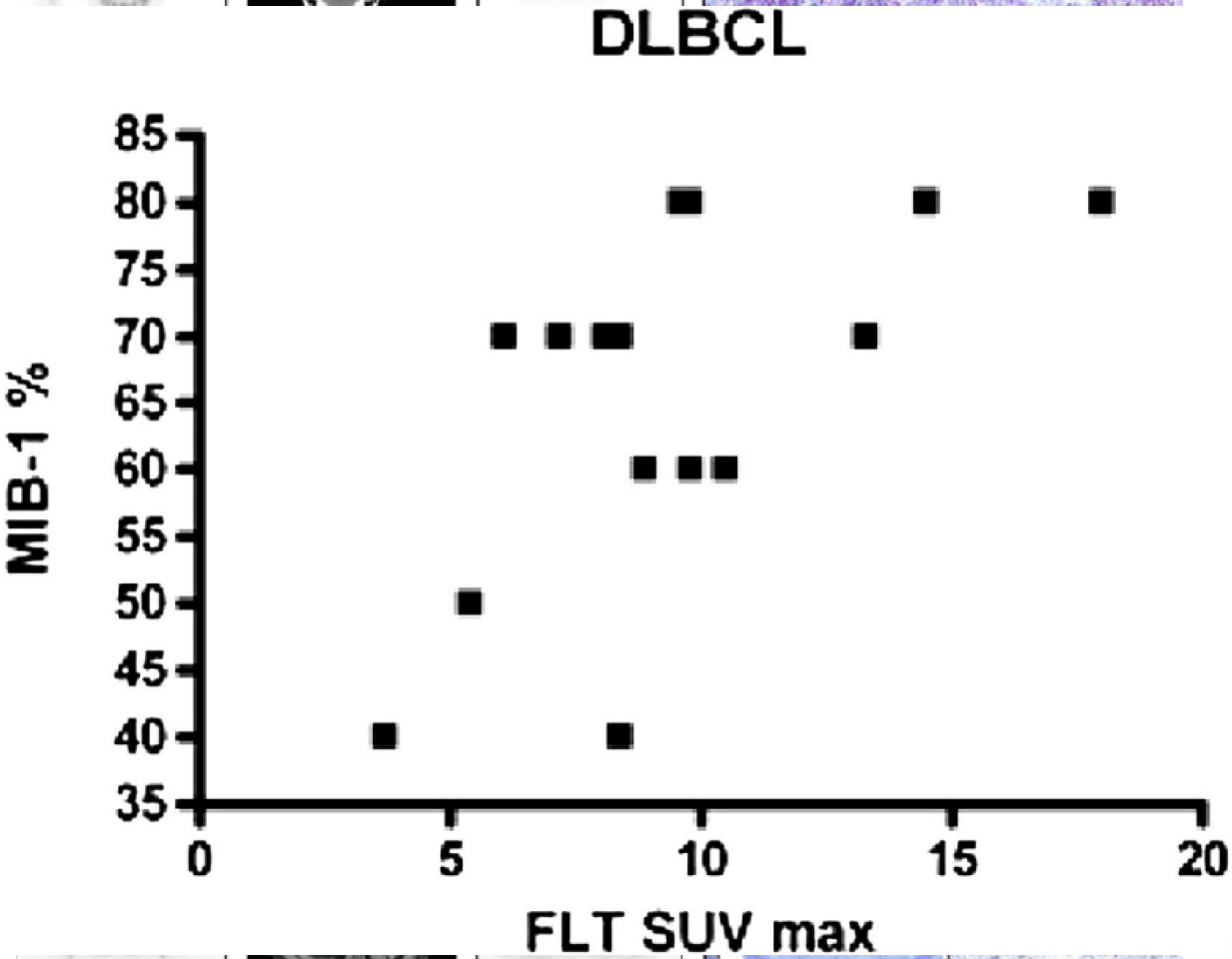


DLBCL化疗：阿霉素

# $^{18}$F-FLT PET/CT vs Ki-67 (DLBCL)


aggressive lymphoma

Ki-67 labeling index: >90%




Low grade lymphoma

Ki-67 labeling index: < 5%

Buck AK, Methods 2009; 48:205

# $^{18}$F-FDG PET /CT建议

- 加强专科临床医生与核医学医生的交流及合作
- PET/CT扫描应标准化
- 基线PET/CT
- 中期PET/CT下周期化疗前4-5天，疗后PET/CT化疗结束后6-8周（放疗后适当延长时间）
- Deauville评分为HL 中期及疗后PET/CT的评价标准，NHL亦可用
- NHL标准为热点，值得研究

We Are “One Step Forward & One Step Back”


谢谢，敬请批评指教