# 18F-FDG PET/CT EN EL MANEJO DE PACIENTES CON LINFOMA

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Sociedad Chilena de Hematología
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# PET/CT

- Técnica hibrida funcional y anatómica, no invasiva, 3D, alta sensibilidad y localización precisa lesiones

- RF más usado: 18F-FDG. Incorporación célular activa (Glut), atrapada en intracelular, equilibrio 60-90 min, T1/2 120 min.

- 18F-FDG se acumula en células alto consumo energético, ** alta tasa mitótica

# FDG PET/CT

- Marcador INESPECÍFICO de compromiso neoplásico
  - FP: Captación elevada en lesiones benignas, ** inflamatorio
  - FN: Baja captación en neoplasias de bajo grado

# LINFOMA

- A mayor agresividad, mayor captación FDG
- Alta utilidad linfomas de alto grado
- Menor utilidad linfomas bajo grado

**Table 2.** FDG Avidity According to WHO Classification

| Histology | No. of Patients | FDG Avid (%) |
|---|---|---|
| HL | 489 | 97-100 |
| DLBCL | 446 | 97-100 |
| FL | 622 | 91-100 |
| Mantle-cell lymphoma | 83 | 100 |
| Burkitt's lymphoma | 24 | 100 |
| Marginal zone lymphoma, nodal | 14 | 100 |
| Lymphoblastic lymphoma | 6 | 100 |
| Anaplastic large T-cell lymphoma | 37 | 94-100* |
| NK/T-cell lymphoma | 80 | 83-100 |
| Angioimmunoblastic T-cell lymphoma | 31 | 78-100 |
| Peripheral T-cell lymphoma | 93 | 86-98 |
| MALT marginal zone lymphoma | 227 | 54-81 |
| Small lymphocytic lymphoma | 49 | 47-83 |
| Enteropathy-type T-cell lymphoma | 20 | 67-100 |
| Marginal zone lymphoma, splenic | 13 | 53-67 |
| Marginal zone lymphoma, unspecified | 12 | 67 |
| Mycosis fungoides | 24 | 83-100 |
| Sezary syndrome | 8 | 100† |
| Primary cutaneous anaplastic large T-cell lymphoma | 14 | 40-60 |
| Lymphomatoid papulosis | 2 | 50 |
| Subcutaneous panniculitis-like T-cell lymphoma | 7 | 71 |
| Cutaneous B-cell lymphoma | 2 | 0 |

NOTE. Data adapted,[64] with additional updates.[18,33,34,65-67]

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FDG, [$^{18}$F]fluorodeoxyglucose; FL, follicular lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

*Only 27% of cutaneous sites.

†Only 62% of cutaneous sites.

**Table 1**

**Clinical Characteristics of the Common Lymphoma Subtypes**

| Disease | Typical Age (y) | Clinical Features | FDG Avidity | Initial Treatment* | Prognosis |
|---|---|---|---|---|---|
| Hodgkin lymphoma (10% of all lymphomas) | Median age, 28; second peak age, 60–70 | Progresses with involvement of contiguous nodal chains with late hematogenous dissemination; B symptoms in 25%; initial presentation: often neck and mediastinum | Typically high FDG uptake† | Early stage: ABVD chemotherapy and IFRT<br>Advanced stage: ABVD or BEACOPP chemotherapy with or without RT | Aim for cure; early stage disease survival > 90%, advanced stage 60%–90% |
| Diffuse large B-cell lymphoma (33% of NHL) | Median age, 64 | Clinically aggressive; usually present with large nodal masses; 60% of patients present with advanced stage (III or IV) disease and 30% with extranodal disease; may arise as transformation from pre-existing indolent lymphoma; B symptoms in 30% | Typically high FDG uptake | Anthracycline-based immunochemotherapy (eg, *R*-CHOP or *R*-EPOCH) alone or with RT | Aim for cure; 20%–40% relapse after first-line therapy |
| Follicular lymphoma (20% of NHL) | Median age, 60 | Most common indolent NHL; patients are often asymptomatic; diffuse adenopathy, peripheral and central; typically diagnosed at advanced stage with frequent marrow involvement; lung, liver, or bone involvement is less common; B symptoms infrequent (< 20%) | Variable (low to moderate FDG uptake) | Localized (stage I–II) disease: RT or observation<br>Advanced disease: watchful waiting versus rituximab alone or in combination with chemotherapy | 20%–60% disease-free at 10 y for localized disease treated with RT; typically chemo-sensitive, median life expectancy > 10 y |
| Marginal zone lymphoma (MZL) (9% of NHL) | Median age, 65–70 | Three distinct clinicopathologic subtypes; Splenic MZL, nodal MZL, and MALT lymphoma | Variable (none to high FDG uptake) | Splenic MZL: If hepatitis C positive, antivirals; in others, watchful waiting, rituximab alone or with chemotherapy, or splenectomy<br>Nodal MZL: Typically managed similar to follicular lymphoma<br>MALT lymphoma: For select gastric MALT cases, *H.pylori* eradication; otherwise, RT for localized disease, observation, or systemic therapy for advanced stage disease | Widely variable; collectively, typically chemosensitive and radiosensitive, median life expectancy > 10 y |
| Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma of CLL type (7% of NHL) | Median age, 72 | Lymphocytosis alone or with adenopathy and hepatosplenomegaly; frequent bone marrow involvement; transformation to diffuse large B-cell lymphoma is rare (2%–8%) | Variable (low to moderate uptake); high avidity suggests malignant transformation† | Watchful waiting versus immunochemotherapy | Variable; prognosis strongly influenced by individual biologic risk |
| Mantle cell lymphoma (MCL) (7% of NHL) | Median age, 68 | Usually (70%–90%) present with stage IV disease; frequent gastrointestinal and bone marrow involvement; leukemic phase in 75%; transformation (to highly aggressive blastoid variant) in 20%–30%. | Variable (low to high FDG uptake) | Immunochemotherapy with or without stem cell transplantation; in select cases, watchful waiting | Variable; aggressive initial therapy achieves median progression-free survival of > 7 y |

Source.—References 3,4,5,20,82,83,84.

Note.—FDG = fluorodeoxyglucose, MALT = mucosa-associated lymphoid tissue; NHL = non-Hodgkin lymphoma; RT = radiation therapy.

* For initial treatment, ABVD regimen = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP regimen = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; IFRT = involved field radiation therapy; *R*-CHOP regimen = rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone; *R*-EPOCH regimen = rituximab, cyclophosphamide, and infusional doxorubicin, etoposide, and vincristine.

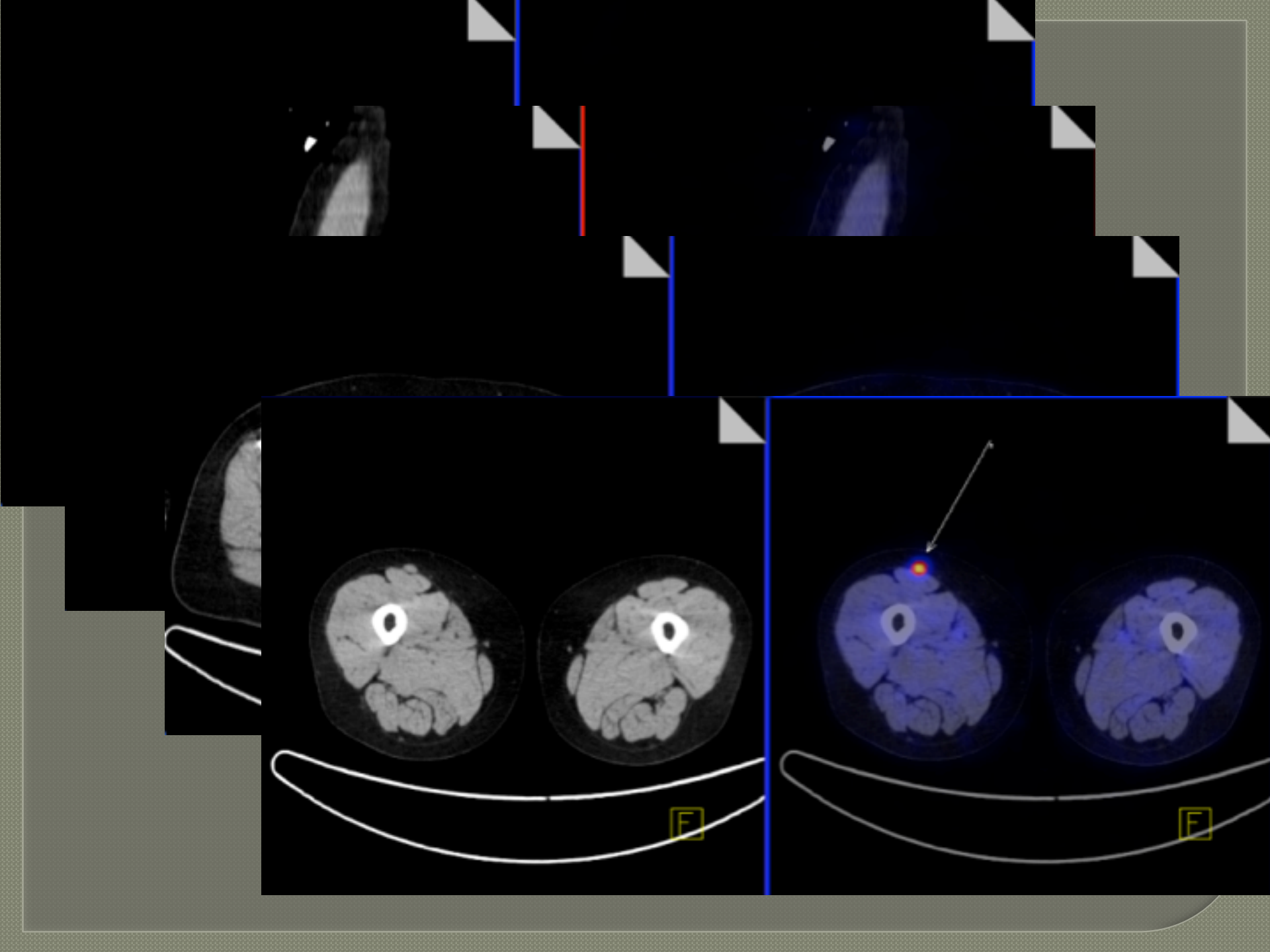
† In general, higher standardized uptake value (SUV) is found with more aggressive lymphoma; SUV > 10 is suspicious for more aggressive lymphoma (29).

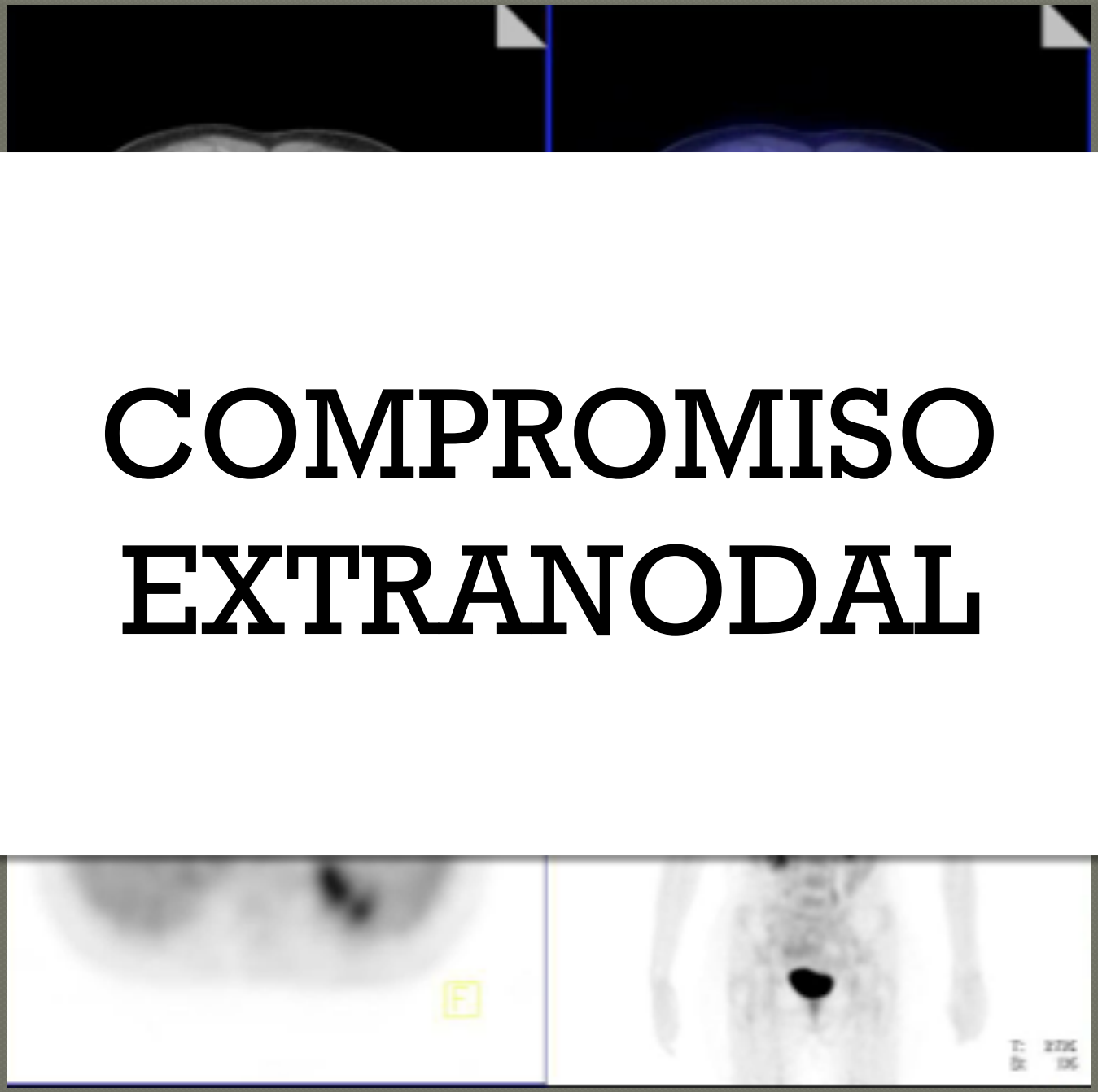
# LINFOMAS DE ALTO GRADO

LH / LDCGB

# ETAPIFICACION

- Mayor sensibilidad que cualquier otra técnica imágenes:
  - Sensibilidad 90-96%
  - Especificidad 94-96%
- Cambio estadío en 20- 30% casos
- Cambio conducta terapéutica 10-20% casos





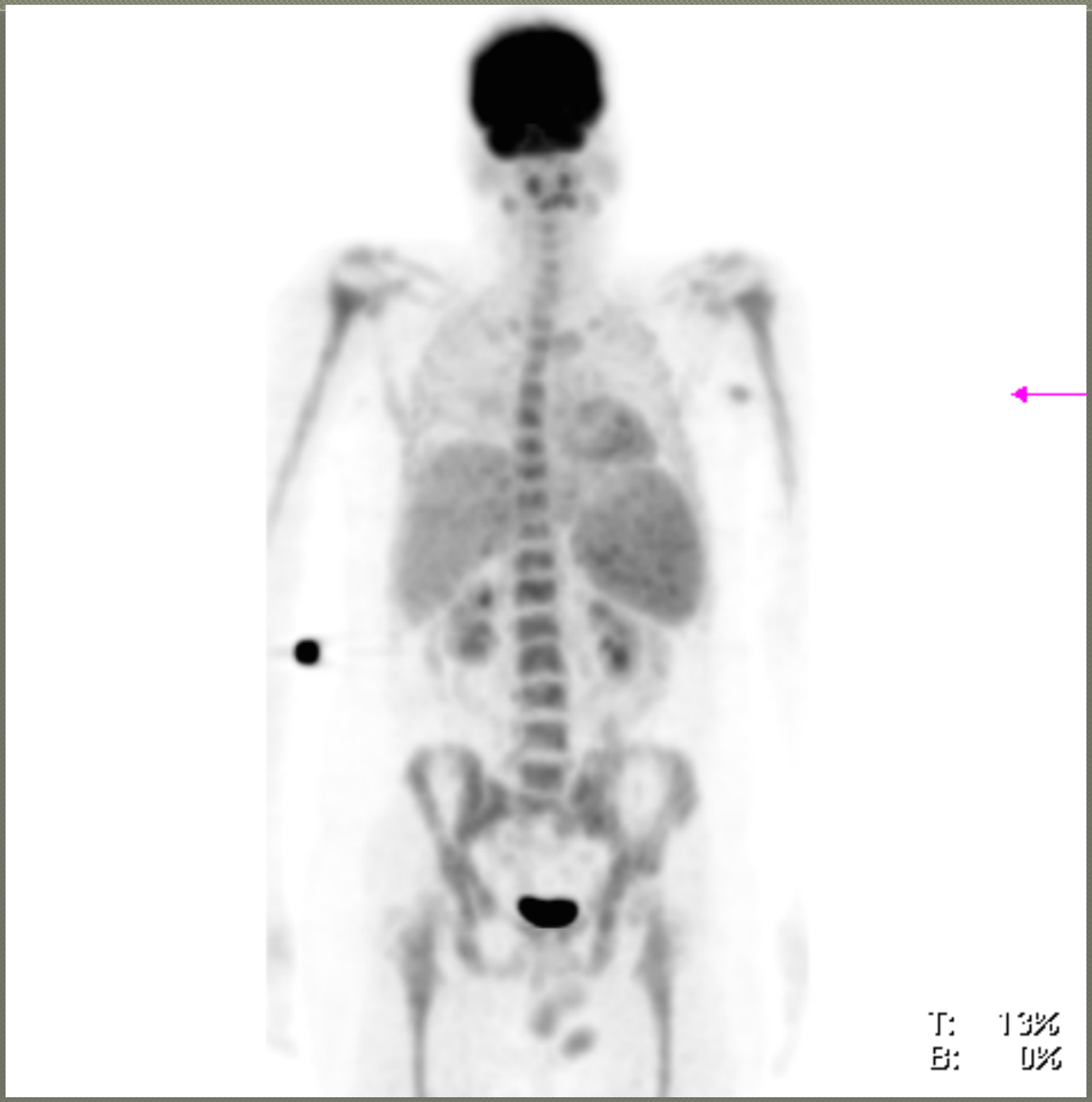
# COMPROMISO EXTRANODAL

# COMPROMISO MEDULA OSEA

# COMPROMISO MEDULA OSEA

- Implica estadío IV, requiere tratamiento agresivo
- LH y LNHDCGB
- Patrón hipercaptación focal sin traducción en CT
- Sensibilidad > 97%

- FP PET/CT: posibles FN de BMB realizada en cresta ilíaca y no en sitios de hipermetabolismo glucídico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*Annals of Oncology* 25: 921–927, 2014
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# Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary?

H. J. A. Adams[1], T. C. Kwee[1]*, B. de Keizer[1], R. Fijnheer[2], J. M. H. de Klerk[3], A. S. Littooij[1] & R. A. J. Nievelstein[1]

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**Table 5.** Results of seven of nine included studies that allowed calculation of sensitivity and specificity

| Study (year) | Sensitivity (%) | | Specificity (%) | |
|---|---|---|---|---|
| | Value | 95% CI | Value | 95% CI |
| Cortés-Romera et al. (2013) [17] | 100 | 75.3–100 | 100 | 92.6–100 |
| Agrawal et al. (2013) [18] | 87.5 | 47.3–99.7 | 100 | 85.2–100 |
| Muzahir et al. (2012) [19] | 100 | 90.5–100 | 100 | 95.8–100 |
| El-Galaly et al. (2012) [20] | 94.9 | 87.4–98.6 | 100 | 99.0–100 |
| Mittal et al. (2011) [22] | 100 | 47.8–100 | 86.7 | 59.5–98.3 |
| Cheng et al. (2011) [23] | 100 | 39.8–100 | 100 | 87.2–100 |
| Moulin-Romsee et al. (2010) [24] | 100 | 81.5–100 | 100 | 94.5–100 |
| Pooled estimate | 96.9 | 93.0–99.0 | 99.7 | 98.9–100 |

**Background:** This study aimed to systematically review and meta-analyze published data on the diagnostic performance of $^{18}$F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma, and to determine whether FDG-PET/CT can replace blind bone marrow biopsy (BMB) in these patients.

**Patients and methods:** The PubMed/Medline and Embase databases were systematically searched for relevant studies. Methodological quality of each study was assessed. Sensitivities and specificities of FDG-PET/CT in individual studies were calculated and underwent meta-analysis with a random effects model. A summary receiver operating characteristic curve (sROC) was constructed with the Moses–Shapiro–Littenberg method. The weighted summary proportion of FDG-PET/CT-negative patients with a positive BMB among all cases was calculated under the fixed effects model.

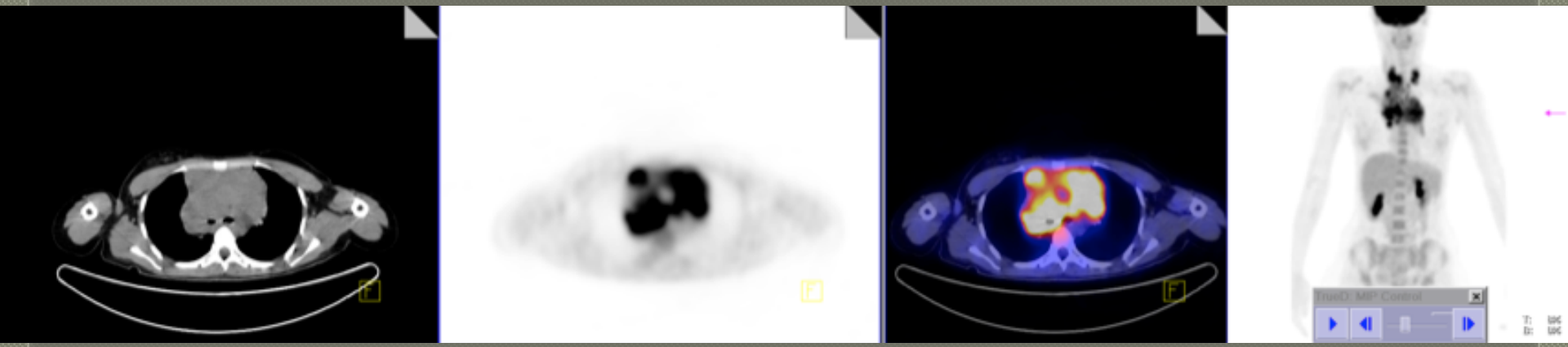
**Results:** Nine eligible studies, comprising a total of 955 patients with newly diagnosed Hodgkin lymphoma, were included. Overall, the studies were of moderate methodological quality. The sensitivity and specificity of FDG-PET/CT for the detection of bone marrow involvement ranged from 87.5% to 100% and from 86.7% to 100%, respectively, with pooled estimates of 96.9% [95% confidence interval (CI) 93.0% to 99.0%] and 99.7% (95% CI 98.9% to 100%), respectively. The area under the sROC curve was 0.9860. The weighted summary proportion of FDG-PET/CT-negative patients with a positive BMB among all cases was 1.1% (95% CI 0.6% to 2.0%).

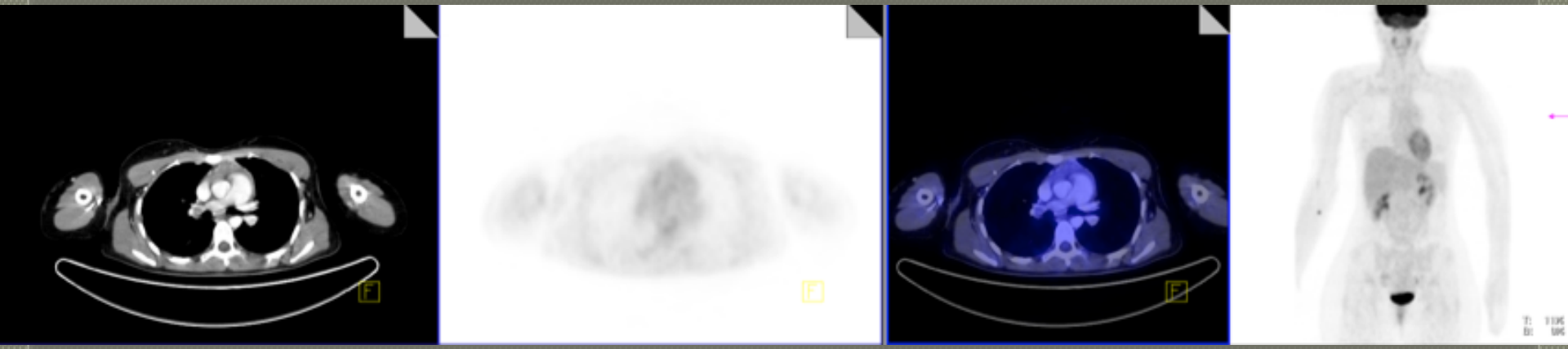
**Conclusion:** Although the methodological quality of studies that were included in this systematic review and meta-analysis was moderate, the current evidence suggests that FDG-PET/CT may be an appropriate method to replace BMB in newly diagnosed Hodgkin lymphoma.

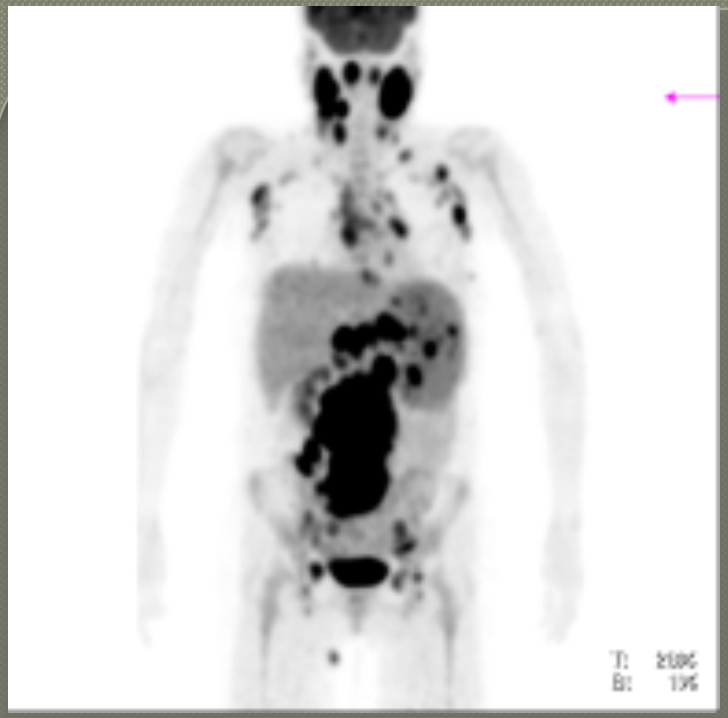
**Key words:** biopsy, bone marrow, FDG-PET/CT, Hodgkin, systematic review, meta-analysis

# CONTROL TERAPIA

- I-PET
- F-PET
- ROL SUV







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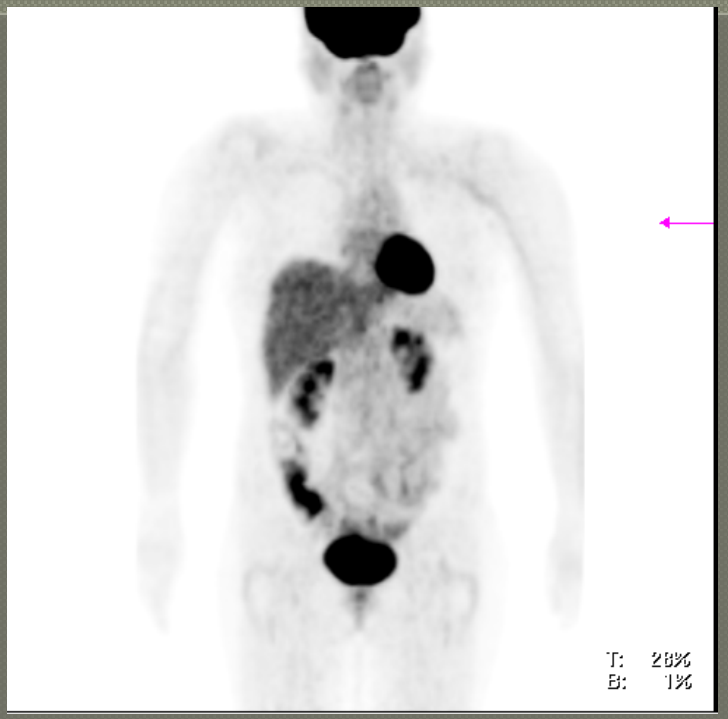

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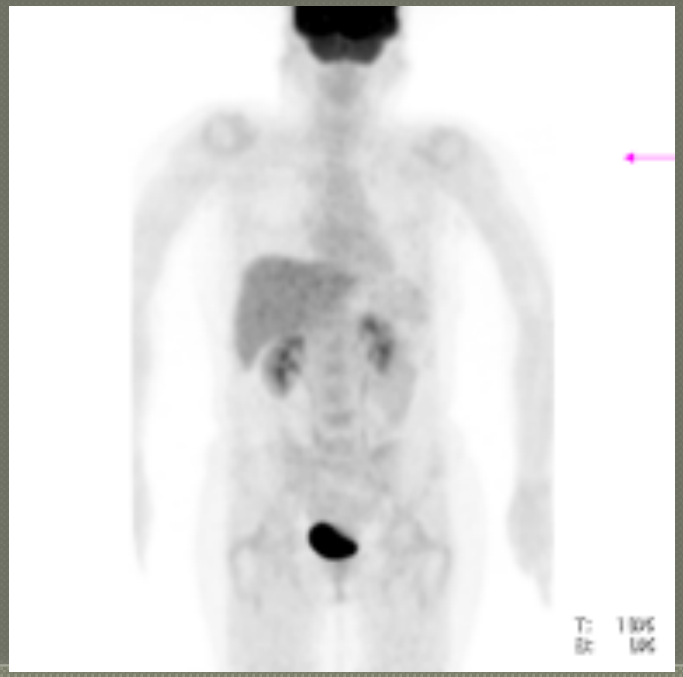

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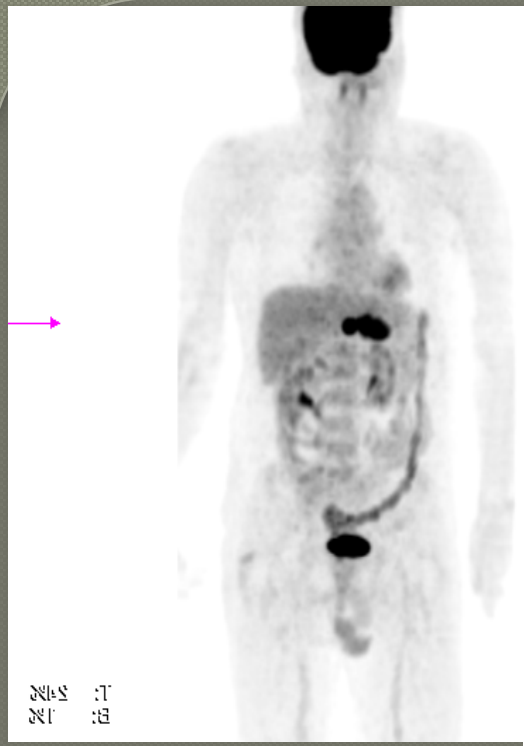

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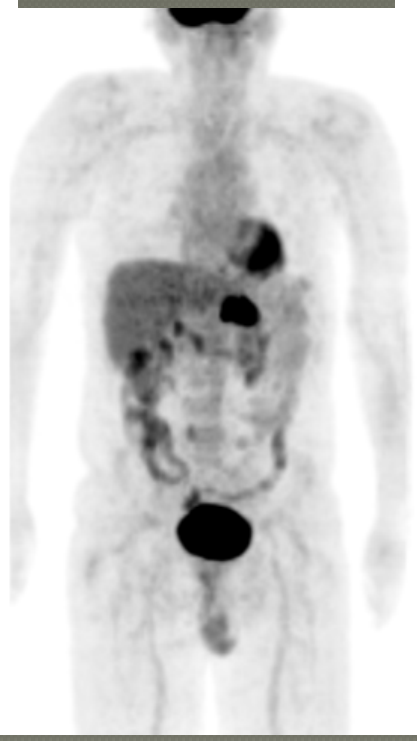

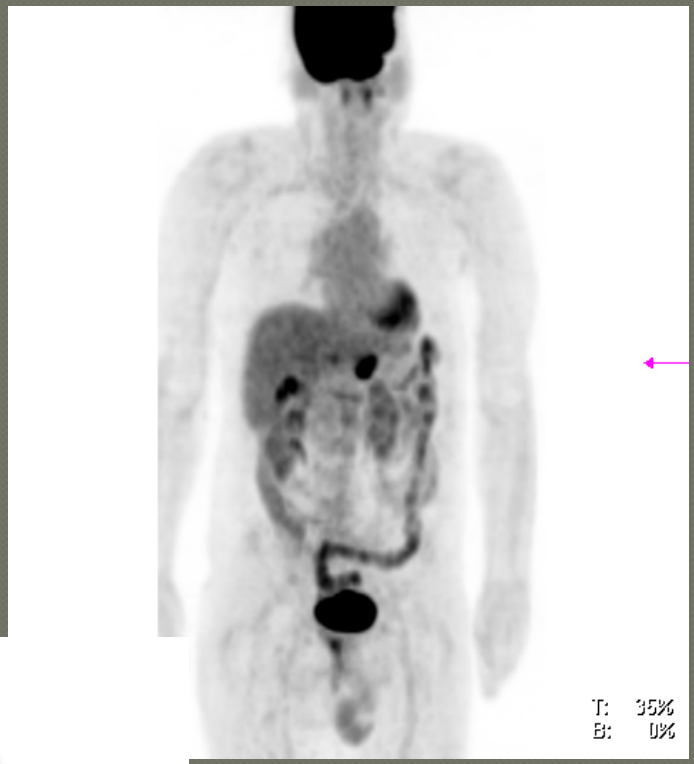

POST 2 CICLOS

8 SEMANAS POST TTO

VOLUME 30 · NUMBER 2 · JANUARY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Interim [$^{18}$F]Fluorodeoxyglucose Positron Emission Tomography Scan in Diffuse Large B-Cell Lymphoma Treated With Anthracycline-Based Chemotherapy Plus Rituximab

*Violaine Safar, Jehan Dupuis, Emmanuel Itti, Fabrice Jardin, Christophe Fruchart, Stéphane Bardet, Pierre Véra, Christiane Copie-Bergman, Alain Rahmouni, Hervé Tilly, Michel Meignan, and Corinne Haioun*

**Table 3.** Summary of the Primary Studies on PET Interim Assessment in Aggressive Lymphoma

| Study Author | No. of Patients | | Treated With Rituximab (%) | Median Follow-Up (months) | Cycles Completed at Time of PET Scan Performed (No.) | End Point | |
|---|---|---|---|---|---|---|---|
| | Total | DLBCL | | | | Negative PET | Positive PET |
| Jerusalem[4] | 28 | 16 | | 17.5 | 2-5 | 2-year PFS: 62%<br>2-year OS: 68% | 2-year PFS: 0%<br>2-year OS: 0% |
| Spaepen[5] | 70 | 47 | | 36.3 | 3-4 | 2-year PFS: 85%<br>2-year OS: 90% | 2-year PFS: 4%<br>2-year OS: 40% |
| Kostakoglu[6] | 30 | 13 | | 19 | 1 | 1.5-year PFS: 85% | 1.5-year PFS: < 15% |
| Mikhaeel[7] | 121 | 75 | ? | 24.4 | 2-3 | 5-year PFS: 89%<br>5-year OS: 90% | 5-year PFS: 16%<br>5-year OS: 63% |
| Haioun[3] | 90 | 85 | 41 | 24 | 2 | 2-year EFS: 82%<br>2-year OS: 90% | 2-year EFS: 43%<br>2-year OS: 61% |
| Dupuis[8] | 103 | 103 | 49 | 33 | 2 | 5-year EFS: 80% | 5-year EFS: 36% |
| Fruchart[9] | 40 | 35 | ? | | 2-3 | 2-year EFS: 85% | 2-year EFS: 30% |
| Casasnovas[25] | 102 | 102 | 100 | 19 | 2-4 | 2-year PFS: 81% | 2-year PFS: 73% |

Abbreviations: EFS, event-free survival; DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

# Role of Functional Imaging in the Management of Lymphoma

*Bruce D. Cheson*

**Table 5.** Interim PET in HL and DLCBL

| Study | No. of Patients With HL | No. of Patients With NHL | Cycles of Therapy | PET Negative (%) | PFS/EFS (%) | PET Positive (%) | PFS/EFS (%) |
|---|---|---|---|---|---|---|---|
| Jerusalem[65] | | 28 | 2-3 | 82 | 100 | 18 | 30 |
| Spaepen[66] | | 47 | 3-4 | 47 | 84 | 53 | 0 |
| Haioun[67] | | 90 | 2 | 60 | 82 | 40 | 43 |
| Mikhaeel[69] | | 121 | 2-3 | 41.3 | 93 | 43 | 30 |
| Kostakoglu[73] | 23 | | 1 | 74 | 100 | 26 | 12.5 |
| | | 24 | | 58 | 100 | 42 | |
| Zinzani[74] | | 91 | Various | 61.5 | 89 | 38.5 | 17 |
| Safar[75] | | 112 | 2 | 63 | 81 | 37 | 41 |
| Cashen[50] | | 50 | 2-3 | 30 | 85 | 30 | 75 |
| Gigli[49] | | 42 | 3 | 67 | 90 | 33 | 55 |
| Micallef[76] | | 76 | 2 | 79 | 73 | 21 | 60 |
| Pregno[77] | | 82 | 2 | 67 | 84 | 33 | 74 |
| Hutchings[70] | 85 | | 2-3 | 72 | 94 | 13 | 38 |
| Hutchings[71] | 77 | | 2 | 79 | 95 | 21 | 31 |
| Zinzani[72] | 40 | | 2 | 80 | 97 | 20 | 12 |
| Gallamini[79] | 260 | | 2 | 81 | 95 | 19 | 14 |
| Markova[78] | 50 | | 4 | 72 | 100 | 28 | 86 |

Abbreviations: PET, positron emission tomography; HL, Hodgkin's lymphoma; DLCBL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma; PFS, progression-free survival; EFS, event-free survival.

# Prospective International Cohort Study Demonstrates Inability of Interim PET to Predict Treatment Failure in Diffuse Large B-Cell Lymphoma

Robert Carr[1], Stefano Fanti[2], Diana Paez[3], Juliano Cerci[4], Tamás Györke[5,6], Francisca Redondo[7], Tim P. Morris[8], Claudio Meneghetti[9], Chirayu Auewarakul[10], Reena Nair[11], Charity Gorospe[12], June-Key Chung[13], Isinsu Kuzu[14], Monica Celli[2], Sumeet Gujral[15], Rose Ann Padua[16], Maurizio Dondi[3], and the IAEA Lymphoma Study Group

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J Nucl Med 2014; 55:1936–1944

**TABLE 1**
Patient and Disease Characteristics

| Characteristic | Brazil | Chile | Hungary | India | Italy | South Korea | Philippines | Thailand | Total |
|---|---|---|---|---|---|---|---|---|---|
| No. of patients | 61 | 47 | 65 | 32 | 49 | 9 | 20 | 44 | 327 |
| Sex (M) | 29 (48) | 27 (57) | 35 (54) | 22 (69) | 23 (47) | 6 (67) | 8 (40) | 23 (52) | 173 (53) |
| Ethnicity | | | | | | | | | |
| Asian | 0 | 0 | 0 | 32 | 0 | 9 | 20 | 44 | 105 |
| Caucasian | 0 | 47 | 65 | 0 | 48 | 0 | 0 | 0 | 160 |
| Chinese | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Mixed | 61 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 61 |
| Age at diagnosis (y) | | | | | | | | | |
| Median | 54 | 59 | 56 | 53 | 55 | 56 | 52 | 55 | 55 |
| Quartiles | 45, 65 | 46, 65 | 43, 68 | 47, 57 | 43, 66 | 54, 60 | 41, 64 | 45, 63 | 44, 64 |
| WHO/ECOG performance status | | | | | | | | | |

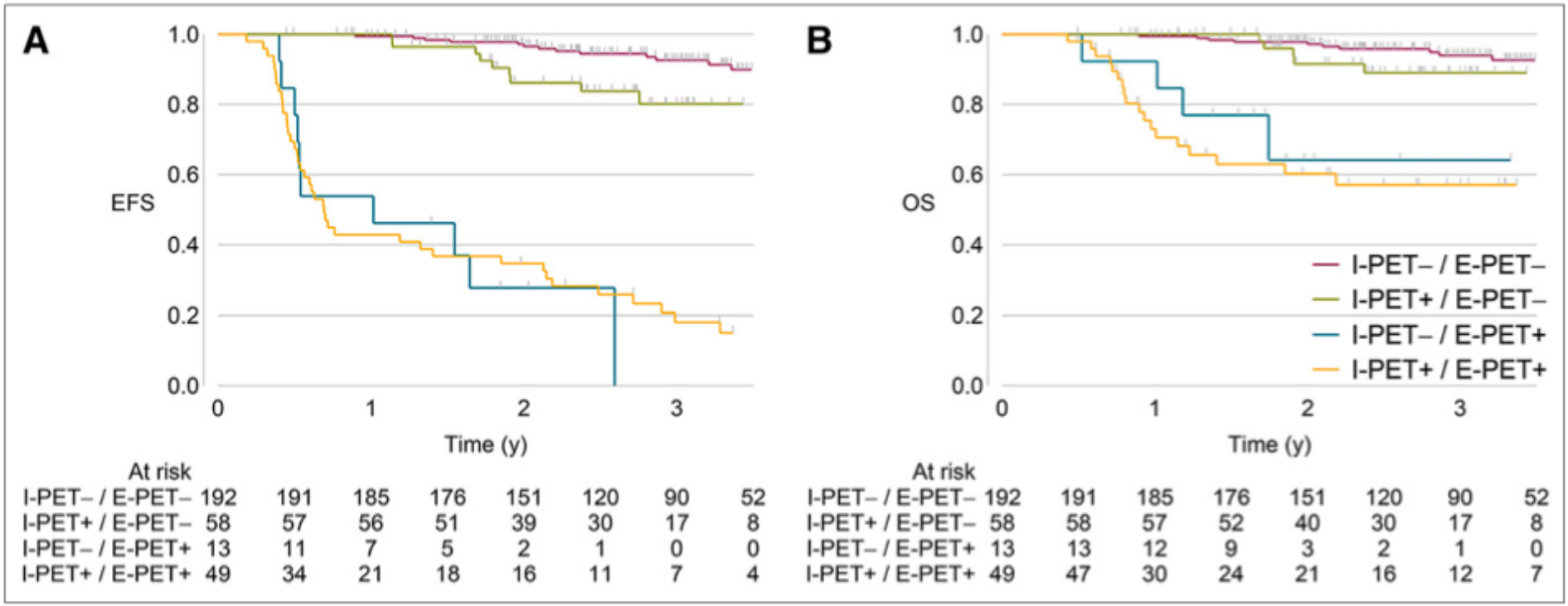



**FIGURE 4.** Kaplan–Meier plots of EFS (A) and OS (B) for cases stratified by both I-PET and E-PET. Number of cases at risk is shown. I-PET–negative/E-PET–negative: EFS, 97% (95% CI, 92%–98%), OS, 97% (95% CI, 93%–99%); I-PET–positive/E-PET–negative: EFS, 86% (95% CI, 73%–93%), OS, 92% (95% CI, 79%–97%); I-PET–negative/E-PET–positive: EFS, 28% (95% CI, 7%–54%), OS, 64% (95% CI, 28%–86%); and I-PET–positive/E-PET–positive: EFS, 35% (95% CI, 22%–48%), OS, 60% (95% CI, 44%–73%).

# I-PET

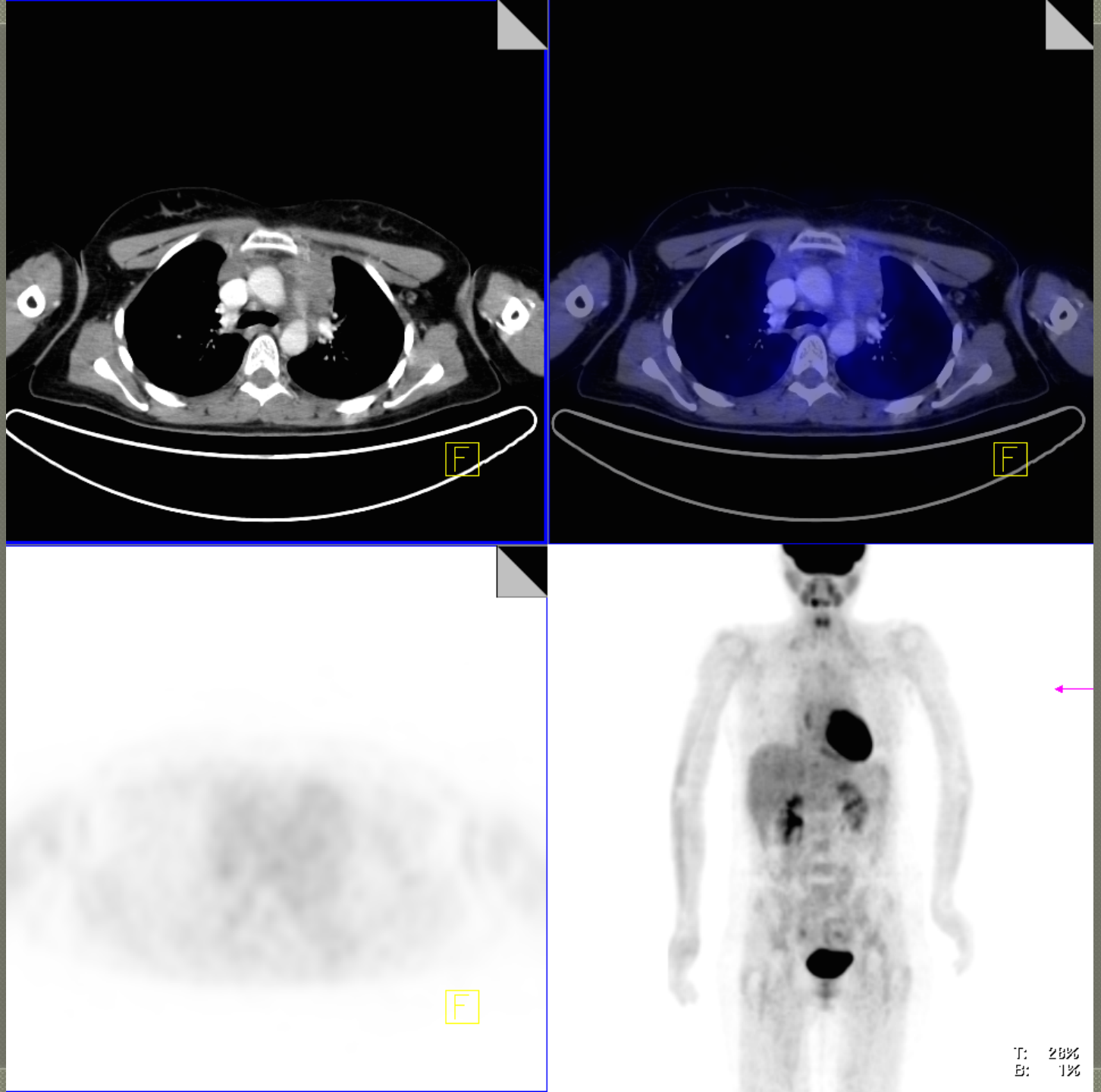
- Valor Pronóstico, impacto en sobrevida… NO CLARO
- Mod VPN (late responders), mod VPP (inflamación Rituximab)
- Trabajos con distinta metodología:
  - N° ciclos: 2, 3, 4…
  - Criterios interpretación imágenes:
    - Visual: escala de IHP, escala de Dauveille
    - Semicuantitativo: requiere basal, cutoff…
- Cambio conducta: ensayos clínicos, requiere confirmación histológica!!!!!

# SUV

- Medida semicuantitativa del metabolismo glucídico
- NO EXISTE VALOR DE CORTE para diferenciar lesiones benignas de malignas
- ESTUDIO BASAL
- Repetir estudios en MISMO CENTRO, MISMO EQUIPO Y MISMAS CONDICIONES

# F-PET

- PPV 95%, NPV 83%
- Mejor predictor pronóstico
- Masas residuales: viabilidad v/s fibrosis
- QT: MINIMO 4 semanas
- RT: MINIMO 8-12 semanas
- Ausencia cuadro infeccioso/inflamatorio intercurrente (FP)
- Antecedentes clínicos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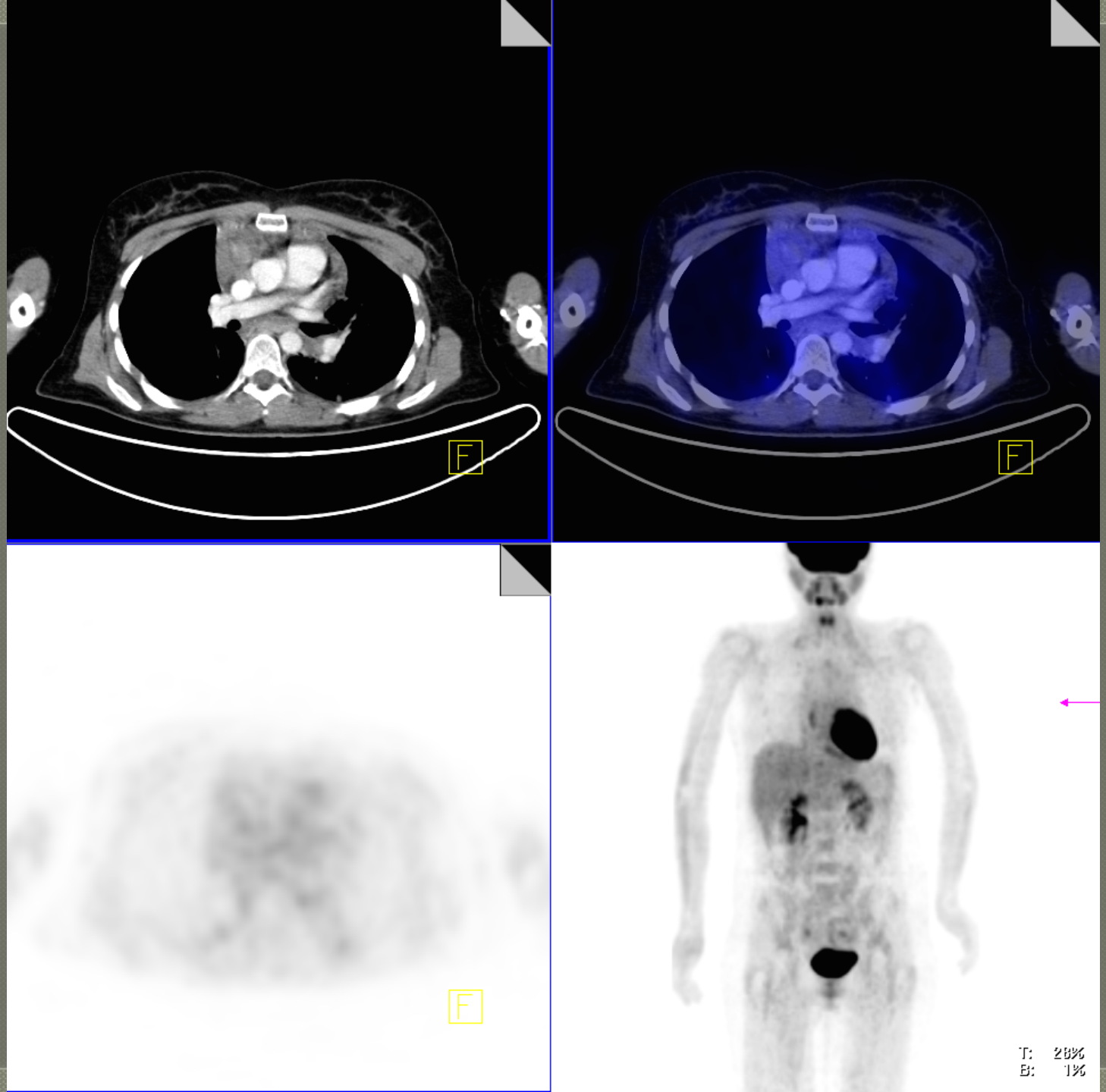
F
T: 28%
B: 1%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T: 28%
B: 1%

# REETAPIFICACION

**Table 4.** PET(CT) in Restaging of Lymphoma

| Study | No. of Patients | PPV (%) | NPV (%) |
|---|---|---|---|
| NHL | | | |
| Bangerter[20] | 89 | 90 | 98 |
| Jerusalem[42] | 35 | 42.9 | 100 |
| Zinzani[47] | 31 | 92.9 | 100 |
| Mikhaeel[44] | 45 | 60 | 100 |
| Naumann[48] | 15 | 85.7 | 88.2 |
| Spaepen[45] | 93 | 70.3 | 100 |
| Cashen[50] | 50 | 80 | 92 |
| Gigli[49] | 42 | 75 | 94 |
| HL | | | |
| Spaepen[46] | 60 | 100 | 91 |
| Engert[51] | 728 | NA | 94.6 |
| Cerci[52] | 130 | 92.3 | 100 |

Abbreviations: PET, positron emission tomography; CT, computed tomography; PPV, positive predictive value; NPV, negative predictive value; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; NA, not applicable.

Cerci et al[52] assessed the cost effectiveness of FDG-PET/PET for patients in unconfirmed CR (CRu) or partial remission (PR) after first-line therapy for HL. FDG-PET demonstrated 95.9% accuracy in restaging and was found to be highly cost effective, with PET contributing only 1% of the cost of HL treatment. In a recent report of the HD15 trial from the German Hodgkin Study Group,[51] post-treatment PET scans were able to reduce the number of patients irradiated for residual disease to 11% from 70% in previous trials.

ALTO VPN

MOD VPP

POSIBLES FP:

REQUIERE CONFIRMACIÓN HISTOLÓGICA

# SEGUIMIENTO

- No recomendado
- Sospecha clínica > 80%
- Bajo VPP
- Recidivas no sospechadas < 10% (***HL)

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SPECIAL ARTICLE

# Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

*Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister*

**Table 1.** Criteria for Involvement of Site

| Tissue Site | Clinical | FDG Avidity | Test | Positive Finding |
|---|---|---|---|---|
| Lymph nodes | Palpable | FDG-avid histologies | PET-CT | Increased FDG uptake |
| | | Nonavid disease | CT | Unexplained node enlargement |
| Spleen | Palpable | FDG-avid histologies | PET-CT | Diffuse uptake, solitary mass, miliary lesions, nodules |
| | | Nonavid disease | CT | > 13 cm in vertical length, mass, nodules |
| Liver | Palpable | FDG-avid histologies | PET-CT | Diffuse uptake, mass |
| | | Nonavid disease | CT | Nodules |
| CNS | Signs, symptoms | | CT | Mass lesion(s) |
| | | | MRI | Leptomeningeal infiltration, mass lesions |
| | | | CSF assessment | Cytology, flow cytometry |
| Other (eg, skin, lung, GI tract, bone, bone marrow) | Site dependent | | PET-CT*, biopsy | Lymphoma involvement |

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
*PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

## INITIAL EVALUATION

## RECOMMENDATION FOR REVISIONS TO STAGING CRITERIA


### *Summary*

Excisional biopsy is preferred for diagnosis, although core-needle biopsy may suffice when not feasible.

Clinical evaluation includes careful history, relevant laboratory tests, and recording of disease-related symptoms.

PET-CT is the standard for FDG-avid lymphomas, whereas CT is indicated for nonavid histologies.

A modified Ann Arbor staging system is recommended; however, patients are treated according to prognostic and risk factors.

Suffixes A and B are only required for HL.

The designation X for bulky disease is no longer necessary; instead, a recording of the largest tumor diameter is required.

If a PET-CT is performed, a BMB is no longer indicated for HL; a BMB is only needed for DLBCL if the PET is negative and identifying a discordant histology is important for patient management.

## ASSESSMENT OF RESPONSE AFTER TREATMENT

## FOLLOW-UP EVALUATIONS

### *Summary*

PET-CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity.

A complete metabolic response even with a persistent mass is considered a complete remission.

A PR requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to six representative nodes or extranodal lesions.

Progressive disease by CT criteria only requires an increase in the PPDs of a single node by ≥ 50%.

Surveillance scans after remission are discouraged, especially for DLBCL and HL, although a repeat study may be considered after an equivocal finding after treatment.

Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retro-peritoneal disease.

## CONCLUDING REMARKS

Accurate pretreatment evaluation and response assessment are critical to the optimal management of patients with lymphoma. With increasing knowledge of the disease, new prognostic factors, and a better understanding of tumor biology comes a need to update prior systems. Despite the importance of a physical examination, imaging studies have become the standard. The present recommendations are directed primarily at initial staging and assessment, and their role in the multiply relapsed setting and early clinical trials remains to be confirmed. A major departure from the Ann Arbor system and the IWG criteria is that PET-CT is included in staging for FDG-avid lymphomas, because it is more sensitive than CT and provides a baseline against which response is more accurately assessed. Patients should be treated based on prognostic factors. Subclassification of A and B is now only indicated if prognostically important (ie, HL). Patients, including those with HL and most with DLBCL, can be spared a staging BMB,[71] and a routine chest x-ray is unnecessary for staging, although it may be useful for monitoring select patients with HL. Although the current definition of bulk is retained for HL, further correlations between maximum tumor diameter and outcome are needed to provide a clinically meaningful definition of bulk with current treatment approaches for NHL. Response assessment is preferred for FDG-avid lymphomas where possible, using the 5-point scale, whereas CT-based response remains important in lymphomas with low or variable FDG avidity, and in multiply relapsed disease, CT criteria for progressive disease can be based on an increase of a single lesion. The better we are able to exploit the biology of lymphomas for therapeutic benefit, the more our treatment strategies will be determined by relevant receptors and pathways, with even less reliance on Ann Arbor staging. Hopefully, the current recommendations will provide the necessary standardization of clinical trial conduct and interpretation that leads to improved therapies for patients with lymphoma.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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## AUTHOR CONTRIBUTIONS

**Conception and design:** All authors
**Collection and assembly of data:** All authors
**Data analysis and interpretation:** All authors
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

# Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

*Sally F. Barrington, N. George Mikhaeel, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Müeller, Lawrence H. Schwartz, Emanuele Zucca, Richard I. Fisher, Judith Trotman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O'Doherty, Roland Hustinx, Alberto Biggi, and Bruce D. Cheson*

*J Clin Oncol 32.* 

**Table 1.** Summary of Recommendations

| Recommendations |
| --- |
| Section 1: Interpretation of PET-CT scans |
| 1. Staging of FDG-avid lymphomas is recommended using visual assessment, with PET-CT images scaled to fixed SUV display and color table; focal uptake in HL and aggressive NHL is sensitive for bone marrow involvement and may obviate need for biopsy; MRI is modality of choice for suspected CNS lymphoma (type 1) |
| 2. Five-point scale is recommended for reporting PET-CT; results should be interpreted in context of anticipated prognosis, clinical findings, and other markers of response; scores 1 and 2 represent CMR; score 3 also probably represents CMR in patients receiving standard treatment (type 1) |
| 3. Score 4 or 5 with reduced uptake from baseline likely represents partial metabolic response, but at end of treatment represents residual metabolic disease; increase in FDG uptake to score 5, score 5 with no decrease in uptake, and new FDG-avid foci consistent with lymphoma represent treatment failure and/or progression (type 2) |
| Section 2: Role of PET-CT for staging |
| 1. PET-CT should be used for staging in clinical practice and clinical trials but is not routinely recommended in lymphomas with low FDG avidity; PET-CT may be used to select best site to biopsy (type 1) |
| 2. Contrast-enhanced CT when used at staging or restaging should ideally occur during single visit combined with PET-CT, if not already performed; baseline findings will determine whether contrast-enhanced PET-CT or lower-dose unenhanced PET-CT will suffice for additional imaging examinations (type 2) |
| 3. Bulk remains an important prognostic factor in some lymphomas; volumetric measurement of tumor bulk and total tumor burden, including methods combining metabolic activity and anatomical size or volume, should be explored as potential prognosticators (type 3) |
| Section 3: Role of interim PET |
| 1. If midtherapy imaging is performed, PET-CT is superior to CT alone to assess early response; trials are evaluating role of PET response–adapted therapy; currently, it is not recommended to change treatment solely on basis of interim PET-CT unless there is clear evidence of progression (type 1) |
| 2. Standardization of PET methods is mandatory for use of quantitative approaches and desirable for routine clinical practice (type 1) |
| 3. Data suggest that quantitative measures (eg, δSUVmax) could be used to improve on visual analysis for response assessment in DLBCL, but this requires further validation in clinical trials (type 2) |
| Section 4: Role of PET at end of treatment |
| 1. PET-CT is standard of care for remission assessment in FDG-avid lymphoma; in presence of residual metabolically active tissue, where salvage treatment is being considered, biopsy is recommended (type 1) |
| 2. Investigation of significance of PET-negative residual masses should be collected prospectively in clinical trials; residual mass size and location should be recorded on end-of-treatment PET-CT reports where possible (type 3) |
| 3. Emerging data support use of PET-CT after rituximab-containing chemotherapy in high–tumor burden FL; studies are warranted to confirm this finding in patients receiving maintenance therapy (type 2) |
| 4. Assessment with PET-CT could be used to guide decisions before high-dose chemotherapy and ASCT, but additional studies are warranted (type 3) |

## DISCUSSION

In response to developments involving PET-CT, recommendations from the ICML imaging group have been made to update practice. These include guidance on reporting of PET-CT for staging and response assessment of HL, DLBCL, and aggressive FL using the 5-PS. PET-CT is recommended for midtreatment assessment in place of CT alone, if imaging is clinically indicated, and for remission assessment. Quantitative imaging parameters for assessing disease burden and response should be explored as potential prognosticators. The standardization of PET-CT methods is mandatory for quantitative analysis and desirable for best clinical practice.

BLOOD, 24 MARCH 2016 • VOLUME 127, NUMBER 12

Plenary Paper

LYMPHOID NEOPLASIA

# PET-CT for staging and early response: results from the Response-Adapted Therapy in Advanced Hodgkin Lymphoma study

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## Key Points

- PET-CT is the modern standard for staging Hodgkin lymphoma and can replace contrast enhanced CT in the vast majority of cases.
- Agreement between expert and local readers is sufficient for the Deauville criteria to assess response in clinical trials and the community.

International guidelines recommend that positron emission tomography-computed tomography (PET-CT) should replace CT in Hodgkin lymphoma (HL). The aims of this study were to compare PET-CT with CT for staging and measure agreement between expert and local readers, using a 5-point scale (Deauville criteria), to adapt treatment in a clinical trial: Response-Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL). Patients were staged using clinical assessment, CT, and bone marrow biopsy (RATHL stage). PET-CT was performed at baseline (PET0) and after 2 chemotherapy cycles (PET2) in a response-adapted design. PET-CT was reported centrally by experts at 5 national core laboratories. Local readers optionally scored PET2 scans. The RATHL and PET-CT stages were compared. Agreement among experts and between expert and local readers was measured. RATHL and PET0 stage were concordant in 938 (80%) patients. PET-CT upstaged 159 (14%) and downstaged 74 (6%) patients. Upstaging by extranodal disease in bone marrow (92), lung (11), or multiple sites (12) on PET-CT accounted for most discrepancies. Follow-up of discrepant findings confirmed the PET characterization of lesions in the vast majority. Five patients were upstaged by marrow biopsy and 7 by contrast-enhanced CT in the bowel and/or liver or spleen. PET2 agreement among experts (140 scans) with a $\kappa$ (95% confidence interval) of 0.84 (0.76-0.91) was very good and between experts and local readers (300 scans) at 0.77 (0.68-0.86) was good. These results confirm PET-CT as the modern standard for staging HL and that response assessment using Deauville criteria is robust, enabling translation of RATHL results into clinical practice.
(*Blood*. 2016;127(12):1531-1538)

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# Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma

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## BACKGROUND

We tested interim positron-emission tomography–computed tomography (PET-CT) as a measure of early response to chemotherapy in order to guide treatment for patients with advanced Hodgkin's lymphoma.

## METHODS

Patients with newly diagnosed advanced classic Hodgkin's lymphoma underwent a baseline PET-CT scan, received two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy, and then underwent an interim PET-CT scan. Images were centrally reviewed with the use of a 5-point scale for PET findings. Patients with negative PET findings after two cycles were randomly assigned to continue ABVD (ABVD group) or omit bleomycin (AVD group) in cycles 3 through 6. Those with positive PET findings after two cycles received BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). Radiotherapy was not recommended for patients with negative findings on interim scans. The primary outcome was the difference in the 3-year progression-free survival rate between randomized groups, a noninferiority comparison to exclude a difference of 5 or more percentage points.

## RESULTS

A total of 1214 patients were registered; 937 of the 1119 patients (83.7%) who underwent an interim PET-CT scan according to protocol had negative findings. With a median follow-up of 41 months, the 3-year progression-free survival rate and overall survival rate in the ABVD group were 85.7% (95% confidence interval [CI], 82.1 to 88.6) and 97.2% (95% CI, 95.1 to 98.4), respectively; the corresponding rates in the AVD group were 84.4% (95% CI, 80.7 to 87.5) and 97.6% (95% CI, 95.6 to 98.7). The absolute difference in the 3-year progression-free survival rate (ABVD minus AVD) was 1.6 percentage points (95% CI, −3.2 to 5.3). Respiratory adverse events were more severe in the ABVD group than in the AVD group. BEACOPP was given to the 172 patients with positive findings on the interim scan, and 74.4% had negative findings on a third PET-CT scan; the 3-year progression-free survival rate was 67.5% and the overall survival rate 87.8%. A total of 62 patients died during the trial (24 from Hodgkin's lymphoma), for a 3-year progression-free survival rate of 82.6% and an overall survival rate of 95.8%.

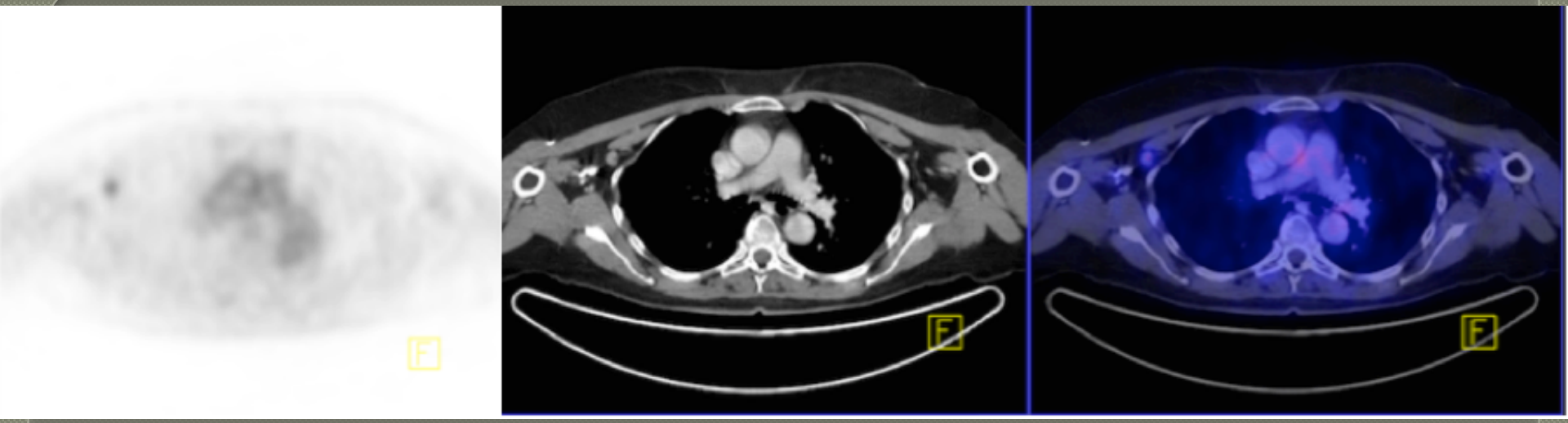
## CONCLUSIONS

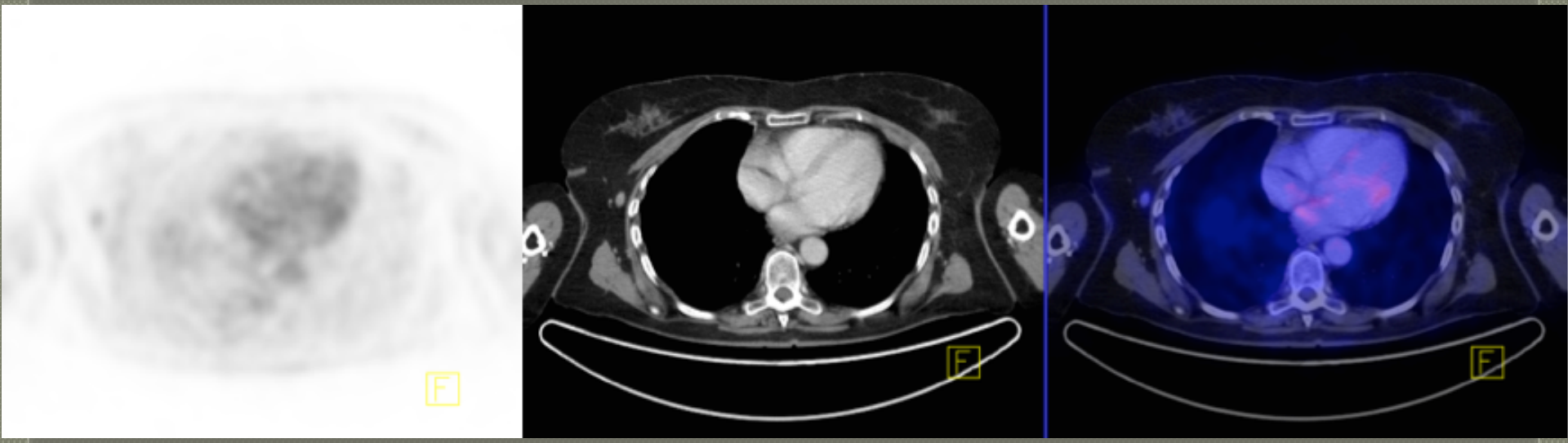
Although the results fall just short of the specified noninferiority margin, the omission of bleomycin from the ABVD regimen after negative findings on interim PET resulted in a lower incidence of pulmonary toxic effects than with continued ABVD but not significantly lower efficacy. (Funded by Cancer Research UK and Others; ClinicalTrials.gov number, NCT00678327.)

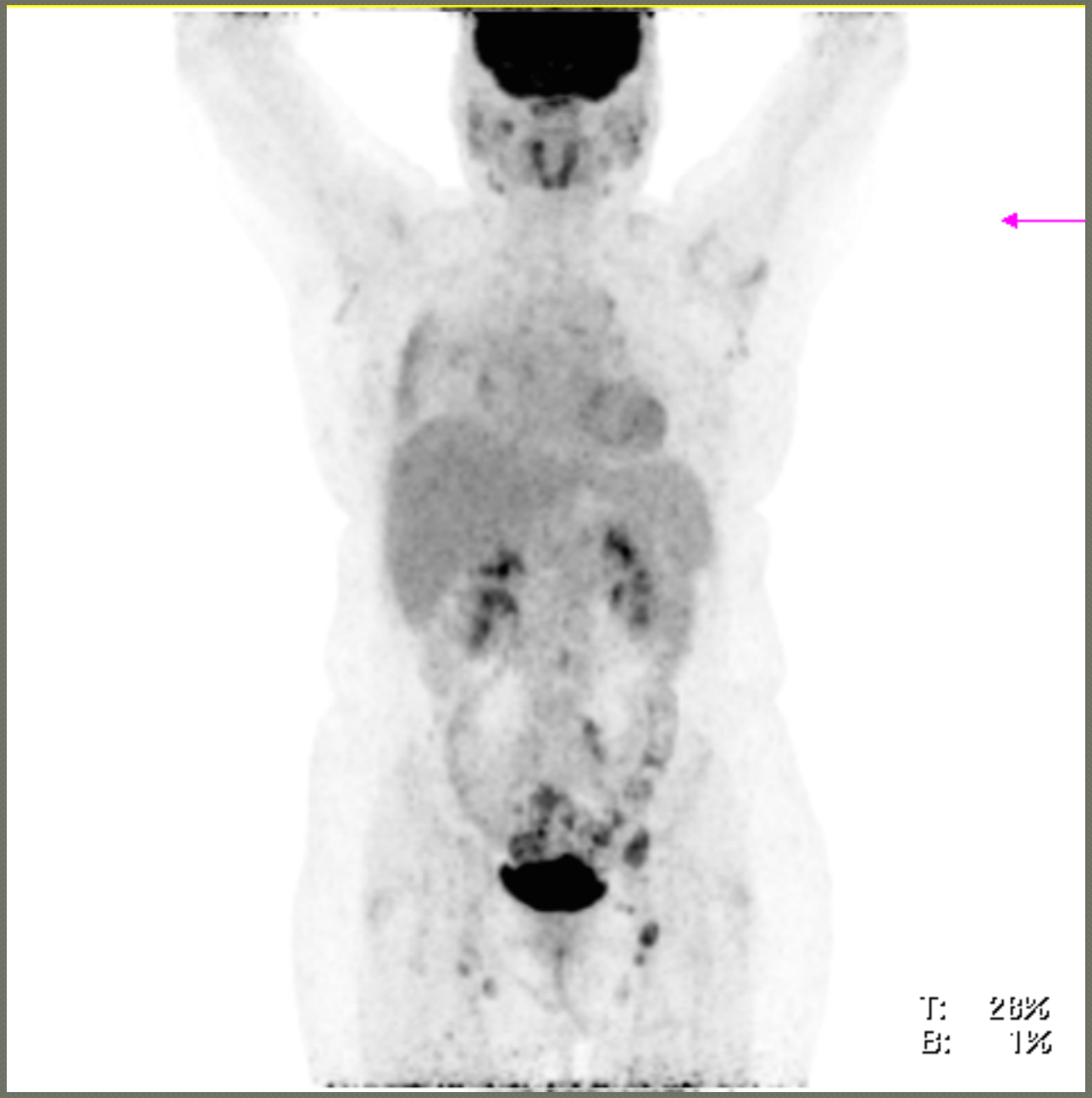
# LINFOMAS DE BAJO GRADO

# TRANSFORMACION

- Punto de quiebre evolución linfomas indolentes
- Requiere cambio terapia e implica cambio pronóstico
- Linfomas indolentes escasa captación 18F-FDG, evidencian focos intensamente hipermetabólicos
- Permite identificar mejor sitio de biopsia



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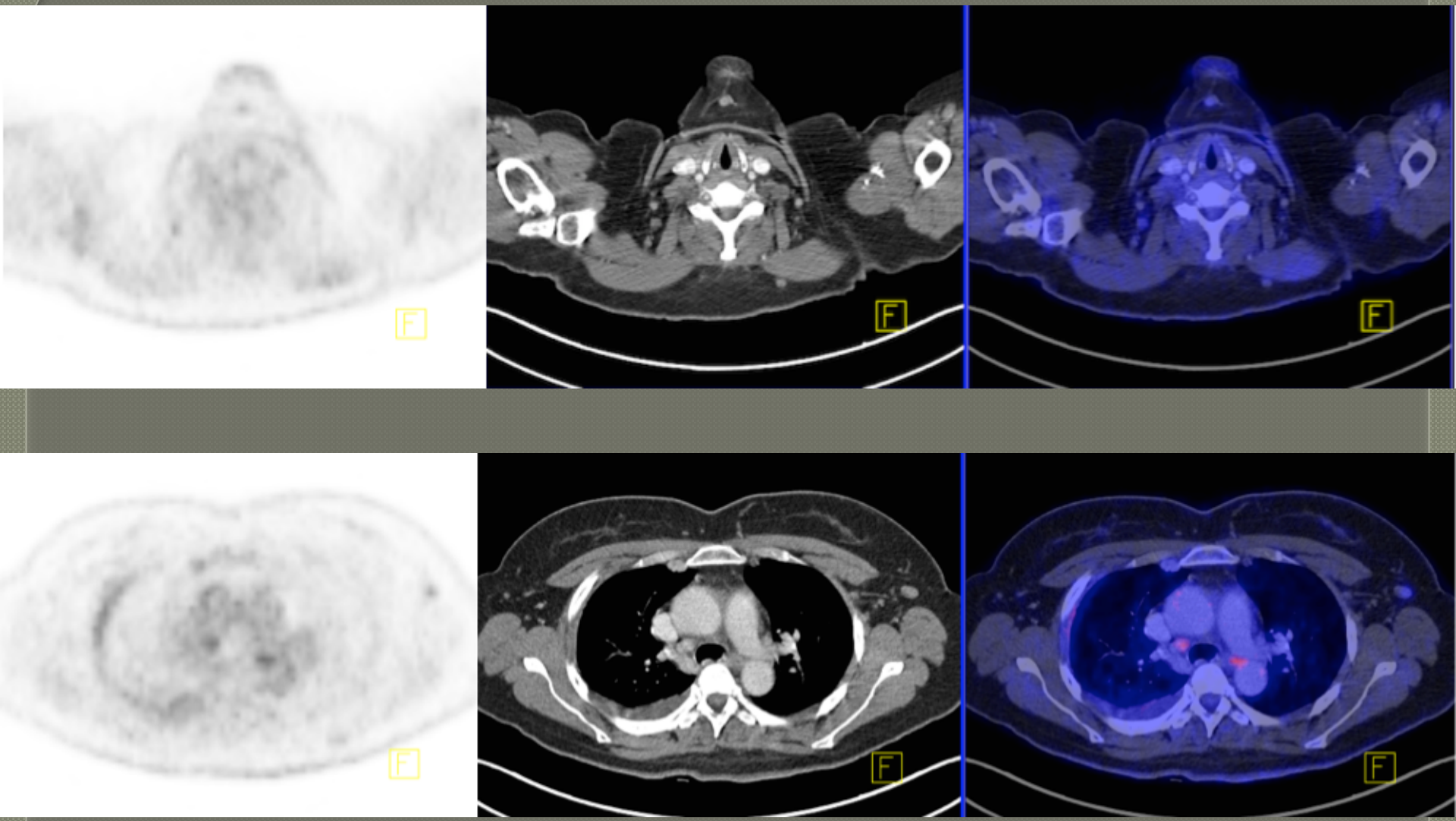

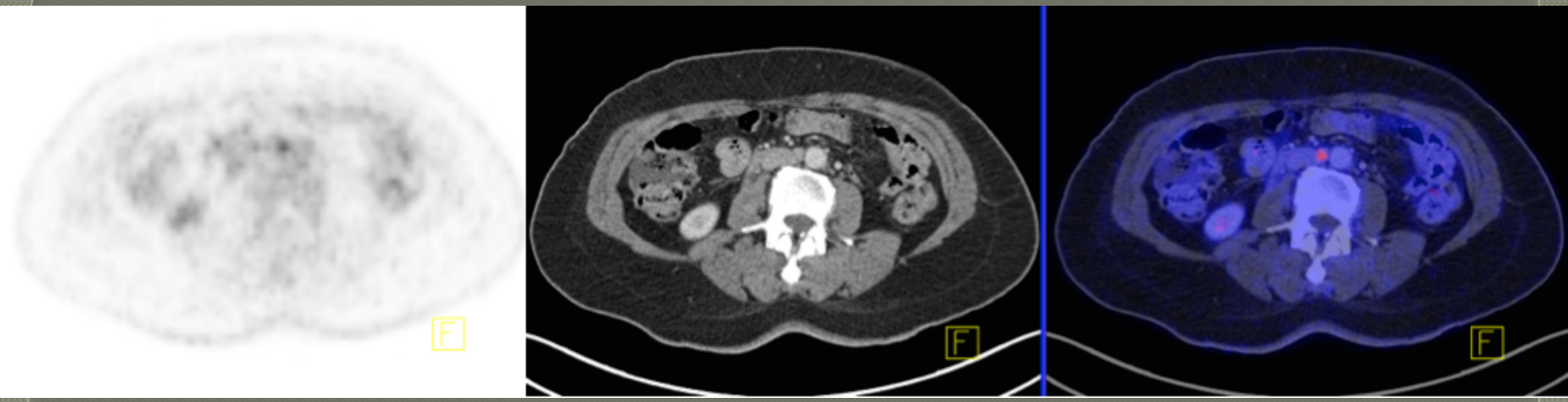

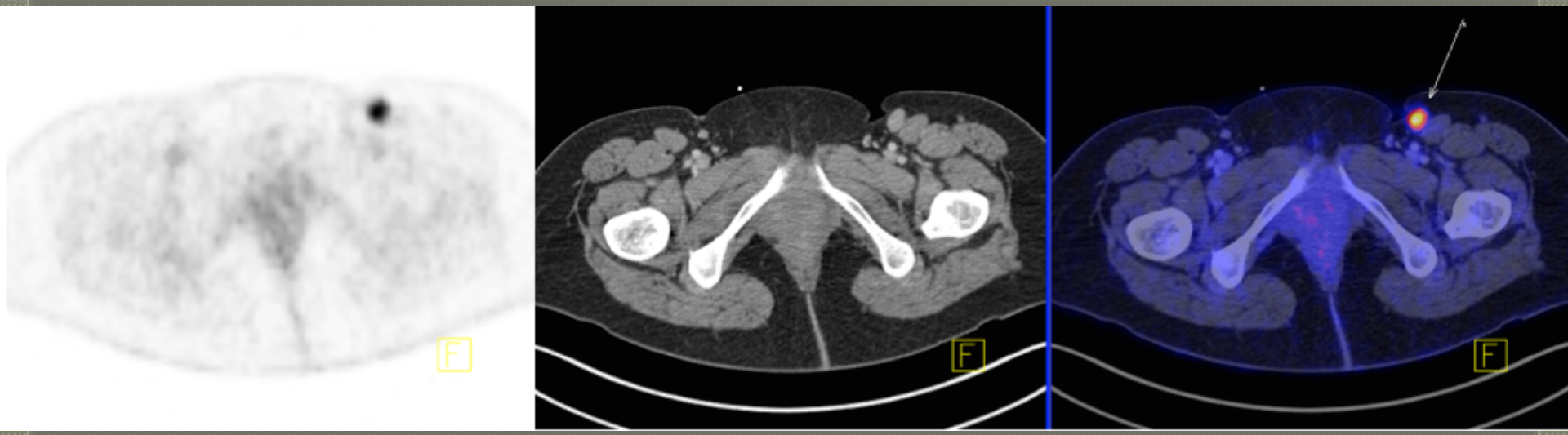

original article

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# The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL)

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**Table 2.** Patients with serial PET scanning at indolent and aggressive diagnosis

| UPIN | Indolent diagnosis | SUV range (g/dl) | SUV at biopsy site (g/dl) | $SUV_{study\text{-}max}$ (g/dl) | Subsequent transformed diagnosis | SUV range | SUV at biopsy site | $SUV_{study\text{-}max}$ (g/dl) |
|---|---|---|---|---|---|---|---|---|
| 4 | FL 3a | 13 | Excised | 13 | DLBCL | 5.4–20.3 | 20.3 | 20.3 |
| 6 | FL 1 | 1.5–3 | Excised | 3 | LCL | 10.9–22.5 | 22.5 | 22.5 |
| 8 | FL 1 | 4.6–8.5 | 4.6–8.5 | 8.5 | LCL | 9–20.8 | 12.1 | 20.8 |
| 12 | MZL | 2.8–6.3 | None | 6.3 | DLBCL | 9.7 | 9.7 | 9.7 |
| 17 | MZL (MALT type) | 4.9–11.5 | 11.5 | 11.5 | DLBCL | 2.6–7.1 | 7.1 | 7.1 |
| 29 | FL 2 | 2.5–10.5 | 6.8 | 10.5 | DLBCL | 2.8–8.2 | Excised | 8.2 |
| 30 | FL 2 | 2–13.5 | 1.5 | 13.5 | DLBC | 3–16.4 | 16.4 | 16.4 |
| 31 | SLL | 5.5–14.5 | 5.5 | 14.5 | DLBCL | 8.1–40 | 33.5 | 40 |
| 32 | MZL | 2–7.1 | 6.2 | 7.1 | DLBCL | 2–15.2 | 15.2 | 15.2 |
| 37 | MZL | 3.4–6.2 | Excised | 6.2 | DLBCL | 9.7 | 9.7 | 9.7 |
| 38 | FL 2 | 3.5–16.1 | 3.5 | 16.1 | DLBCL | 2.6–8 | Excised | 8 |
| 39 | MZL | 1.3–3.8 | 1.7 | 3.8 | DLBCL | 2–13.8 | 13.8 | 13.8 |

PET, positron emission tomography; SUV, standardized uptake value; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; LCL, large-cell lymphoma; MZL, marginal zone lymphoma; MALT, mucosa-associated lymphoid tumor; UPIN, unique patient identification number.

# CONCLUSIONES

# PET/CT Y LINFOMA

1. Tipo histológico (alto grado v/s bajo grado)
2. Alto grado:
    1. Etapificación (compromiso extranodal)
    2. Control terapia (precoz y final)
    3. Compromiso MO
    4. Detección ante sospecha de recurrencia
3. Bajo grado:
    1. Transformación
    2. Elección sitio biopsia
4. Estandarización