Bone marrow involvement in Hodgkin & Non- Hodgkin Lymphomas

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Martin Hutchings

Therapeutic implications of BMI

- Bone marrow involvement means extranodal disease and by definition stage IV
- BMI detected by BMB is a poor prognostic feature in most lymphomas
- In HL BMI is relatively rare
- BMI is more common in DLBCL and other aggressive NHL subtypes
  - Occasional clinical important upstagings occur
- Identification of indolent, discordant BMI in DLBCL patients influences prognosis and follow-up

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Role of imaging : PET-CT

Utility of PET relates to the pattern of involvement:

FOCAL

- HL, DLBCL , Burkitt Lymphoma

high accuracy for PET-CT > Biopsy

DIFFUSE

- Indolent lymphomas, many FL
- Low volume eg small cell lymphomas

lower sensitivity for PET-CT , Biopsy better

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Detection of BMI in HL & DLBCL

HL:

El-Galaly et al *JCO 2012*

n = 454 PET 18% vs BMB 6%

Weiler-Sagie et al *EJNMMI 2014*

n = 336 PET15% vs BMB 3%

DLBCL:

Khan et al *Blood 2013*

n = 130 PET 27% vs BMB 11%

Berthet et al *JNM 2013*

n = 133 PET 24% vs BMB 6%

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Interpretation of marrow uptake

FOCAL

- Focal (often multifocal) FDG uptake in marrow
- No evidence of other bone pathology on CT

- Resolves or progresses on treatment in parallel with other disease sites

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Interpretation of marrow uptake

DIFFUSE

- Diffuse uptake may indicate hyperplasia in HL
- Diffuse uptake occurs with chemotherapy and GCSF
- Diffuse uptake can indicate BMI in DLBCL
- Interpreting diffuse uptake as BMI in DLBCL improves accuracy of marrow assessment

(Adams *EJNMMI 2014)*

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Interpretation of marrow uptake

- Some studies use liver to decide BMI at staging
- After treatment liver may not be best
- Stimulation of normal marrow means often > liver
- Use uptake at site with no marrow disease at diagnosis as arbiter
- Ablation → photopenia
- ↑ uptake in Normal marrow + ↓ uptake in Treated marrow

MIRROR image

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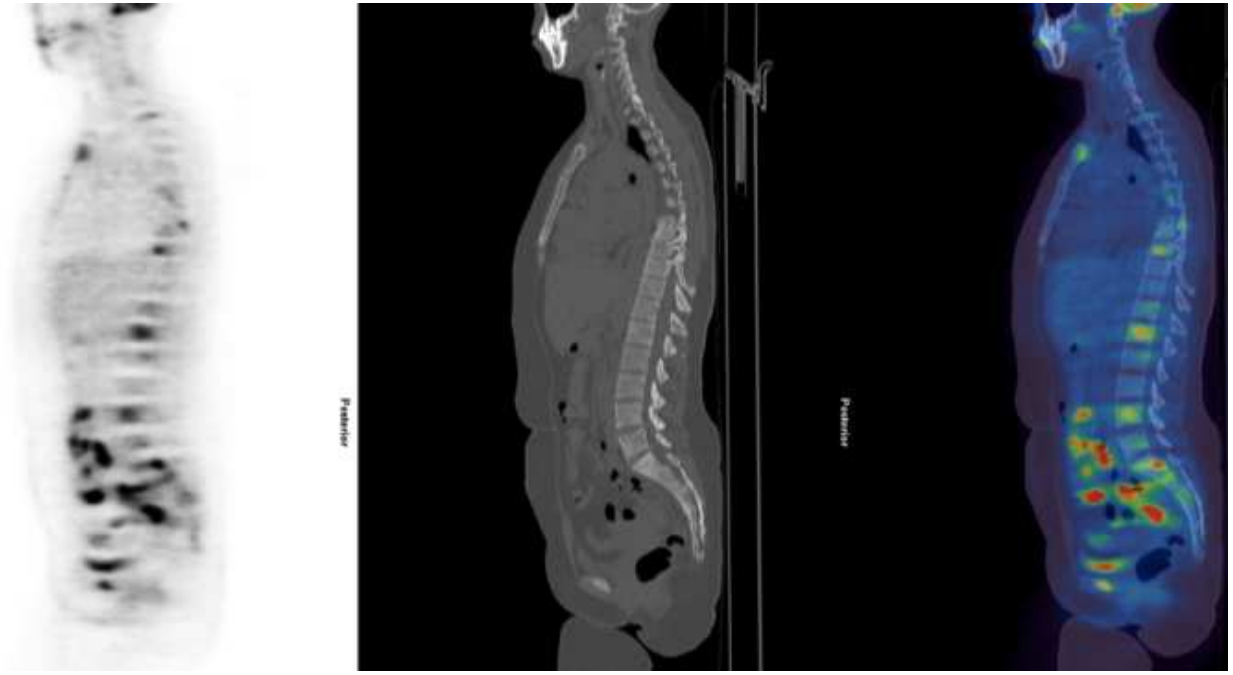
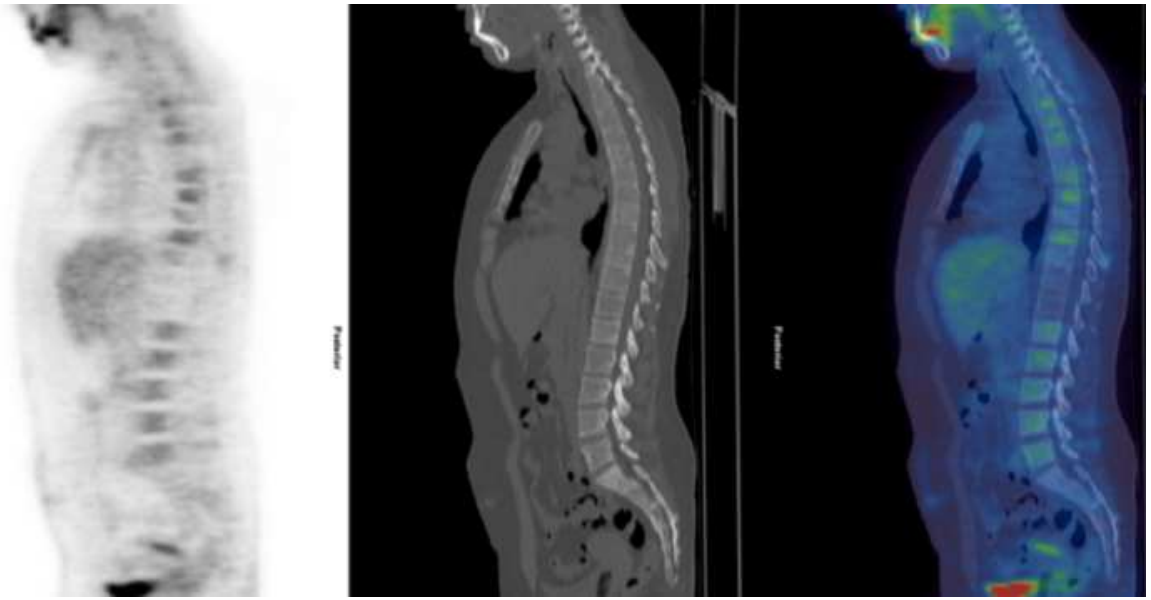
Pre treatment



Post treatment



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Interpretation of marrow uptake

‘High physiological uptake can occur in some sites…

e.g. Waldeyers ring , gut, bone marrow after chemotherapy or GCSF treatment with ‘physiologic’ uptake > normal liver

In this case, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue’

Barrington SF et al JCO 2014 online 10.1200/JCO.2013.53.5229

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review

Annals of Oncology 00: 1–7, 2013
doi:10.1093/annonc/mdt533

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

N = 955 patients ; weighted summary proportion of patients PET/CT negative and BMB positive 1.1% (95% CI 0.6 – 2.0 %)

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HL effect of BMB on management

454 patients HL

82 (18%) focal PET lesions in marrow

27 (6%) had BMB involvement

No patients with stage I or II had +ve BMB

BMB upstaged 5 patients from III to IV

BMB changed treatment in NONE

El Galaly et al JCO 2012

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Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-013-2623-4

REVIEW ARTICLE

FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis

Hugo J. A. Adams · Thomas C. Kwee · Bart de Keizer · Rob Fijnheer · John M. H. de Klerk · Rutger A. J. Nievelstein

Reference	Sensitivity (%)		Specificity (%)	
	Value	95 % CI	Value	95 % CI
Khan et al. [23]	94.3	80.8 – 99.3	100	96.2 – 100
Cortes-Romera et al. [24]	95.8	78.9 – 99.9	100	93.9 – 100
Berthet et al. [25]	93.9	79.8 – 99.3	99.0	94.6 – 100
Hong et al. [26]	70.8	48.9 – 87.4	100	94.5 – 100
Pelosi et al. [27]	84.0	63.9 – 95.5	100	96.2 – 100
Ribrag et al. [29]	88.9	51.8 – 99.7	100	89.7 – 100
Pooled estimate	88.7	82.5 – 93.3	99.8	98.8 – 100

N = 654 patients ; weighted summary proportion of patients
PET/CT negative and BMB positive 3.1% (95% CI 1.8 – 5.0 %)
PET/CT positive and BMB negative 12.5% (95% CI 8.4 – 17.3 %)

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Undetected BMI in DLBCL

1. Low volume involvement < 10-20% marrow

(Campbell J et al Eur J Haem 2006)

2. Discordant small cell involvement

Treatment and survival no different for patients with no BMI and those with low grade BMI in DLBCL

(Conlan MG et al JCO 1990 Hodges GF et al AM J Clin Path 1994)

Khan A et al Blood 2013

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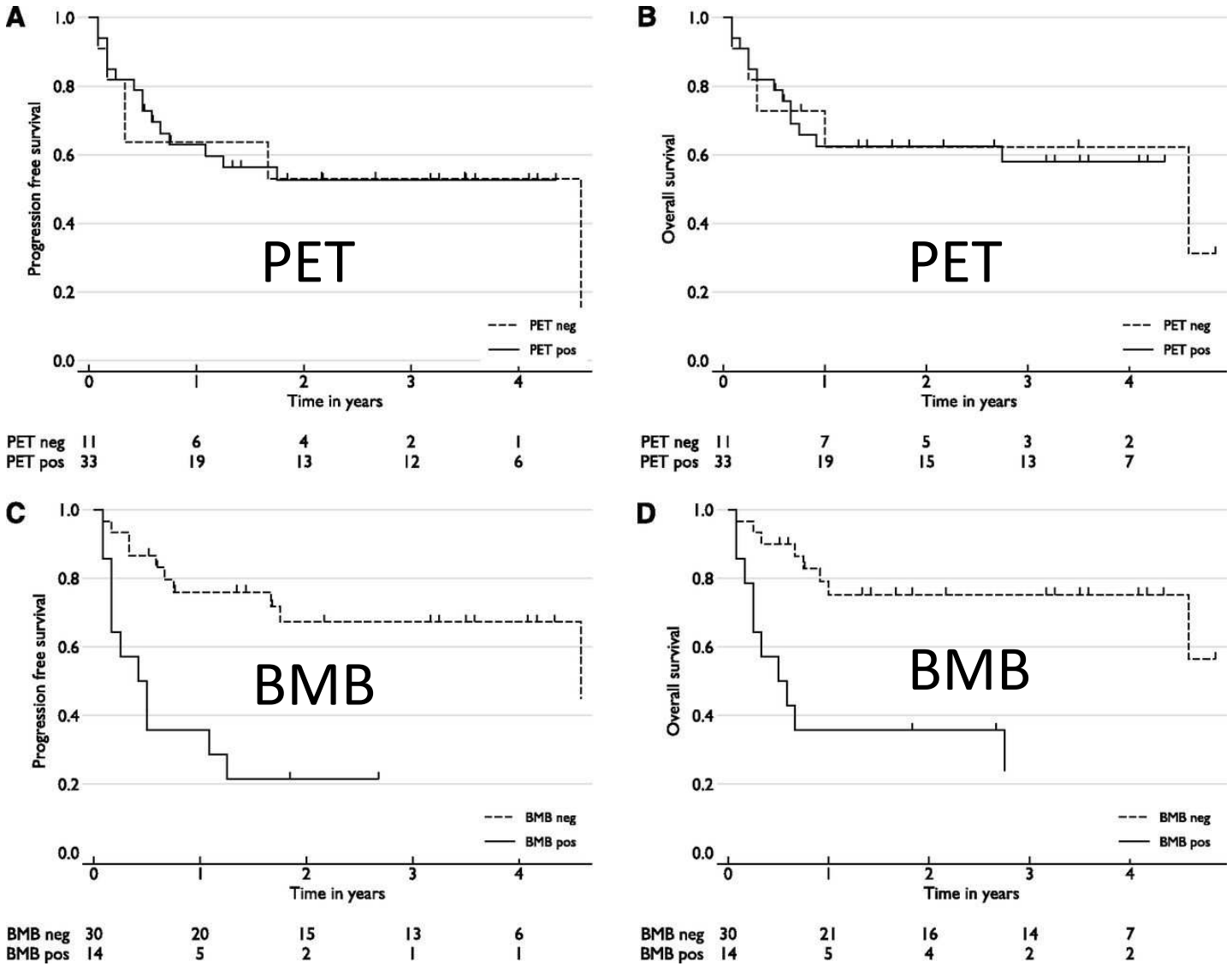
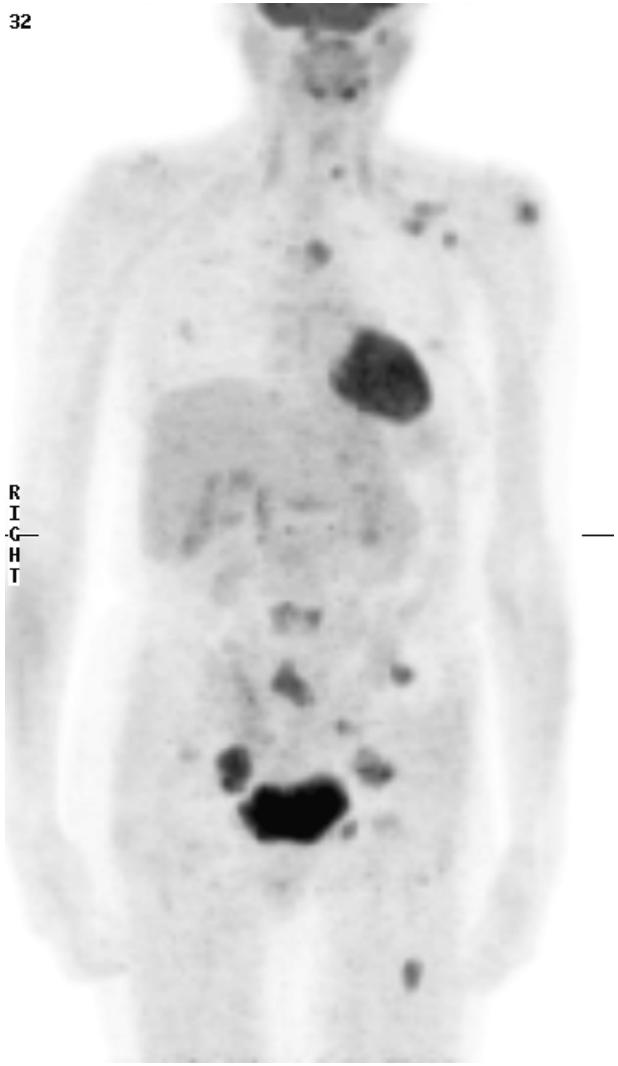
(A-D) PFS and OS analysis of stage IV patients, by marrow status.



blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Khan A B et al. Blood 2013;122:61-67 SB



Patient 1

Patient 2

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F-18 FDG PET for Evaluation of Bone Marrow Involvement in Non-Hodgkin Lymphoma

A Meta-analysis

Yen-Kung Chen, MD, PhD,† Chia-Lu Yeh, MD,* Chih-Cheng Tsui, MSc,* Ji-An Liang, MD,‡§ Jin-Hua Chen, PhD,¶ and Chia-Hung Kao, MD§‖*

TABLE 4. Meta-analysis of Sensitivity and Specificity Data

Type of Scan	Type of NHL	No.	TP	FP	TN	FN	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	Accuracy (95% CI)
PET	Aggressive	134	37	7	77	13	0.74 (0.62–0.86)	0.92 (0.86–0.98)	0.85 (0.79–0.91)
PET/CT	Aggressive	237	67	29	117	24	0.74 (0.65–0.83)	0.80 (0.74–0.87)	0.78 (0.72–0.83)
PET or PET/CT	Aggressive	321	67	36	194	24	0.74 (0.65–0.83)	0.84 (0.80–0.89)	0.81 (0.77–0.86)
PET or PET/CT	Indolent	156	26	7	92	31	0.46 (0.33–0.59)	0.93 (0.88–0.98)	0.76 (0.69–0.82)

Sensitivity low for BMI indolent NHL,
Mantle cell Lymphoma, MZL, SLL, MALT
Also in FL

Chen et al Clin Nucl Medicine 2011
Pakos et al JNM 2005
Pelosi et al QJ Nucl Med 2010

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PET vs Biopsy in Bone Marrow (BM) assessment in FL

	BMB+	BMB-	
PET BM+	**23**	**12**	35
PET BM -	**46**	**62**	108
	69	74	

- PET and BMB agreement is low (60%; K= 0.2)
- BM involvement in FL is usually diffuse and low volume

Luminari et al. Ann Oncol 2013

Slide c/o Dr S Luminari

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PET-CT

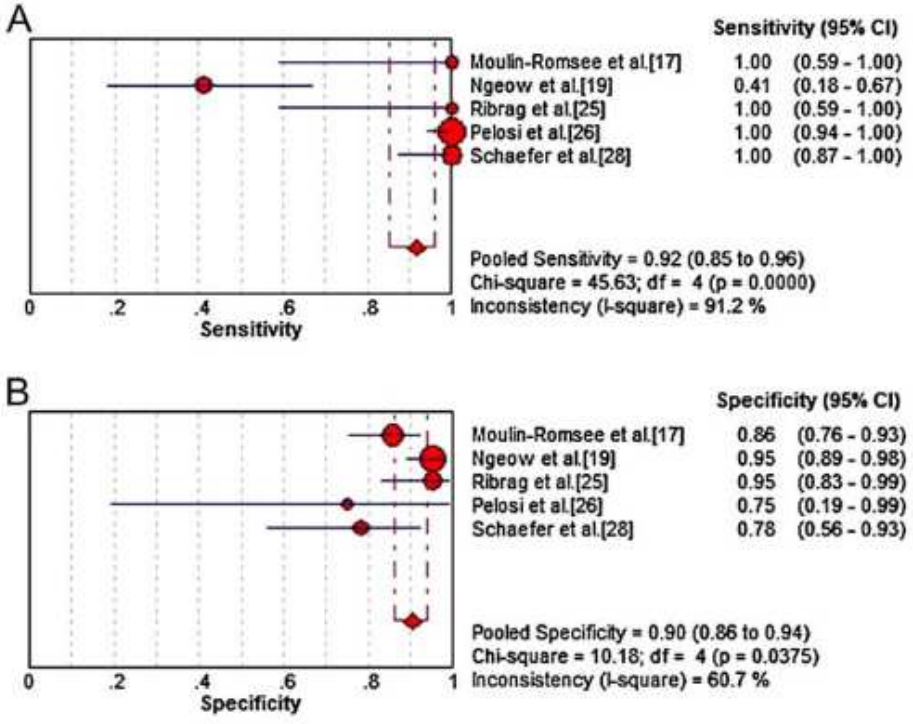

Fig. 4. Forest plot of pooled sensitivity and specificity of PET/CT for evaluation of bone marrow infiltration in staging of lymphoma. (A) Sensitivityand (B) specificity.

MR

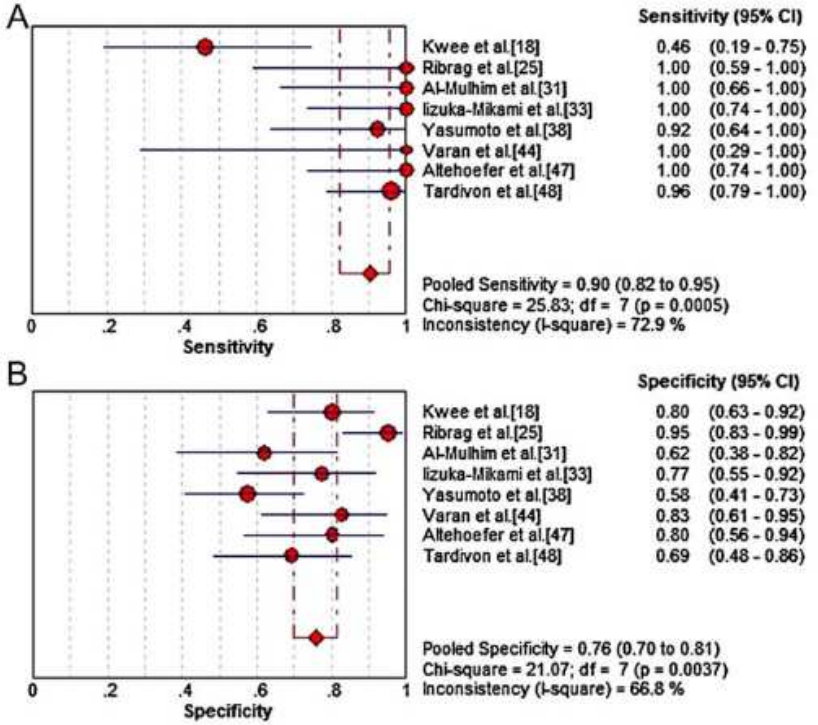

Fig. 5. Forest plot of pooled sensitivity and specificity of MRI for evaluation of bone marrow infiltration in staging of lymphoma. (A) Sensitivityand (B) specificity.

Pooled sensitivity 0.92 (0.85-0.96)

Pooled specificity 0.90 (0.86 -0.94)

Pooled sensitivity 0.90 (0.82-0.95)

Pooled specificity 0.76 (0.70 -0.81)

Wu et al Eur J Radiol 2012; 81: 303-11

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Bone marrow assessment
Lugano Classification

Bone marrow biopsy is no longer indicated for HL

PET may also obviate the need for biopsy in DLBCL unless discordant histology is considered important for management

(*as a negative PET does not rule out small cells in the marrow)*

Bone marrow biopsy is required for other lymphomas, with IHC and flow cytometry as well as TCR rearrangement analysis for T-NHL

Cheson BD et al JCO 2014 online 10.1200/JCO.2013.54.8800

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Thanks for your attention