

Imaging techniques to characterize spleen involvement in patients with Hodgkin lymphoma

Marco Picardi, MD

Ematologia, Azienda Ospedaliera Universitaria

Federico II, Naples, Italy

5th International Workshop on PET in Lymphoma

Palais de l'Europe. Menton, France

September 19, 2014

Spleen invasion in Hodgkin lymphoma

Issue 1: How is splenomegaly defined?

Issue 2: What is the best imaging technique to detect splenic focal lesions?

Issue 3: What is the best imaging tool to characterize the nodules in the spleen?

Issue 1: How is splenomegaly defined?

Availability of different tools for sizing the spleen!

Palpation: ≥ 1 cm from the costal border (in the midclavicular line), but it is associated with 35%-40% false-negative findings*

**Picardi M et al. Haematologica 2003; 88: 794-800*

Ultrasonography scan: excellent tool for sizing the spleen

- Easy to perform in routine practice (at the patient's bedside)
- Safe: no ionizing radiation
- Less expensive than radiological tools
- Performable by hematologists

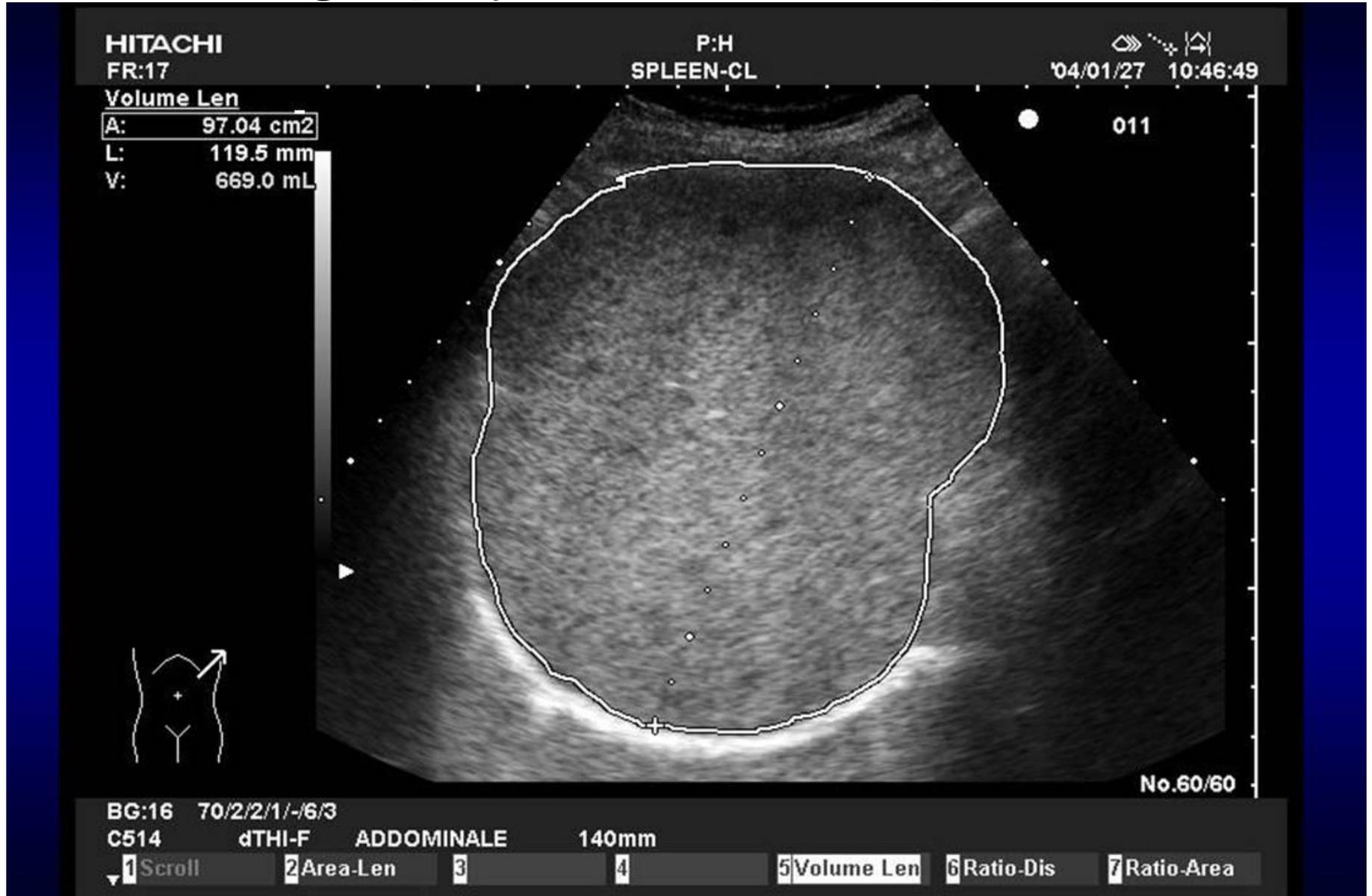
Picardi M et al. Bone Marrow Transplantation 1999; 24: 173-177

Picardi M et al. Blood 2002; 99: 4228-4230

Picardi M et al. Haematologica 2003; 88: 794-800

Issue 1: How is splenomegaly defined?

Ultrasonography-calculated splenic volume



Ultrasonography-measured longitudinal diameter



Results in 30% of false-negative findings*

Spleen may have various shapes*

*Picardi M et al. *Blood* 2002; 99: 4228-4230

*Picardi M et al. *Haematologica* 2003; 88: 794-800



Spleen sizing by ultrasound scan and risk of pneumococcal infection in patients with chronic GVHD: preliminary observations

M Picardi, C Selleri and B Rotoli

Division of Hematology, Federico II University Medical School, Naples, Italy

blood

2002 99: 4228-4230
doi:10.1182/blood.V99.11.4228

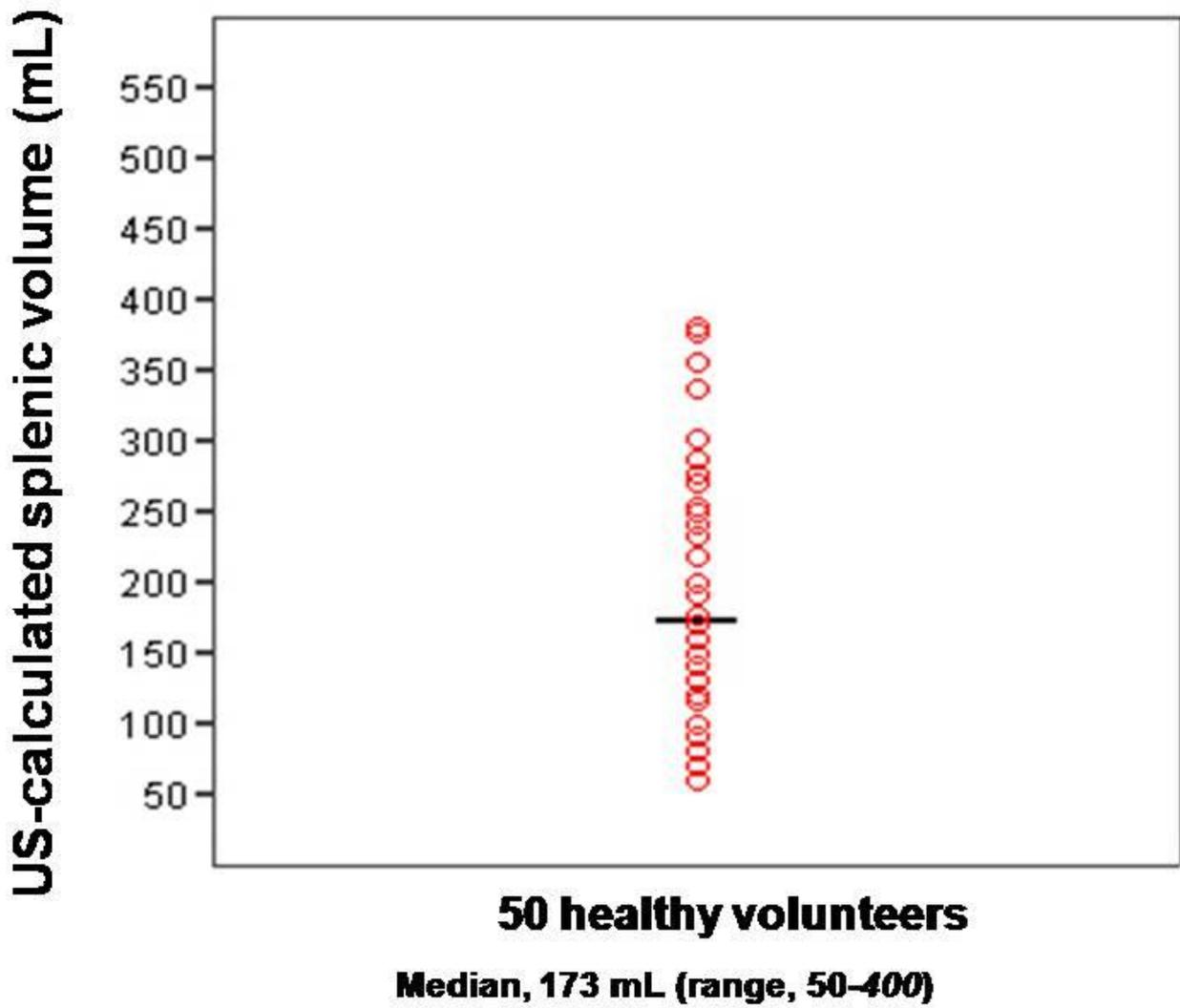
Measurement of spleen volume by ultrasound scanning in patients with thrombocytosis: a prospective study

Marco Picardi, Vincenzo Martinelli, Rosanna Ciancia, Ernesto Soccia, Roberto Morante, Antonio Sodano, Giuliana Fortunato and Bruno Rotoli

Spleen enlargement following recombinant human granulocyte colony-stimulating factor administration for peripheral blood stem cell mobilization

MARCO PICARDI, GENNARO DE ROSA, CARMINE SELLERI, NICOLA SCARPATO, ERNESTO SOCCIA, VINCENZO MARTINELLI, ROSANNA CIANCIA, BRUNO ROTOLI

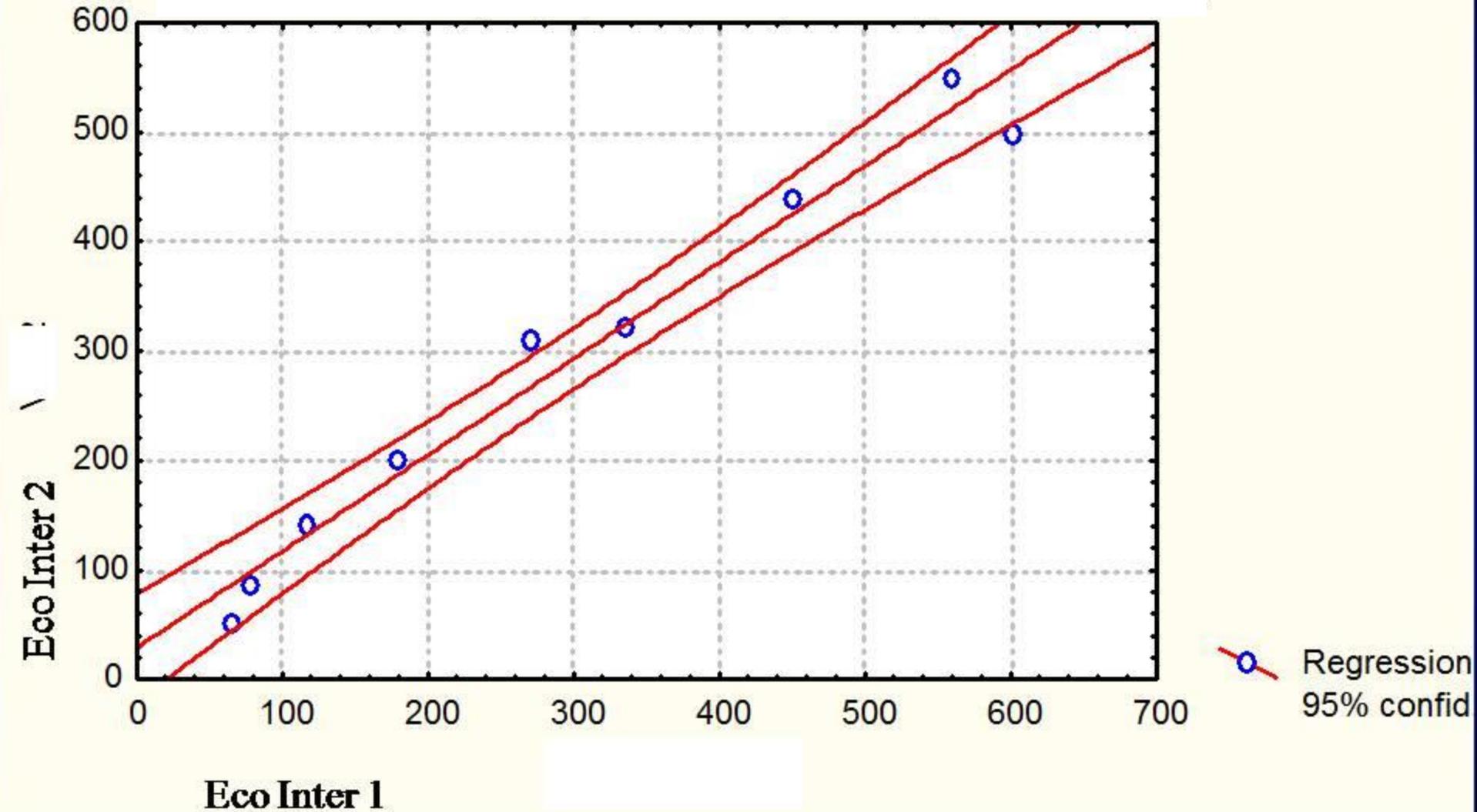
Haematologica 2003; 88: 794-800



VAR1 vs. VAR2 (Casewise MD deletion)

$$\text{VAR2} = 28,745 + ,87897 * \text{VAR1}$$

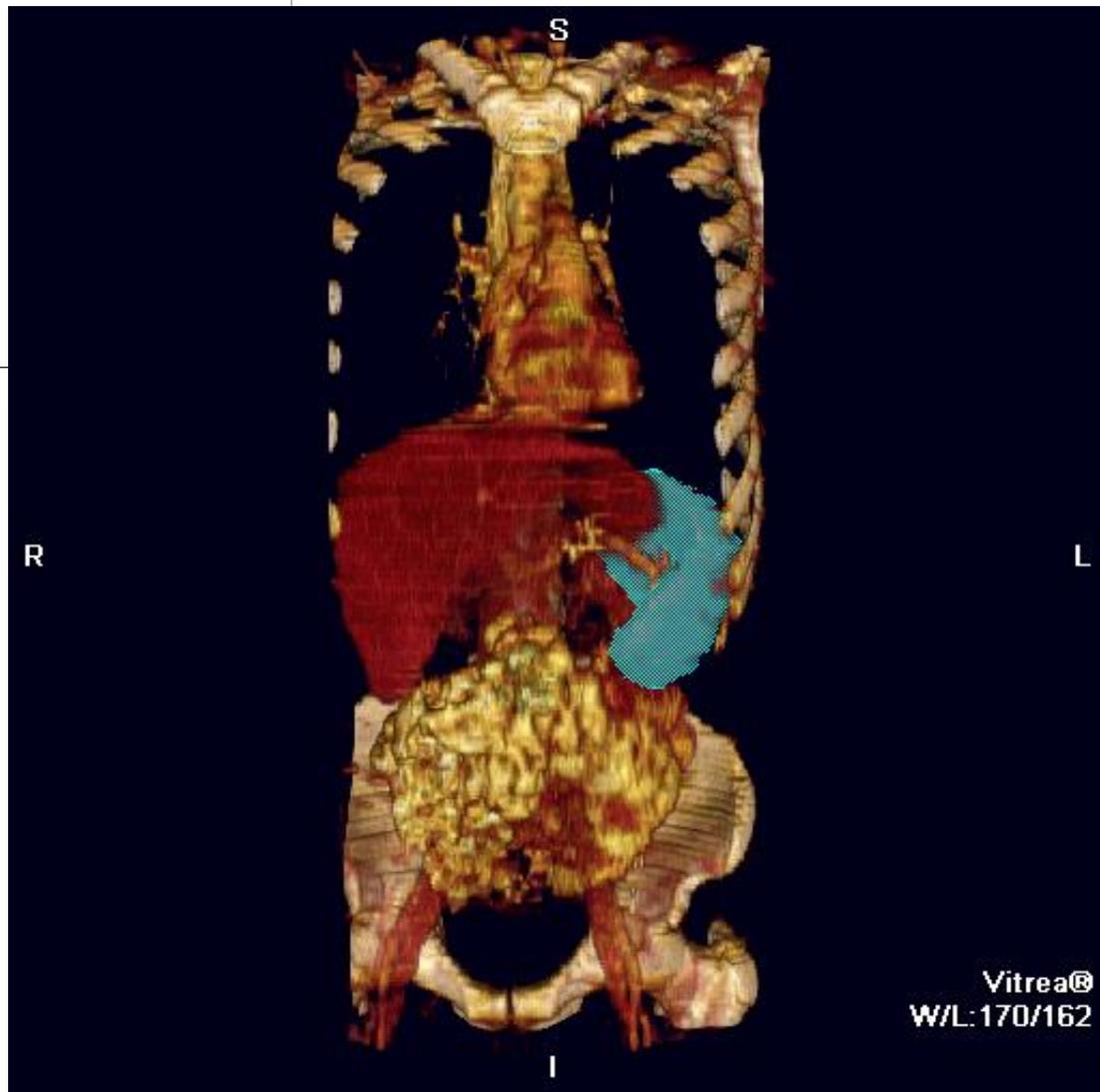
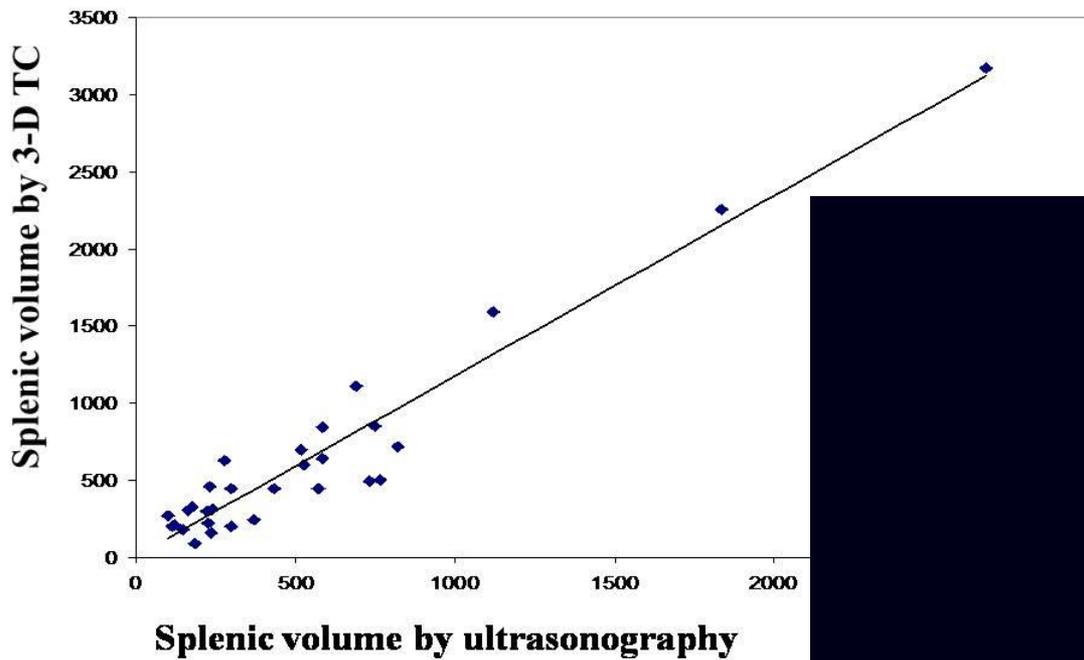
Correlation: $r = ,98499$



US-calculated splenic volume inter-observer variability

R= 0.9

P< 0.0001



Issue 1: How is splenomegaly defined?

Ultrasonography-calculated volume: >400 mL

Splenomegaly may occur even if the spleen is not affected by HL (hyperplastic or congestive enlargement), and involvement does not necessarily imply spleen enlargement*

**Glatstein E et al. Cancer 1969; 24: 709–718*

Issue 2: What is the best imaging technique to detect splenic focal lesions?

Excellence in ultrasound imaging techniques:

- High resolution
- Real-time tissue harmonic compound
- SonoCT
- **Contrast-enhanced**



The ultrasonography features of splenic focal lesions

One or more distinct hypoechoic, ovoid, well-circumscribed, macro-nodule (>1 cm) or micro-nodule (\leq 1 cm) by measuring the long axis.

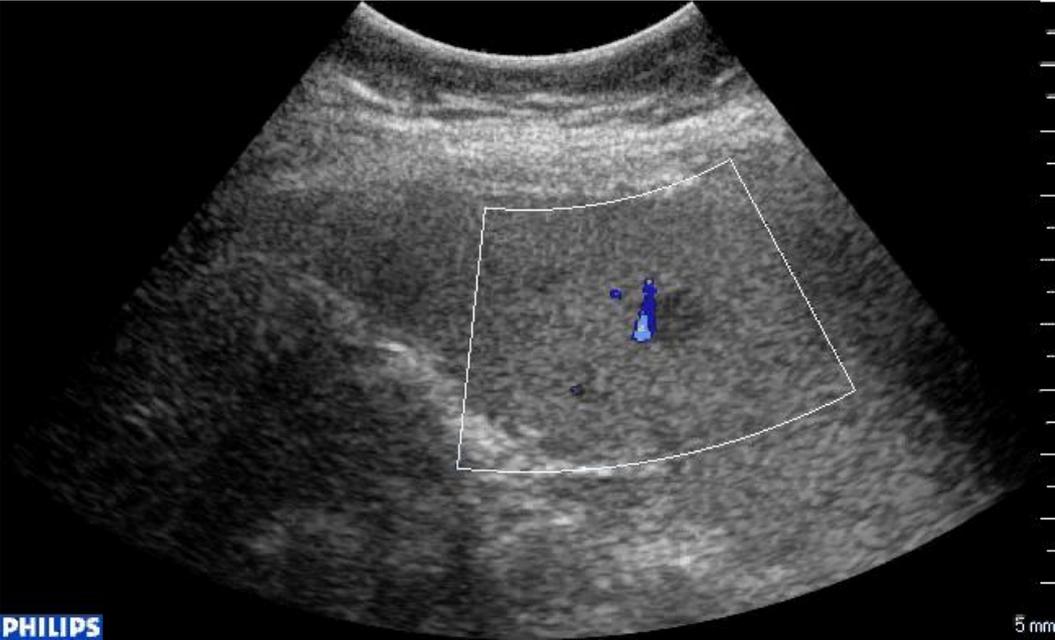
Nodule behaves differently at i.v. infusion of contrast agent containing sulfur hexafluoride-filled phospholipid-stabilized microbubbles, including the arterial phase (starting 10 sec after injection) and the parenchymal phase (starting 40 sec after injection, until 7-9 min)



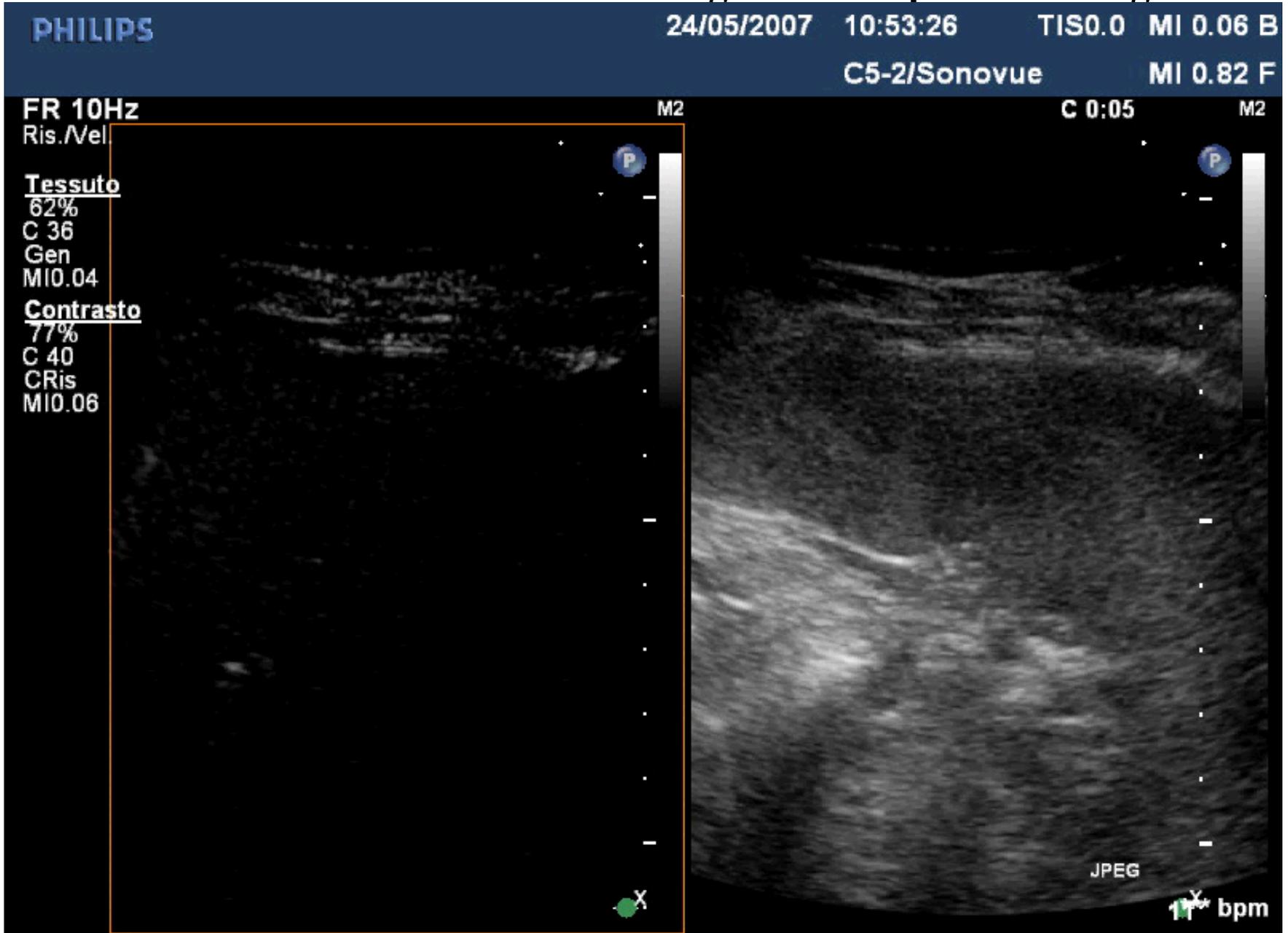
Staging in a patient with HL: focus on spleen (FDG PET \ominus)

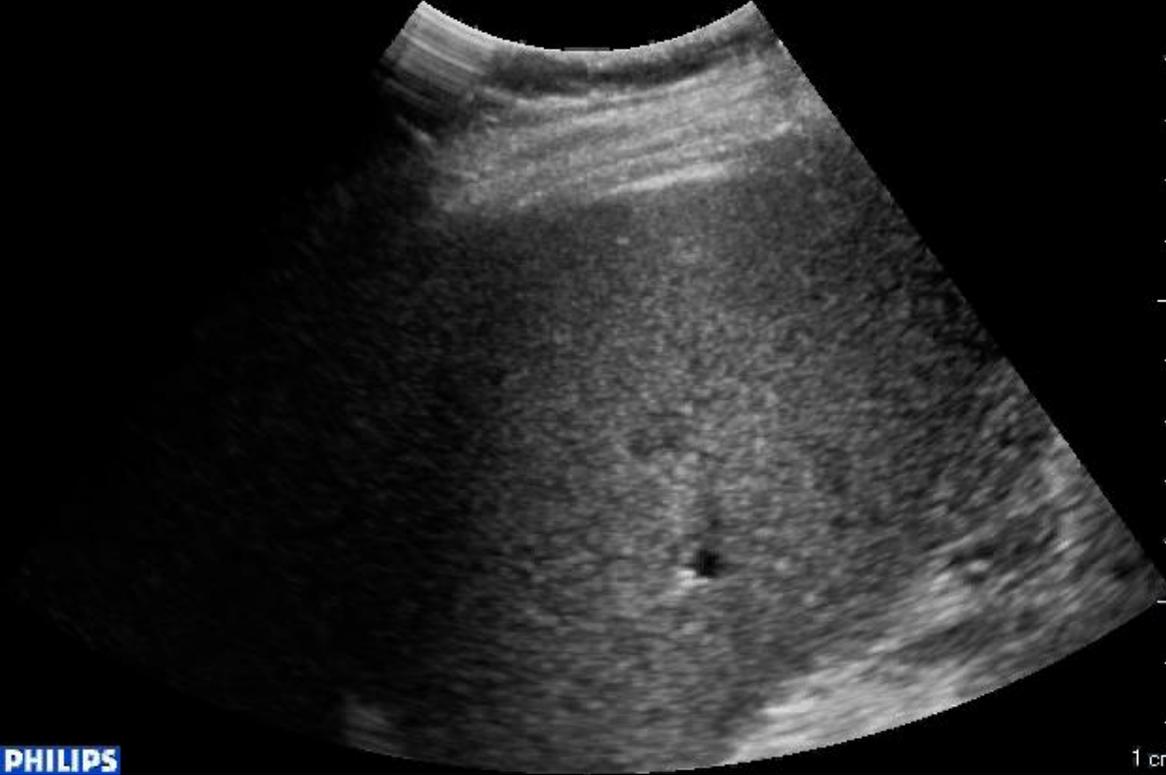
Nonenhanced harmonic compound US shows 1 cm nodule

Color-Doppler examination



Perfusion (arterial and parenchymal) phase contrast-enhanced US shows the isoechoic and isoenhanced nodule. Diagnosis was splenic hemangioma

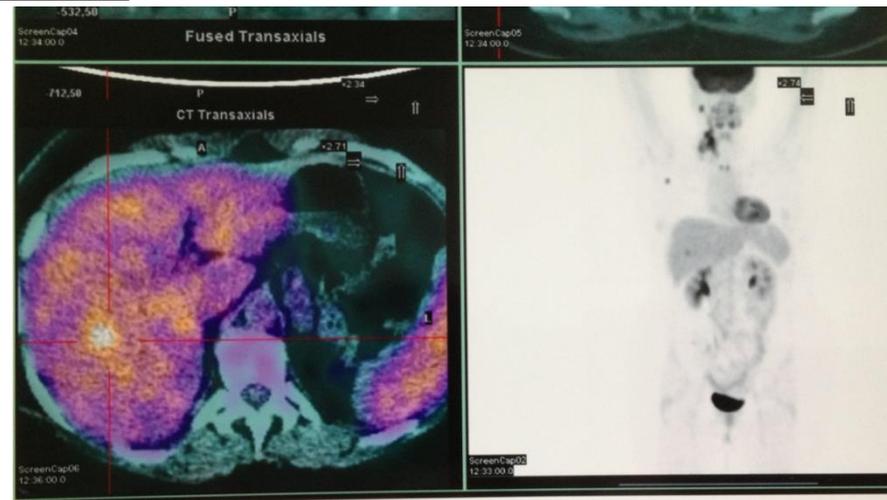




Patient with suspected HL relapse in the liver, post-bone marrow transplantation

Nonenhanced harmonic compound US shows 1 cm nodule in the liver (V seg)

FDG PET/CT scan ⊕



0:18

Diagnosis:
micotic abscess
(biopsy-proven)

PHILIPS

1 cm



Perfusion phase contrast-enhanced US shows the rim-enhancement of the nodule



0:28

PHILIPS

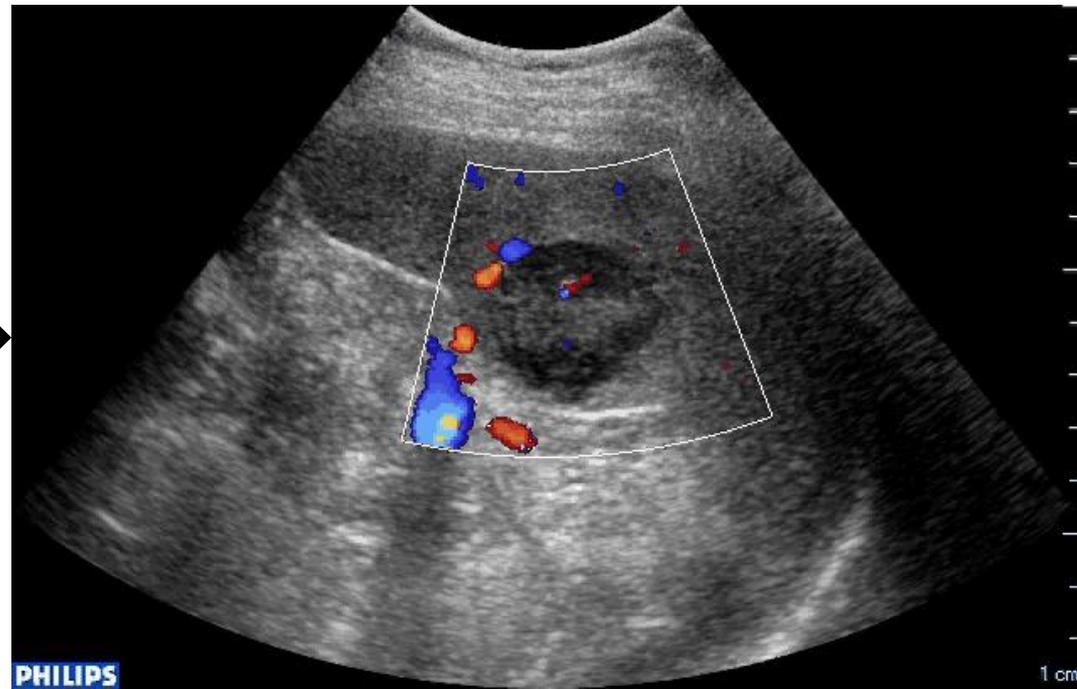
1



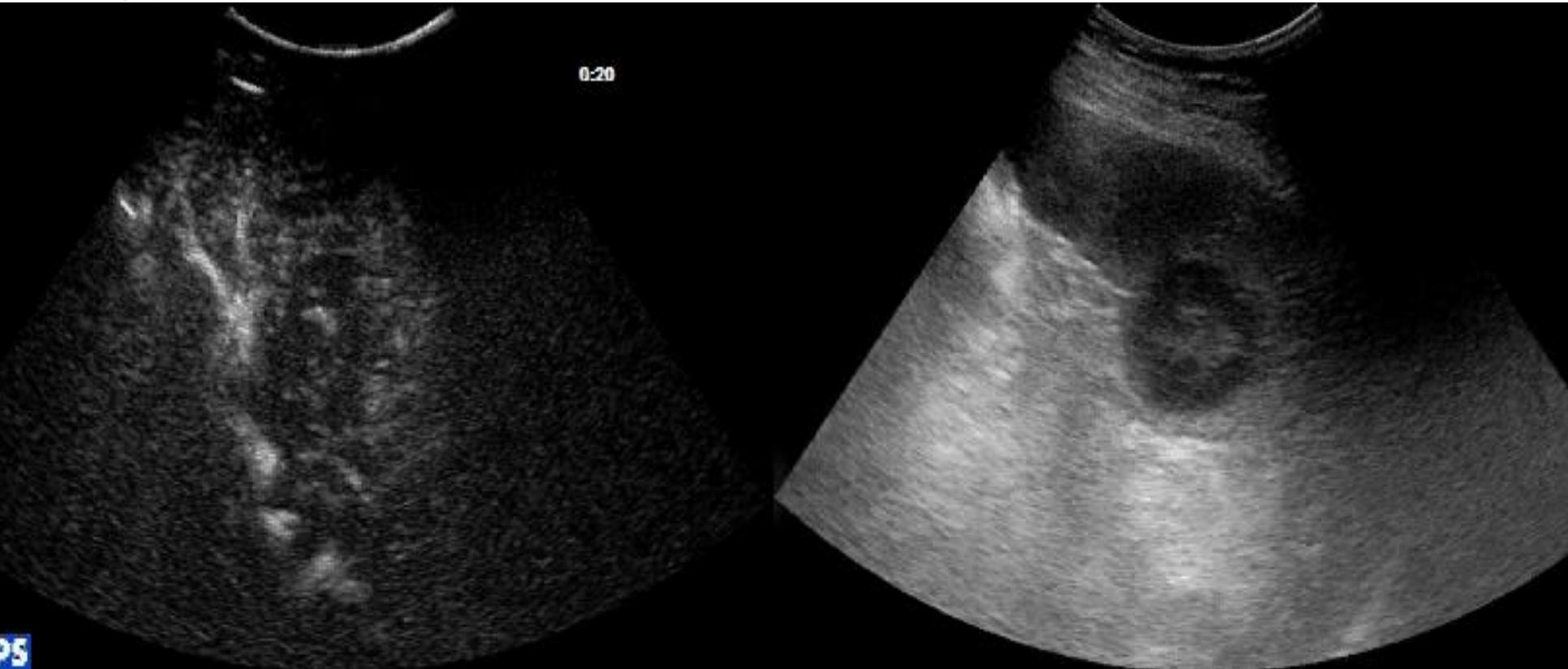
Staging in a patient
with HL: focus
on spleen (FDG PET \oplus)

Nonenhanced
harmonic compound
US shows a 3-cm
nodule

Color-Doppler
examination



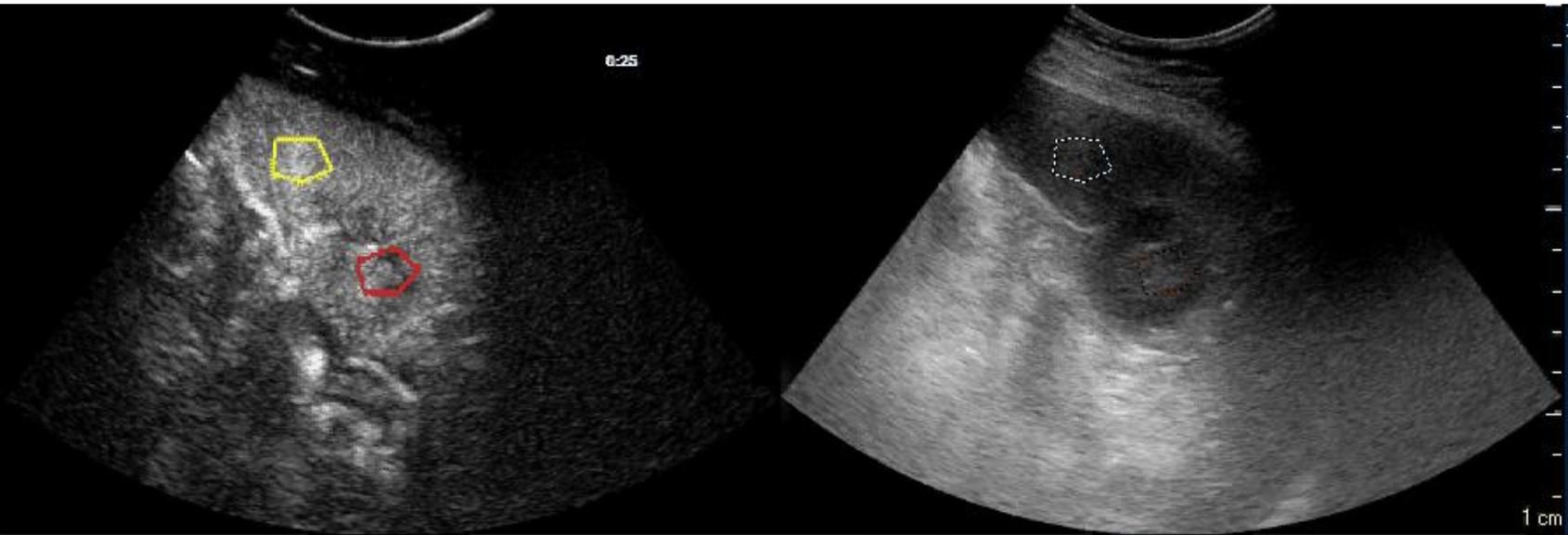
Arterial phase contrast-enhanced US shows an isoechoic and isoenhanced nodule. Parenchymal phase contrast-enhanced US shows a clear hypoechoic defect in the nodule.



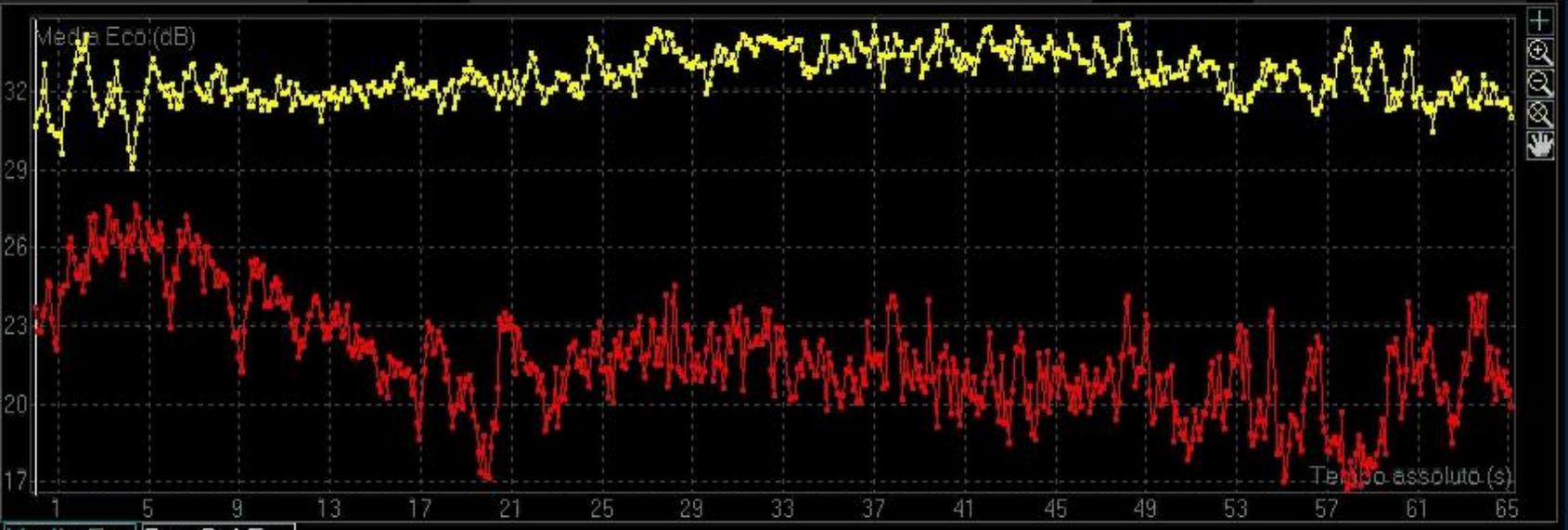
Diagnosis: nodular infiltration in the spleen by HL (biopsy-proven)

ROI=I / T

Red-line= Hodgkin lymphoma / Yellow-line= normal tissue



Media Eco
ROI 1 = 23.74 dB
ROI 2 = 30.69 dB



Media Eco Dev Std Eco

Issue 3: What is the best imaging tool to characterize the nodules in the spleen?

ORIGINAL RESEARCH ■ ULTRASONOGRAPHY



Contrast-enhanced Harmonic Compound US of the Spleen to Increase Staging Accuracy in Patients with Hodgkin Lymphoma: A Prospective Study¹

Radiology

Picardi M et al. Radiology 2009; 251: 574-582

Characteristics of the Study

Population

Variable	Value
No. of men/women	53/47
Mean age (y)	
Men	30 (18–71)
Women	32 (18–74)
Age of entire population (y)	
Median	30
Range	18–74
Histologic type (World Health Organization classification)	
Nodular sclerosis	75
Mixed cellularity	16
Lymphocyte predominance	5
Lymphocyte rich	2
Lymphocyte depleted	2
B symptoms*	55
Erythrocyte sedimentation rate \geq 50	58
Duration of staging process (d) [†]	
Median	9
Range	1–14

Aim of the study

To prospectively compare the efficacy of contrast-enhanced US, diagnostic CT (with hepatic arterial and portal venous phases, at 30 and 60 seconds after contrast injection) and FDG PET (with nonenhanced low-dose CT for segmented attenuation correction) in detecting nodular infiltration in the spleen of patients with newly diagnosed HL, at pre-treatment staging.

Figure 3

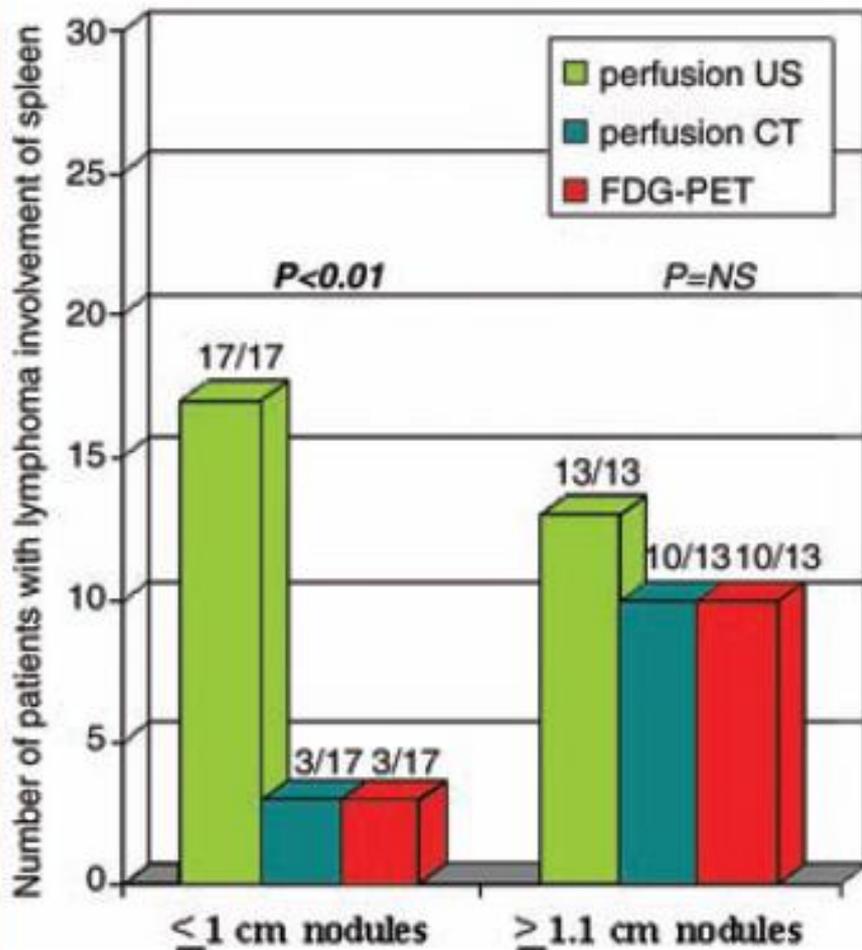


Figure 3: Graph depicts the diagnostic sensitivity of each imaging technique in detecting nodules involved by lymphoma according to nodule size (long axis). *NS* = not significant.

According to the Reference Standard*: Overall 30/100 patients had splenic nodular infiltrations

Sensitivity rates:

- Perfusion US 100% (30/30 nodular infiltrations)
- FDG PET 43% (13/30 nodular infiltrations)
- Perfusion CT 43% (13/30 nodular infiltrations)

False-negative rates:

- FDG PET 57%
- Perfusion CT 57%

*Picardi M et al. Radiology 2009; 251: 574-582

13 patients were upstaged, moving from an originally limited disease (stage I and stage II with only supradiaphragmatic involvement) to a more extended disease (stage IIIs with supradiaphragmatic and splenic involvement)

Table 2

Effect of Contrast-enhanced Harmonic Compound US on the Ann Arbor Stage

Conventional Staging Plus Contrast-enhanced Harmonic Compound US

Conventional Staging	I	II	III	III _s	IV	IV _s	Total
I	7	—	—	3	—	—	10
II	—	52	—	10	—	—	62
III	—	—	7	4	—	—	11
III _s	—	—	—	9	—	—	9
IV	—	—	—	—	4	—	4
IV _s	—	—	—	—	—	4	4
Total	7	52	7	26	4	4	100

Note.—Data are the number of patients.

The best imaging tool to detect splenic nodular involvement by HL!

Report of a Committee Convened To Discuss the Evaluation and Staging of Patients with Hodgkin's Disease: Cotswolds Meeting

By T.A. Lister, D. Crowther, S.B. Sutcliffe, E. Glatstein, G.P. Canellos, R.C. Young, S.A. Rosenberg, C.A. Coltman, and M. Tubiana

The Ann Arbor classification for describing the stage of Hodgkin's disease at initial presentation has formed the basis upon which treatment is selected and has allowed comparison of results achieved by different investigators for almost two decades. A meeting was convened to review the classification and modify it in the light of experience gained in its use and new techniques for evaluating disease. It was concluded that the structure of the classification be maintained. It was particularly recommended: (1) that computed tomography (CT) be included as a technique for evaluating intrathoracic and infradiaphragmatic lymph

nodes; (2) that the criteria for clinical involvement of the spleen and liver be modified to include evidence of focal defects with two imaging techniques and that abnormalities of liver function be ignored; (3) that the suffix 'X' to designate bulky disease (greater than 10 cm maximum dimension) be introduced; and (4) that a new category of response to therapy, unconfirmed/uncertain complete remission (CR[u]), be introduced to accommodate the difficulty of persistent radiological abnormalities of uncertain significance.
J Clin Oncol 7:1630-1636. © 1989 by American Society of Clinical Oncology.

Fused FDG PET/contrast-enhanced CT as a single front-line imaging tool to stage and to guide treatment strategy

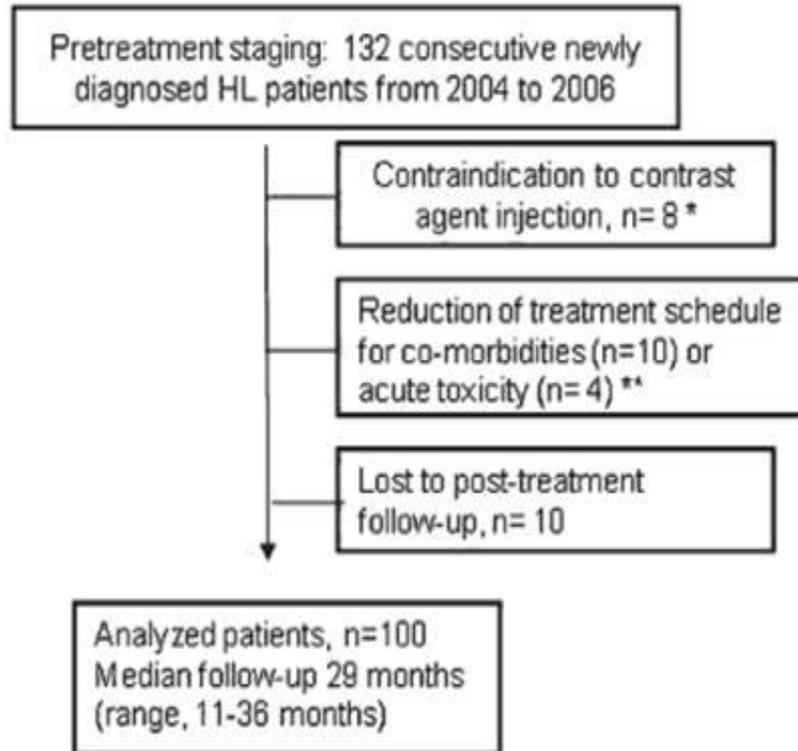
**Fused FDG–PET/contrast-enhanced CT detects occult
subdiaphragmatic involvement of Hodgkin’s lymphoma
thereby identifying patients requiring six cycles of
anthracycline-containing chemotherapy and
consolidation radiation of spleen**

M. Picardi¹, A. Soricelli², F. Grimaldi¹, E. Nicolai², A. Gallamini³ & F. Pane^{1*}

¹Division of Hematology, Department of Biochemistry and Medical Biotechnology, University of Naples 'Federico II' University Medical School, Naples; ²Fondazione SDN, Naples; ³Hematology Department, S. Croce e Carle Hospital, Cuneo, Italy

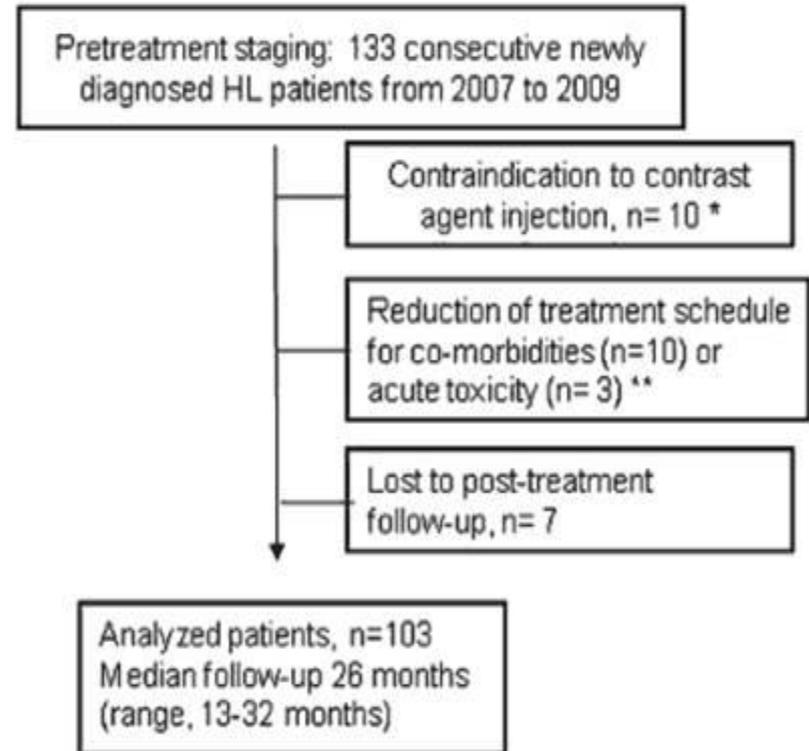
Efficacy of a combined treatment strategy

Historical cohort
(patients staged with separate PET and diagnostic CT acquisitions)



- * These patients did not receive study treatment strategy
** Nine of these 14 patients did not achieve complete remission at the end of treatment

Fused PET/CT group



- * These patients did not receive study treatment strategy
** Seven of these 13 patients did not achieve complete remission at the end of treatment

Table 2. Difference in staging between the two series of patients

Variable	Fused PET/CT group (<i>n</i> = 103)	Historical cohort (<i>n</i> = 100)	<i>P</i>
Ann Arbor stage			0.04
I	13	12	
II	45	58	
III	32	20	
IV	13	10	
Subdiaphragmatic lymph node involvement	26	28	NS
Spleen involvement	31	14	0.005
Extranodal disease			
Liver	10	3	0.05
Bone	6	6	NS
Lung	10	10	NS
International prognostic index ^a			
0–1	13	10	NS
2–3	17	12	
4–7	15	8	

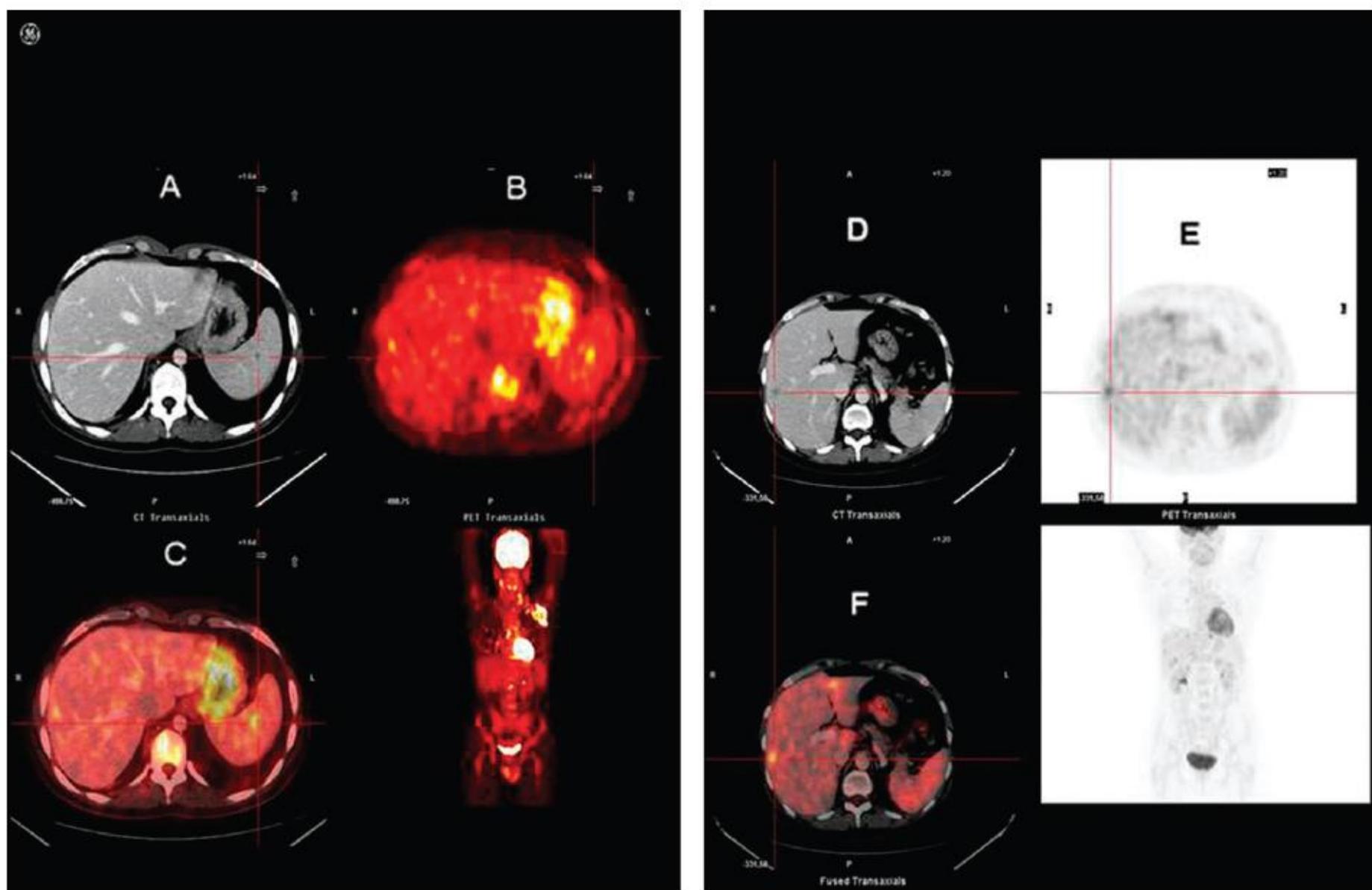


Figure 3. Splenic lymphoma nodule, as revealed by fused PET/contrast-enhanced CT: (A) a subcentimeter nodular hypodensity in respect to the surrounding tissue during the portal phase of perfusion study at CT, (B) FDG focal uptake at PET scans, and (C) imaging of fusion of the nodule. Liver lymphoma nodule, as revealed by fused PET/contrast-enhanced CT: (D) a centimeter nodular hypodensity in respect to the surrounding tissue during the portal phase of perfusion study at CT, (E) FDG focal uptake at PET scans, and (F) imaging of fusion of the nodule. CT, computed tomography; FDG–PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography.

Table 3. Chemotherapy and radiotherapy received according to pretreatment staging

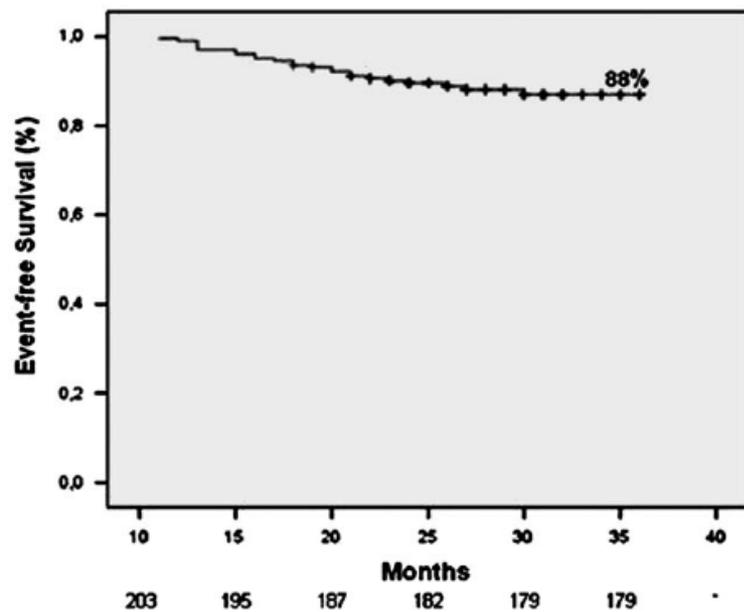
	<i>n</i>	Chemotherapy		Irradiated fields						Residual mass	Spleen area	None
		No. of cycles of VEBEP		Supradiaphragmatic				Subdiaphragmatic				
		4	6	Localized	Extended			Para-aortics	Inverted Y			
			Neck	Axilla	T-field	Mantle						
Historical cohort	100											
Limited stage	70	70	–	10	8	25	17	6	4			
Advanced stage	30	–	30							7	7	16 ^a
Fused PET/CT group	103											
Limited stage	58	58	–	8	6	22	15	4	3			
Advanced stage	45	–	45							7	18	20 ^a

Data are the numbers of patients. VEBEP is the induction chemotherapy regimen used in the study (see text). T-field: irradiation of low neck and mediastinum; mantle: irradiation of the lymph node sites above the diaphragm; inverted Y: irradiation of para-aortic and pelvic lymph nodes; residual mass: irradiation of residual nodes at the initial bulky sites; spleen area: irradiation of spleen plus splenic hilar region in cases of pretreatment massive spleen involvement.

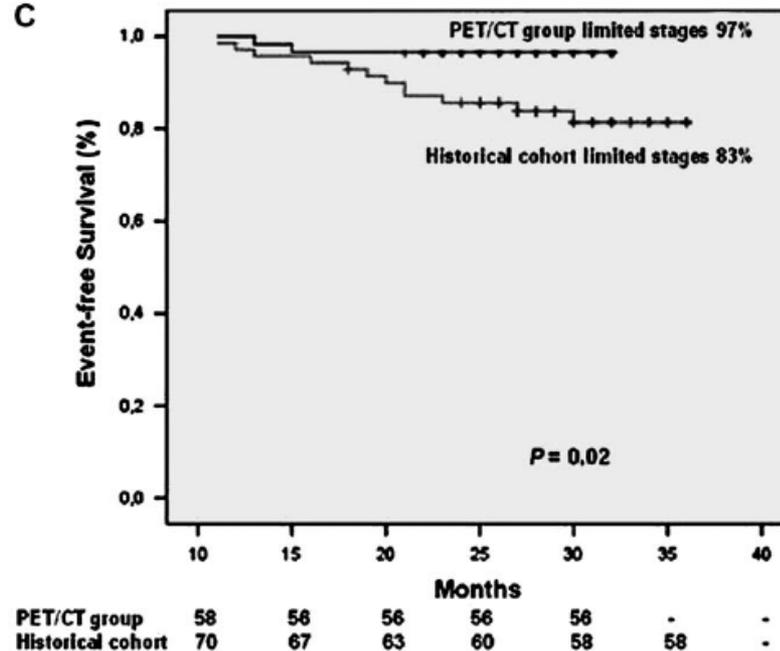
^aThese patients after the completion of the six courses of chemotherapy underwent observation without further therapy.

CT, computed tomography; PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose-positron emission tomography.

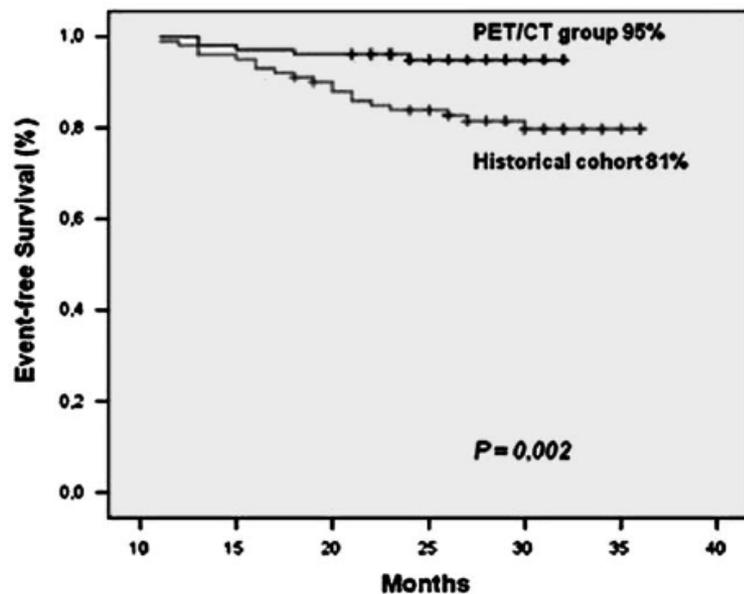
A



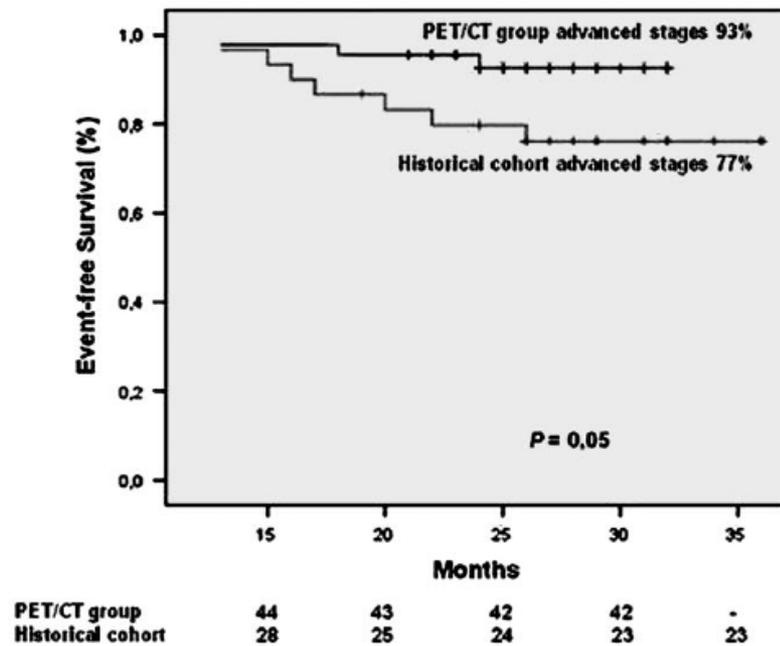
C



B



D



PET/CT group
Historical cohort

103
100100
9599
8898
8498
81-
81-
-

PET/CT group
Historical cohort

44
2843
2542
2442
23-
23-
-

In conclusion

We should use integrated imaging
(at least two techniques
supported by *i.v.* contrast
agents) to detect
spleen invasion in patients
with Hodgkin lymphoma.

Thank you for your attention



Naples, Italy