Estimation of bulky lymph nodes by power Doppler ultrasound scanning in patients with Hodgkin's lymphoma: a prospective study

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The accuracy of standard methods in estimating bulky lesions requires validation. We used clinical/computed tomography (CT) evaluation and power Doppler ultrasound (US) to detect bulky disease in 137 consecutive Hodgkin's lymphoma patients, and analyzed the prognostic relevance of each method. Bulky disease was detected by clinical/CT evaluation in 47% of the patients and by power Doppler US in 20%. After treatment, at multivariate analysis power Doppler US-selected bulky disease was the parameter that best correlated with freedom from treatment failure ($p<0.001$). Power Doppler US, a readily available imaging technique, provides a better prognostic classification by detecting true bulky disease more accurately.

Key words: Hodgkin's lymphoma, power Doppler ultrasound scan, bulky disease.

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Size and extension of lymphadenopathies are important factors in defining the prognosis and designing the most appropriate treatment in Hodgkin's lymphoma, bulky disease and advanced stage being recognized adverse prognostic factors.[1] In many institutions, clinical and computed tomography (CT) examination are considered to provide sufficient information to map disease sites and estimate tumor burden.[1] However, non-palpable histologically significant malignant lymph nodes or enlarged reactive or necrotic lymph nodes may bias such a staging procedure.[2] High-resolution ultrasound (US) with power Doppler is a recent imaging technique that accurately defines the morphologic and vascular characteristics of a lymph node. Power Doppler US has proven useful to identify malignant lesions, detecting more flow signals than gray-scale and color Doppler US.[3,4] We tested the accuracy of power Doppler US in detecting bulky lymph nodes in patients with Hodgkin's lymphoma at initial presentation, verifying its prognostic relevance.

Design and Methods

Study design

In four years, 137 consecutive newly diagnosed Hodgkin's lymphoma patients were submitted to staging procedures. The lymph nodes most suspected of having bulky characteristics were detected using clinical/CT scan examination and power Doppler US in all patients. The study aim was to compare the value of power Doppler US-defined bulky disease with that of clinical/CT-defined bulky disease in predicting freedom from treatment failure (FFTF). In addition, other clinical variables routinely used as prognostic factors were evaluated in the statistical analysis.[5] Patients were informed of the study aim, and signed a consent form according to the Helsinki declaration.

Clinical/CT scan evaluation

Lymph node evaluation was performed by physical examination and CT using a multirow helical instrument and i.v. contrast medium (Mx 8000; Marconi Medical Systems, Cleveland, OH, USA). For each patient, the region containing a bulky disease, defined as any lymph node mass with a long axis ≥5 cm, was looked for and recorded.

Power Doppler US procedure

Patients underwent US exploration of all superficial lymph node areas and any abnormal lymph node was examined by power Doppler, using a high-resolution US instrument equipped with power Doppler (EUB 6500; Hitachi, Tokjo, Japan) and a 13-6 MHz broad-band linear probe. Lymph nodes were assessed by gray-scale to define their anatomic site, depth, size, shape and hilus and by power Doppler to investigate their intranodal vascularization.[6] Size was studied by measuring the perimeter, cross-sectional diameter and area (defined as the maximum measurements with nodal borders and angles clearly defined); thereafter, the volume in mL was automatically calculated by the US machine software. As for Doppler spectral analysis, the resistive index (RI) of

arterial vessels was calculated as defined by Pourcelot.[7] The presence of an abnormal vascular pattern combined with a RI value ≥0.65 fulfilled the requirement for intranodal hypervascularization. The combination of volume ≥30 mL and intranodal hypervascularization was the main criterion used to define a lymph node as bulky. In 13 patients the bulky lymph node was studied by repeated US volume measurements on two occasions at 1-hour intervals by the same operator (to test intraobserver reproducibility) and by another operator unaware of the previous result, always using the same US machine (to test interobserver reproducibility). The same 13 patients underwent whole-body fluorine-18-fluoro deoxyglucose positron emission tomography (FDG-PET)/CT scans, to examine the correlation between bulky lymph nodes selected by power Doppler US and those selected by PET/CT [the superficial mass with the highest standardized uptake value (SUV) and with 3-dimensional volume ≥30 mL].[8]

Therapeutic plan and response evaluation

All patients underwent ABVD-like chemotherapy courses repeated every 4 weeks. The response to chemotherapy was defined according to standardized criteria.[9,10] All patients considered responders received involved field radiation with a linear accelerator (planned dose 32Gy, without boost on initial bulky sites).

Statistical analysis

Univariate and multivariate analyses based on the Cox proportional hazards regression model were carried out to assess the prognostic factors significantly contributing to FFTF. Other statistical evaluations included χ^2, unpaired Student's t test, and analysis of variance with Bonferroni's correction. SPSS for Windows (version 12.0; SPSS, Chicago, IL, USA) was the software used.

Results

The patients' characteristics are summarized in Table 1. All patients received six courses of chemotherapy, in a median time of 6 months. A total of 125 patients (91%) achieved complete responses and underwent radiotherapy as planned. Patients were then observed for a median of 20 months (range, 7-43); 117 of them remained in sustained complete remission. Overall, a total of 20 patients suffered from events: five patients did not respond to chemotherapy, seven had a partial response, and eight relapsed.

Clinical/CT scan results

Sixty-five patients (47%) were assigned to the bulky group, having superficial (n=33) and/or mediastinal (n=44) lymph node masses. Twelve simultaneously had superficial and mediastinal masses. The median of long axis measurements of the masses was 7 cm (range, 5-12). No patient had abdominal bulky lymph nodes. The remaining 72 patients had lymph nodes with a diameter < 5 cm.

Table 1. Characteristics of the entire study population.

Characteristics	*No.*	*(%)*
Total patients	137	
Sex		
Male	79	(57)
Female	58	(43)
Age, years		
Median	30	
Range	15-74	
Histology		
Nodular sclerosis	96	(70)
Mixed cellularity	34	(25)
Lymphocyte Predominance	7	(5)
No. of nodal sites involved		
2	47	(34)
3	50	(36)
> 3	40	(30)
Contiguous extranodal involvement*	22	(16)
Ann Arbor Stage		
I	14	(10)
II	90	(66)
III	28	(20)
IV	5	(4)
Splenic involvement°	20	(14)
B symptoms	75	(55)
Erythrocyte sedimentation rate ≥ 50 mm	80	58)
Mediastinal bulky	44	(32)
Clinical/CT-selected superficial bulky disease	33	(24)
Power Doppler US-selected bulky disease	26	(20)

**an extranodal extension of the disease confined to a single lung lobe, or to sites such as pericardium/pleura/chest wall/pharynx, contiguous to the lymph nodes involved; °focal lesion(s) visible on CT, FDG-PET and/or US scanning.*

Power Doppler US results

The average time required for the power Doppler US examination was 30 minutes (range, 20-50). Intraobserver and interobserver measurement reproducibility was excellent, with a Pearson's value of 0.9 and 0.88, respectively. Twenty-six patients (20%) were assigned to the power Doppler US-defined bulky group. The median of the selected lymph node volume measurements was 37.5 mL (range, 30-180); depth was between 1 and 4 cm, and the site was cervical in four, supraclavicular in five, axillary in 13, pectoral in two, and inguinal in two. Lymph nodes were round in 18 cases and oval in eight; the hilus was absent in 16 cases and truncate in ten. Intranodal vascular mapping was mixed in 13 cases, chaotic in ten, peripheral in two, and central/hilar in one (Figure 1). At Doppler spectral analysis, the median RI value was 0.74 (range 0.65-0.95). There was complete agreement on bulky disease identification between power Doppler-US and PET/CT scans in 13 patients studied by both methods; the volume of the PET/CT-selected bulky lymph nodes ranged from 30 to 60 mL and the SUV from 7 to 13. The remaining 111 patients had superficial lymph nodes with a volume < 30 mL or ≥30 mL without hypervascularization.

Overall, the designation of superficial sites containing bulky disease was concordant between clinical/CT scans and power Doppler US in 18 patients and discordant in 23 patients.

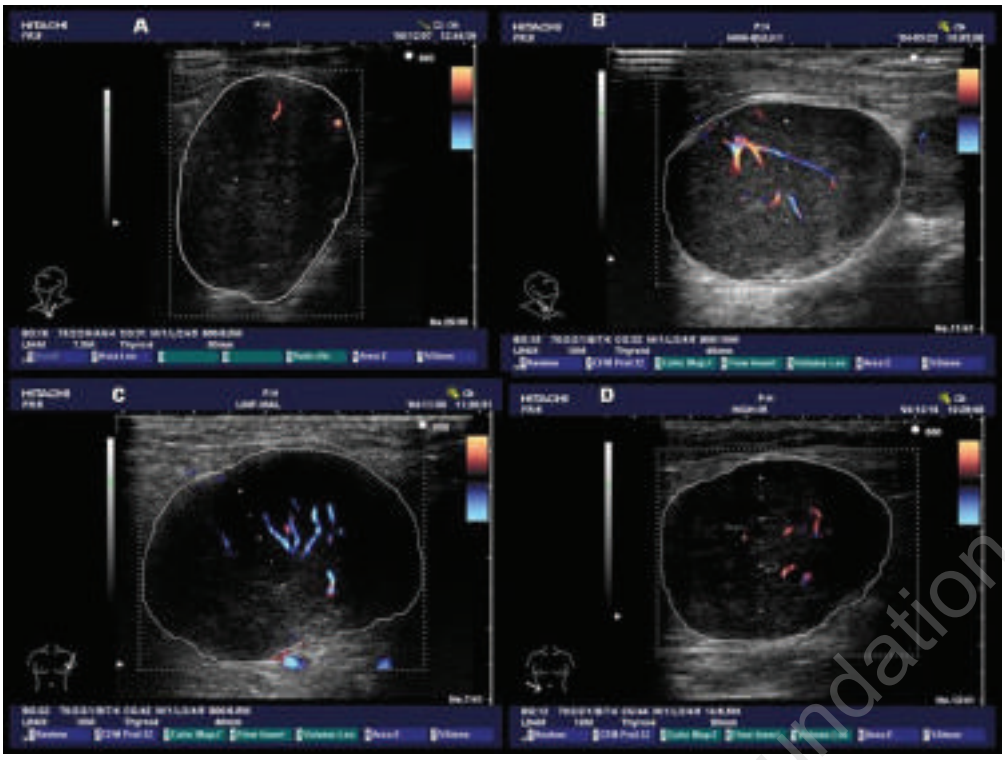

Figure 1. Power Doppler ultrasound (US) features. Peripheral type (A), mixed type (B), chaotic type (C), and central type (D) vascularization in bulky lymph nodes (volume ≥30 mL) as revealed by power Doppler US scanning in patients with Hodgkin's lymphoma.

Risk factors for FFTF

In a univariate analysis for prognostic factors, power Doppler US-selected bulky disease surpassed the mediastinal and superficial bulky disease selected by clinical/CT scan evaluation and any other analyzed factor as a significant predictor of FFTF. When a multivariate analysis was performed, only power Doppler US-selected bulky disease and advanced stage retained statistically significant prognostic value, and again power Doppler US was the best indicator of prognosis. Mediastinal bulky disease retained borderline statistical significance (Table 2).

Discussion

Stringent criteria for defining bulky disease are still controversial. According to various authors, bulky disease is considered any node mass whose largest diameter is at least 5 cm, 7 cm, or 10 cm.[1,11-13] However, one-dimensional measurement is often inaccurate in reliably determining lymph node size. On the other hand, not all enlarged lymph nodes are involved by the main disease entity; there is a risk of considering as malignant satellite lymph nodes that are reactive, necrotic or steato-fibrotic. We designed the present prospective study to test the hypothesis that a combined study of lymph node volume and angioarchitecture by power Doppler US may provide a more accurate estimation of bulky disease in patients with Hodgkin's lymphoma. The low intraobserver and interobserver variability of US assessment of volume, and the strong correlation between bulky lymph node selected by power Doppler US and PET/CT scanning (that measure both mass volume and activity) confirmed the high reliability of the method. The results of this study show that power

Table 2. Search for factors predicting freedom from treatment failure: univariate and multivariate analyses.

Factor	FFTF (%)	p univariate	HR	95% CI	p multivariate	HR	95% CI
Female/Male	82 (78)	0.73	1.1	0.46-3.01	0.2	0.51	0.18-1.44
Age, years: <45/≥45	78 (69)	0.097	0.48	0.2-1.14	0.92	0.94	0.27-3.27
Stage: I/II vs III/IV	86 (68)	**0.002**	3.88	1.63-9.26	**0.02**	3.61	1.25-10.41
B symptoms: No/Yes	95 (67)	**0.003**	6.02	1.78-20.3	0.26	2.2	0.56-8.6
Nodal sites involved: <3/≥3	87 (70)	0.25	1.56	0.735-3.29	0.41	0.58	0.16-2.11
Contiguous extranodal involvement*: No/Yes	82 (67)	**0.02**	2.79	1.17-6.64	0.61	1.31	0.46-3.77
Erythrocyte sedimentation rate: <50/≥50	86 (70)	0.17	1.8	0.771-4.22	0.95	1.04	0.35-3.07
Mediastinal bulky: No/Yes	88 (62)	**0.03**	2.56	1.11-5.93	0.06	3.07	0.93-10.16
Clinical/CT-selected superficial bulky: No/Yes	82 (78)	0.64	1.25	0.49-3.2	0.11	0.34	0.09-1.3
Power Doppler US-selected bulky: No/Yes	88 (47)	**<0.001**	7.9	3.37-18.5	**<0.001**	9.86	3.1-31.39

**an extranodal extension of the disease confined to sites contiguous to the lymph nodes involved.*

Doppler US leads to a better prognostic classification than does clinical/CT scan evaluation and surpasses several other commonly evaluated risk factors, predicting FFTF more properly.

The reason why lymph nodes estimated by different methods may have variable prognostic significance has anatomical bases. Clinical/CT scan evaluation using one-dimensional measurement, without informations on the vascular characteristics of the lymph node, is generally unable to differentiate between viable tumor and necrosis, inflammation or fibrosis in the mass. In power Doppler US-selected lymph nodes, the magnitude of neoangiogenesis is probably the most relevant finding. The various steps of neoplastic angiogenesis lead to the development of abnormal vascularization, with defective wall structure, stenoses, occlusion, vessel dilation or arterovenous shunts.[14] The neoangiogenesis network is recognized as being critical for tumor growth, invasion and metastasis. *In situ* data in lymphoma tissue showed that angiogenesis increases with tumor progression (in terms of increasing grade of malignancy).[15,16]

In conclusion, power Doppler US may provide more standardized and uniform criteria for detecting true bulky disease. These results need to be confirmed in large prospective studies, which may include the use of contrast agent enhanced US.[17] Our data support the concept of clinical heterogeneity in patients with Hodgkin's lymphoma. Neoangiogenesis-induced hypervascularization of bulky lymph nodes may be implicated in more aggressive behavior of the disease; thus, patients with true bulky disease may benefit from more intensive treatment.[11-13]

MP performed the ultrasound examinations, and prepared the manuscript; BR supervised the analysis and the interpretation of data, and prepared the manuscript; RC, ADR, BM, FP performed the physical examinations; GC and PZ performed the histological examinations; DD conducted all the statistical analyses; RL performed the biopsies of lymph nodes; EN, CS, and MS performed CT and PET examinations. All authors contributed to the interpretation of the data, revised the manuscript, and approved its final version. The authors declare that they have no potential conflicts of interest. *Work supported by grants from Associazione Italiana contro le Leucemie (Salerno), INTAS, AIRC (Milano), CNR PF Biotecnologie (Roma), MURST-COFIN (Roma), and Regione Campania, Italy.*

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