

Lymphomatous superficial lymph nodes: limitations of physical examination for accurate staging and response assessment

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Background and Objectives. Superficial lymph nodes in lymphoma management are usually evaluated by physical examination. However the accuracy of this assessment has not been thoroughly tested and so it remains debated whether physical examination can meet the international requirements for clinical evaluation and response assessment.

Design and Methods. Palpatory size estimates of lymph nodes in 97 lymphoma patients were separately compared with ultrasonographic (US) measurements in cervical, supraclavicular, axillary and inguinal regions. Comparisons were made between the products of lymph node cross-sectional diameters, whose changes are critical to assess response. Statistical analysis was carried out by simple linear regression, in which the palpatory estimate was entered as the mean of the measurements separately taken by two different clinicians and the dependent variable was the US measurement.

Results. Physical examination tended to underestimate the lymph node size in all regions but appeared to be closely related to US measurements. However, while R^2 was very high for cervical and inguinal lymph nodes (0.902 and 0.802, respectively), it was disappointingly low for lymph nodes in supraclavicular and axillary regions (0.529 and 0.368, respectively).

Interpretation and Conclusions. This indicates that, with the current response criteria, pre- and post-treatment evaluation of cervical and inguinal lymph nodes makes substantial errors in 20-30% of cases when left to physical examination alone. Errors are even more numerous in supraclavicular and axillary regions. Thus, physical evaluation of superficial lymph nodes should be integrated by US or other imaging techniques for accurate fulfilment of the current standardized guidelines for response assessment.

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Physical examination is traditionally considered to be a sufficient – besides necessary – procedure for the correct evaluation of superficial lymph node status in patients affected with malignant lymphomas. International Committees (activated at the Conferences of Rye,¹ Ann Arbor,² Cotswolds³) have periodically updated the clinical examinations required for adequate staging of patients with Hodgkin's disease and many of the concepts thus devised have been successfully extended to the other lymphomas.⁴ But while in the last thirty years different approaches have been subsequently developed and recommended for the assessment of deep lesions (by means of laparotomy, abdominal lymphangiography, computed tomography, etc.), there has been unchanged consensus on the assumption that a careful and thorough physical examination, performed by a physician experienced in the management of lymphoma patients, stands as sufficient in the majority of cases.² In addition, the Cotswolds Meeting experts suggested that a measurement of the largest mass in each region must be taken.

However, while the difficulty in evaluating deep lymphomatous involvement in the chest and abdomen has stimulated the use of increasingly sophisticated and expensive imaging techniques, the evaluation of superficial lymph nodes has been constantly accepted to be left to physical examination alone, unless individual and particular diagnostic problems arise.⁵ Since the historic work by Carbone and Spurr,⁶ which introduced dimensional and standardized criteria in the evaluation of treatment response, an accurate baseline measurement of two perpendicular diameters of all measurable lesions has been considered important and fully adequate for the assessment of therapy-related changes.^{3,7}

So far, the accuracy of palpation in detecting superficial lymphadenopathy has been evaluated with special reference to the discrimination between *normal* and *involved* lymph nodes, to the change in clinical staging allowed by modern imaging techniques,^{8,9} and to the optimal number

of lesion diameters to be measured,¹⁰ but no comparison of the dimensional estimates made by palpation and instrumental techniques has been attempted. Investigating the possible error made by physical examination may be of some interest in relation to the accuracy of response assessment and to the ability to recognize early relapses in the superficial lymph nodes in regions other than those currently explored with imaging techniques.

Design and Methods

Ninety-seven patients with histologically proven malignant lymphomas, diagnosed and staged between October 1st, 1994 and December 31st, 2000, were enrolled in the present study; all patients were treated and followed in the same institution. Thirty-nine patients presented the *classical* Hodgkin histology and 58 showed non-Hodgkin histologic subtypes (6 lymphocytic/lymphoplasmacytoid, 7 mantle-cell, 18 follicular, 19 diffuse large cell, 2 primary mediastinal large B-cell, 3 anaplastic large cell and, finally, 2 peripheral T-cell lymphomas).

All patients were evaluated according to the standard procedures recommended for initial staging, i.e. physical examination, routine hematochemical tests, chest X-ray, computed tomography (CT) scan of chest and abdomen, ultrasound (US) scan of the abdomen and unilateral bone marrow biopsy. In particular, and for the study purposes, baseline physical examination was carried out by either *EM* or *EA*, the two most practised physicians in the institution, with 37 and 43 years' experience, respectively, in the management of malignant lymphomas. The patients received a further, independent and blind physical evaluation of the superficial lymph nodes by a second physician (*PGG*, with 27 years' clinical experience with lymphomas), just before undergoing US scan of the superficial lymphatic regions as an additional investigational procedure. Clinicians were asked to record, to their best, the number and size, with at least two diameters, of all appreciable lymph nodes in each superficial region, apart from the evaluation of these as involved or uninvolved. For each lymphatic mass the first measurement (in cm) was the greatest diameter of the lesion and the second one was the greatest measurable diameter perpendicular to the first one, both generally being on a plane roughly parallel to the skin surface. The palpatory measurement of a third diameter, perpendicular to the first two and to the skin level, was disregarded, even when feasible, as not reliable enough. Palpatory measurements were made with-

out calipers, but with a pocket-ruler, marked in centimeters, as the reference tool — as is frequently the case in everyday practice.

US evaluation of the lymph nodes in bilateral cervical, supraclavicular, axillary and inguinal regions was performed with a Sonolayer Toshiba 270 SSA unit, provided with a 7.5 MHz linear transducer, by two clinically well-trained and conscientious operators (*GCM* and *AR*). They had to number and measure every lymph node found in each region recording at least two perpendicular diameters lying on a plane roughly parallel to the skin surface (thus comparable with palpatory measurements); a third diameter perpendicular to these was also measured for volumetric evaluations¹¹ but was not entered into the present analysis. US operators were aware of the results of the palpatory evaluations made by clinicians and so they were asked to identify and measure every single lymph node found on palpation. The operators were allowed to disregard only the lymph nodes with US diameters smaller than 5 mm if missed by palpation (for the present study 5 mm was chosen as a reasonable sensitivity threshold for palpation), but to measure and record even smaller lymph nodes if they had been identified and evaluated by at least one clinician. Lymph nodes bigger than 5 mm and missed by palpation were included in the comparison. Lymph node clusters evaluated as a single tumor mass on palpation were ultrasonographically measured as a single mass even when they could have been split into individual lymph nodes grown together. Thus, the size of each superficial lymph node or lymph node cluster had two independent palpatory evaluations (with two diameters each) and one US measurement (with the corresponding diameters). The combined evaluation was carried out in 32 of 97 patients also after treatment, among the procedures for response evaluation, and/or in case of relapse.

Though the aim of this study was not a comparison of clinicians' skills, we checked the differences in physical evaluations by means of a t-test for paired data,¹² separately performed for each lymphatic region and directly involving the products of the two diameters evaluated by each of the two clinicians for every individual lymph node or lymph node cluster.

The palpatory estimates were compared with US measurements as the means of the products of the two perpendicular diameters recorded by both physicians (predictive variables) and were plotted against the products of the corresponding cross-sectional diameters measured at US (as dependent

variables). Simple linear regression was used to compare data from physical examinations and US scans. The regression coefficient was taken as the measure of the true correlation between variables and the squared correlation coefficient as an expression of predictivity.¹²

Results

Table 1 shows the means and standard deviations of the palpatory estimates independently made by the two physicians. Interoperator variability was slightly higher in supraclavicular and axillary regions than in cervical and inguinal areas but the difference was not statistically significant. This finding is consistent with an acceptable heterogeneity of the estimates from physical examinations carried out by different physicians, which does not, however, necessarily reflect accuracy.

Table 2 reports the rate of errors > 50% recorded in the mean estimates of the products of two perpendicular diameters from physical examination versus US measurements. Palpation gave substantial errors (> 50%) in 19 to 75% of cases; errors were more numerous in defect than in excess and more frequent in supraclavicular and axillary regions than in cervical and inguinal ones.

As shown in Figure 1, the regression curves of the products of two perpendicular diameters, as measured at US and on palpation, are invariably characterized by highly statistically significant regression coefficients, whichever the superficial region considered. Further information can be drawn from the data in this figure. First, the constantly positive value of the regression coefficients and intercepts in the equations for each region suggests that palpation tends to underestimate actual lesion size. Second, the squared correlation coefficients are satisfactorily high in cervical and inguinal regions, where 90 and 80%, respectively, of the variability of the products of cross-sectional diameters measured by US can be predicted by palpation. Third, the same coefficients are disappointingly low in supraclavicular and axillary areas, where only 53 and 37%, respectively, of the variability of US cross-sectional measurements can be correctly assessed by palpation. This would mean that clinicians' semeiologic estimates of lymph node size can be acceptably accurate only in laterocervical or inguinal regions and not in the other superficial ones.

Discussion

Size is probably the most important and standardized criterion for physical evaluation of superficial lymph nodes, followed by shape, consistency,

Table 1. Palpatory estimates (in cm) of the products of two perpendicular lymph node diameters recorded in each superficial region by two different clinicians (A and B).

Region	Cervical		Supraclavicular		Axillary		Inguinal	
	A	B	A	B	A	B	A	B
Mean	1.24	1.39	1.85	2.34	1.12	1.31	4.07	5.26
SD	1.06	1.15	1.51	2.13	0.84	0.98	3.69	4.23
p (t-test)	0.63		0.37		0.29		0.57	

Table 2. Cases (%) with an error in the palpatory estimate > 50% of the US measurement. Evaluations were made with the products of two perpendicular diameters. The means between the estimates made by two clinicians were used for palpatory data.

Region	Cervical	Supraclavicular	Axillary	Inguinal
No. of evaluations	114	44	54	48
Errors > 50%	31.5%	75.0%	46.3%	18.8%
underestimates	30.7%	70.5%	35.2%	16.7%
overestimates	0.8%	4.5%	11.1%	2.1%

mobility with respect to both underlying and superficial tissues, together with color and temperature of the covering skin. Such semeiologic findings are often good indicators of the inflammatory, lymphomatous or neoplastic nature of the processes affecting lymph nodes. In lymphoproliferative diseases the only slightly increased consistency of lymphomatous versus normal lymph nodes makes size assessment even more important from a clinical point of view, with particular reference to response evaluation. The criteria for evaluating post-treatment changes in lymph node size are one of the most critical issues in the standardized guidelines for response assessment drawn up by an international panel of lymphoma experts.¹³ According to the workshop recommendations, a lymph node with a greatest transverse diameter exceeding 1 cm at diagnosis should be considered to be involved by lymphoma. In response assessment, complete response requires that lymph nodes originally sized > 1.5 cm regress to \leq 1.5 cm in greatest transverse diameter, while those with pre-treatment size < 1.5 cm regress to \leq 1 cm after therapy. The reason is that a number of changes, such as inflammation, fibrosis, necrosis, may inter-

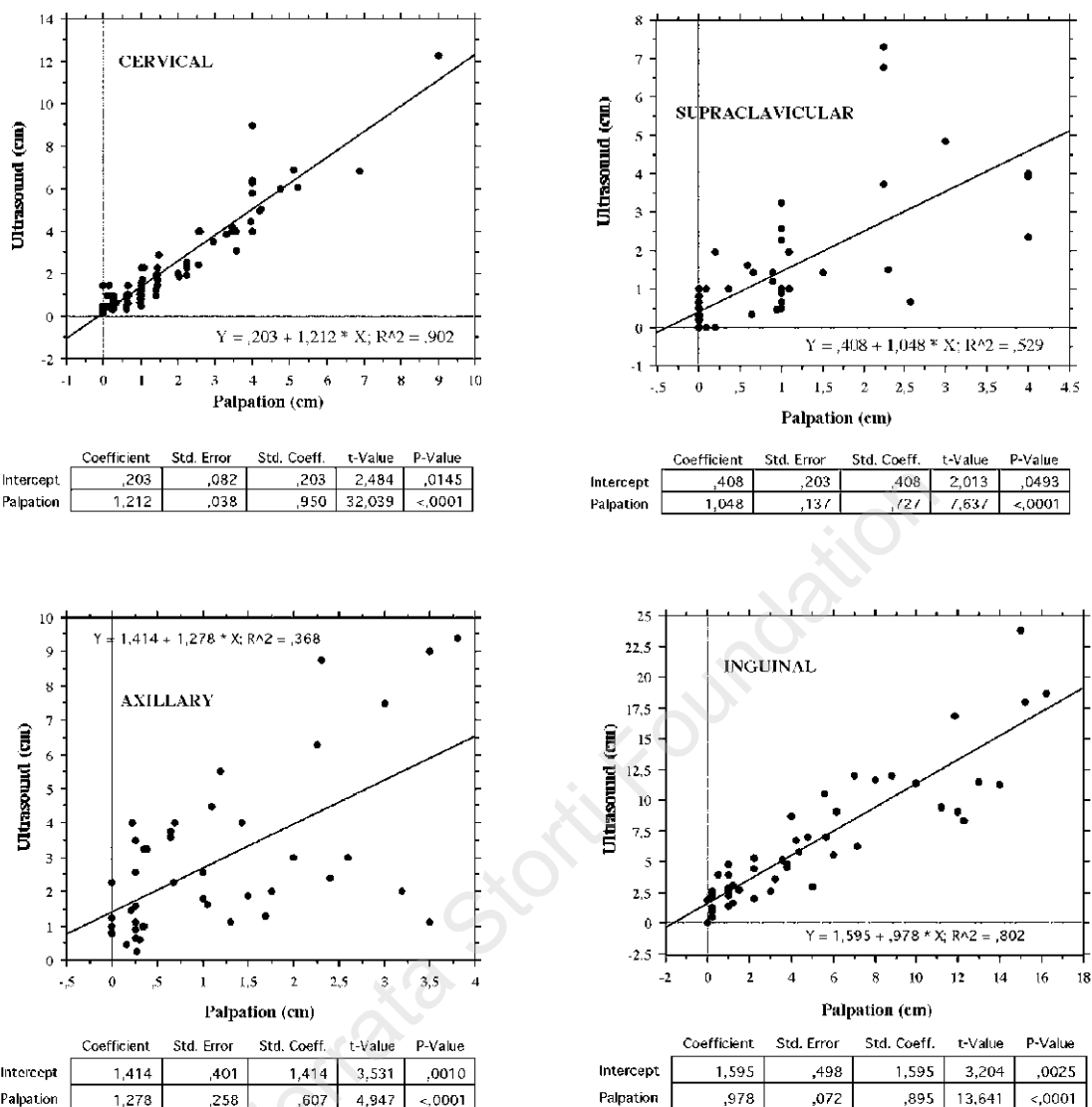


Figure 1. Regression plots of palpatory estimates versus US measurements of lymph node size, separately drawn by anatomical region. The palpatory data were entered as means of the two independent evaluations made by two clinicians.

ferre with restoration to normal size and are more likely to occur the greater the original lymph node size.

Such evaluations can easily be made for any lesion scanned by CT or several other imaging techniques. However, superficial lymph nodes are often excluded from, or only partially included in, the fields routinely studied with CT, as allowed by the current recommendations on lymphoma staging. Superficial lymph nodes may thus be evaluated differently from deep ones, producing a potential

source of inaccuracy for the reliability of response assessment. Grillo-López *et al.*¹⁴ demonstrated that marked variability in response rates occurs when even minor differences are introduced into the dimensional criteria for response. The same can obviously happen when not only measurable criteria of response but also accuracy in lesion measurements varies substantially.

Few studies on the value of imaging techniques in the examination of superficial lymph nodes in lymphoma patients can be found in the literature.

Gerrits *et al.*,⁹ in a series of 47 patients, mainly focused on the number of lymphadenopathy cases missed by physical examination but detected at US (and further confirmed by cytology or histology) and showed that lymph node enlargement was missed at physical examination, but correctly detected at US, in 13% of patients. A previous study, carried out in 120 patients by Bruneton *et al.*,⁸ provided similar overall results (12% of clinically undetected lymphadenopathies), interestingly with further differences according to the superficial regions examined. US showed clinically impalpable lymphatic lesions in an average 10.8% of cases in the cervico-supraclavicular region, 17.9% in the axillary region, and 4.1% in the inguinal region. This work provided the first evidence that diagnostic difficulty may differ between superficial lymphatic regions.

It is noteworthy that the main end-point of these studies was the basic discrimination between *normal* or *involved* superficial lymph nodes. Today misdiagnosis of 12-13% of superficial lymphadenopathies seems hard to tolerate in lymphoma staging, especially if it can be obviated by a relatively simple and inexpensive procedure such as US. In the present study we checked the rate of palpatory errors > 50% in the measurement of cross-sectional diameters as a meaningful example of the possibility of mistaking partially for completely remitting lymph nodes or *vice versa*.

It appears fully reasonable and desirable that accurate evaluations be easily made for all the lymph nodes in the regions currently explored by imaging techniques (US, CT, PET).

However instrumental studies are not always carried out in the main superficial node-bearing regions. Latero-cervical and inguinal regions are often excluded and the supraclavicular and axillary ones partially included in the areas explored with chest and abdomen CT. Our study demonstrates the large error rate which can be expected in the palpatory estimates of the cross-sectional diameter products in supraclavicular and axillary regions and thus suggests that a comparable error rate may be found in response assessment in such lymphatic areas when it is made by palpation alone.

Conversely, lymph node palpation has proved to be relatively more accurate in the cervical and inguinal regions, where information from cross-sectional diameters might be useful even for volume estimates, given the well-known relationship between tridimensional and bidimensional measurements in lymphoma lesions.¹⁰

A possible reason for the greater inaccuracy of the palpatory estimate of supraclavicular and axillary lymph nodes than of cervical and inguinal ones is the different topographic arrangement of lymph nodes in such anatomical regions. In the supraclavicular and axillary regions lymph nodes are deep, and closely surrounded by adipose and muscle tissues; in the cervical or inguinal regions they are more superficial, with a nearly subcutaneous displacement. So, in supraclavicular and axillary regions it is more difficult to evaluate all their diameters by palpation. In this view, the achieved results seem to be reasonable.

If we agree that response criteria be strictly applied for both careful management of patients and accurate comparability of information from clinical trials, we must also conclude that physical examination of superficial lymph nodes can be an important guide to possible complementary imaging techniques, but that it should not always be the only examination for baseline and follow-up evaluations.

Contributions and Acknowledgments

PGG designed the study and was primarily responsible for this article in all its sections. CB collected and analyzed the data. Both PGG and CB prepared the first draft of the article. GCM and AR made the ultrasound evaluations. PGG, EM and EA performed the palpatory measurements.

Disclosures

Conflict of interest: none.

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What is already known on this topic

Superficial lymph nodes in lymphoma patients are usually evaluated by physical examination.

What this study adds

Evaluation of superficial lymph nodes by physical examination makes substantial errors in about one fourth of lymphoma patients.

Potential implications for clinical practice

Physical evaluation of superficial lymph nodes should be integrated by ultrasonography in lymphoma patients.

Mario Cazzola, Editor-in-Chief (Pavia, Italy)