PERGAMON

European Journal of Cancer 38 (2002) 2382–2387

European Journal of Cancer

www.ejconline.com

Focal liver lesions in non-Hodgkin's lymphoma: investigation of their prevalence, clinical significance and the role of Hepatitis C virus infection

G. Civardi*, D. Vallisa, R. Bertè, A. Lazzaro, C.F. Moroni, L. Cavanna

1a Divisione di Medicina ed Ematologia, Programma Oncologia Ematologia, Azienda USL di Piacenza, Ospedale Civile, V. Taverna, 49, 29100 Piacenza, Italy

Received 8 October 2001; received in revised form 2 July 2002; accepted 21 August 2002

Abstract

Imaging techniques like ultrasonography (US) or computed tomography (CT) allow full liver scanning and the accurate detection of focal lesions of the liver parenchyma. The occurrence of such lesions in concomitance with non-Hodgkin's lymphoma (NHL), both at the onset of the disease and during follow-up, is of great significance, because it affects staging, prognosis and therapeutic choices. Moreover, the occurrence of focal liver lesions in the setting of a lymphoma is generally considered to be a marker of liver involvement. Nonetheless, data on the prevalence and clinical significance of focal liver lesions occurring in these clinical conditions are limited. Therefore, we retrospectively evaluated the prevalence, nature and clinical significance of focal liver lesions diagnosed by imaging techniques (US and CT) in 414 consecutive NHL patients. The nature of the lesions was established either by US-guided biopsy or by evaluation of the response to chemotherapy for the underlying disease and confirmed by clinical and US follow-up. Subtype of NHL (aggressive or indolent) and Hepatitis C virus (HCV) status were also considered. We detected 129 focal liver lesions (76 at onset and 53 during the follow-up). Hepatic involvement by NHL was found in 69 cases (53%). We observed 7 cases of Hepatocellular Carcinoma (HCC) and 3 cases of metastasis. At onset, only 39% of the detected lesions were due to lymphoma and 58% were benign. Conversely, 74% of the liver lesions detected during the follow-up were due to NHL while 15% to a malignancy other than NHL. All HCC cases occurred in HCV-positive patients with chronic liver disease. We concluded that the focal liver lesions detected at onset in NHL patients are frequently benign and unrelated to the underlying disease. Conversely, most focal liver lesions detected during the follow-up period are malignant and the possibility of HCC occurrence in HCV-positive patients should always be considered. Therefore, these lesions should undergo a full diagnostic work-up, including US-guided biopsy.

Keywords: Non-Hodgkin's lymphoma; Liver tumours; Hepatitis C virus; Ultrasonography

1. Introduction

The prevalence of liver involvement in the course of non-Hodgkin's lymphoma (NHL) is reported to be 15–27% at the onset of the disease [1] and more than 50% in necropsy studies [2]. Diffuse microscopic infiltration was reported in the past as the most frequent pathological pattern [3].

The diagnosis of liver involvement by NHL is clinically relevant, because its occurrence indicates disseminated disease (stage IV of the Ann Arbor classification): so prognosis and the therapeutic decisions are heavily conditioned by this finding. Therefore, diagnostic imaging techniques like Ultrasonography (US) and Computed tomography (CT) are routinely employed, allowing an accurate detection of focal liver lesions in the course of NHL. Considering these data, the detection of a focal liver lesion by US or CT in a NHL patient both at the onset of the disease or during the follow-up is generally regarded as being indicative of liver involvement.

In particular, US is a simple and effective diagnostic technique to detect focal liver lesions in the setting of NHL [4] and is generally employed as the first-line

* Corresponding author. Tel.: +39-0523-303280; fax: +39-0523-303281.

E-mail address: giuciv@tin.it (G. Civardi).

0959-8049/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0959-8049(02)00481-1

diagnostic imaging technique. When necessary, the pathological nature of these lesions can be easily assessed by US-guided biopsy [4,5]. This procedure is also very effective for the early diagnosis of lymphoma [6].

This imaging technique has been used to describe the prevalence and the pattern of liver involvement in NHL patients. By US examination, Ginaldi and colleagues [7] reported a 5% prevalence of focal liver lesions in a population of NHL patients. Wernecke and colleagues [8] reported liver involvement in 9 out of 167 NHL patients (5.4%). As mentioned above, these investigators described only the detection rate of the liver lesions, but little, if any, information was given regarding the type and clinical significance of the detected lesions.

However, the diagnostic evaluation of NHL patients has recently became more complex because of the improved survival of these patients, the increasing occurrence of second malignant neoplasms [9] and the recently reported [10–13] high prevalence of Hepatitis C virus (HCV) infection (a well-known risk factor for the occurrence of hepatocellular carcinoma (HCC)) in NHL patients. Furthermore, remarkable improvements in diagnostic imaging technologies have considerably influenced the diagnostic approach to this clinical setting.

However, there are no systematic studies describing the type and the clinical relevance of focal liver lesions in course of NHL in large patient populations. To this purpose, we retrospectively evaluated a NHL patient population with the following aims:

1. to detect the prevalence, nature and clinical significance of the focal liver lesions diagnosed by imaging techniques in patients with NHL and occurring both at onset and during the clinical follow-up;
2. to evaluate the role of HCV infection in these patients, with respect to the prevalence and nature of the focal liver lesions.

2. Patients and methods

We retrospectively evaluated the clinical findings of all patients suffering from NHL consecutively observed in our Center from 1 January 1985 to 31 December 1999 with a follow-up time at least of 12 months. The data were retrieved from the clinical records. The diagnoses were confirmed by histological examination of a surgically excised lymph node or of biopsy specimens from other tissues (such as bone marrow, liver, spleen, stomach, etc.) and classified according to the Revised European American Lymphoma (REAL) classification.

The following data were collected: age, gender, histological subtype of NHL and clinical stage at onset, nodal or extranodal primary occurrence, serum HCV status, presence of objective findings of chronic liver disease (in HCV-positive patients), presence and nature of the focal liver lesions detected by imaging techniques at onset and during the follow-up period.

At the time of the first diagnosis, all patients underwent routine examination and standard staging procedures (US of the abdomen, chest and abdominal CT scan, bone marrow biopsy), while laparoscopy with liver biopsy was performed in only 63 cases. All detected focal liver lesions were studied with the usual diagnostic imaging techniques (including magnetic resonance imaging (MRI) and 'double' liver nuclear scanning using Tc99 labelled albumin aggregates and Tc99 labelled autologous red cells in cases of suspected haemangioma): in cases of suspected malignancy, US-guided biopsy was performed using both cytological and histological sampling, as previously reported in Ref. [5]. In those cases where US-guided biopsy yielded insufficient or inadequate material, laparoscopy with large bore needle biopsy was performed. After chemotherapy and/or radiotherapy, US and CT scan were performed again to re-stage the disease. Subsequently, US was performed every 3–6 months during first 2 years of the follow-up and thereafter every 12 months. CT scan was performed every year for the first 2 years of follow-up and in all cases in which US examination was inconclusive or revealed a focal lesion of the liver. All focal liver lesions detected at least three months after the end of the therapy were considered as new lesions occurring in the follow-up period and were submitted to a complete diagnostic work-up, including US-guided fine needle biopsy in all cases.

All patients underwent a clinical and US follow-up for more than 12 months. The parameters considered for diagnostic confirmation were the disappearance or reduction of the lesion after proper chemotherapy; no change in the benign lesions over the follow-up time; increasing size of the lesion for unresponsive neoplasms. Moreover, three cases of primary liver cancer were confirmed at surgical liver resection. The diagnosis of chronic liver disease in HCV-positive patients was based on the result of a liver biopsy or on US findings, clinical data and laboratory tests (only in cases of overt cirrhosis). HCV status was diagnosed by serum enzyme-linked immunosorbent assay (ELISA) II assay: positive results were confirmed by HCV RIBA II test and HCV RNA detected by reverse transcriptase-polymerase chain reaction (RT-PCR). RNA sequences of HCV were investigated using a 'one-tube-nested' assay; primers located in the 5′ non-coding highly conserved sequences of viral genome were employed [14]. In 78 cases, HCV status was unavailable at the time of diagnosis and was subsequently determined on stored frozen (−80 °C) serum taken at the onset of the disease.

The patients were also subdivided into two groups on the basis of the pathological diagnosis (indolent versus

aggressive NHL) according to criteria defined by Shipp and colleagues [15]. Moreover, all clinical and US findings were analysed in the group of HCV-positive patients and compared with those of the group as a whole.

Statistical analysis was performed using the Chi square test and Fisher's Exact text for small groups: a P value of less than 0.05 was considered significant.

3. Results

In our retrospective study we identified 414 patients (with NHL) (211 male, 203 female, mean age: 64.3 years).

Among these, 234 patients had aggressive NHL (122 male, 112 female) and were followed for a mean time of 33.2 months. The remaining 180 patients (89 male, 91 female) had indolent NHL and presented at a mean follow-up of 45.3 months. The histological subtyping of the NHL cases according to the REAL classification is summarised in Table 1.

Table 1
Hystological subtype of our NHL cases according to the REAL classification: number of patients in stage III/IV and with extranodal involvement at onset are also reported

Hystology	HCV-negative cases	HCV-positive cases
Indolent (180)		
Lymphocytic	4	2
Immunocytoma	8	12
Marginal zone	40	11
Mantle cell	20	4
Follicular	49	12
Small cell n.d.	10	5
Peripheral T cell	3	–
Aggressive (234)		
Diffuse large cell	130	47
Lymphoblastic	6	2
Anaplastic large cell	15	2
Large cell n.d.	23	2
Angioimmunoblastic	6	1
Total	314	100
Stage III/IV at onset	104	61
Extranodal involvement:		
• Liver	25	5
• Spleen	44	12
• G.I. tract	48	13
• Skin	17	4
• Rhinopharynx	22	5
• Salivary/lacrimal glands	9	3
Total	165	42

G.I., gastrointestinal; HCV hepatitis C virus; NHL, non-Hodgkin's lymphoma; REAL, Revised European American Lymphoma; n.d., not defined

In all of these patients, we observed 129 cases of focal liver lesions: among these, 76 were detected at onset of the disease and 53 during the follow-up period. At onset of the disease, 30 lesions (39%) were due to hepatic involvement by NHL (Fig. 1), 2 (3%) were malignant other than lymphoma (both HCCs) and 44 (58%) were benign lesions. Among the liver lesions detected during the follow-up period, 39 (74%) were due to hepatic NHL, eight (15%) were malignant lesions other than lymphoma (five HCCs and three metastases) and six (11%) were benign lesions (focal liver steatosis). The type of all detected focal liver lesions according to NHL group and detection time are shown in Table 2.

The benign lesions detected at onset included 22 cysts, 15 haemangiomas and seven so-called 'skip areas' in the setting of liver steatosis (Fig. 2), i.e. relatively spared

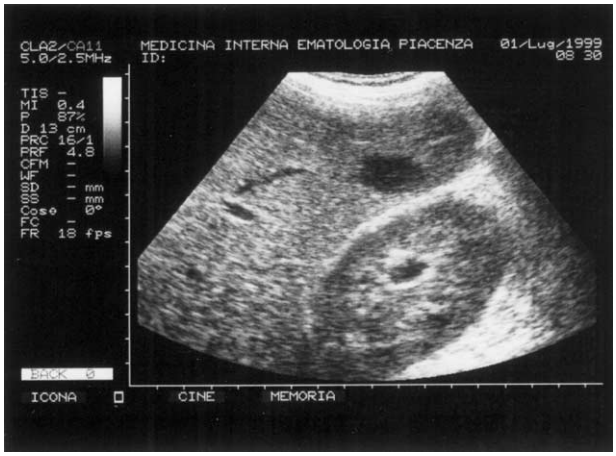

Fig. 1. Ultrasonographic (US) image of hepatic localisation of non-Hodgkin's lymphoma. The lesion appears hypoechogenic.

Table 2
Focal liver lesions detected in our series of 414 patients with non-Hodgkin's lymphoma, according to disease histology, type of lesions and time of occurrence

Type of liver lesions	Onset	Follow-up	Total
Aggressive NHL (234 patients)			
Lymphoma	27	34	61
Hepatocellular carcinoma	1	2	3
Metastasis	–	2	2
Cysts	11	–	11
Haemangiomas	6	–	6
Focal steatosis	3	3	6
Total	48	41	89
Indolent NHL (180 patients)			
Lymphoma	3	5	8
Hepatocellular ca.	1	3	4
Metastasis	–	1	1
Cysts	11	–	11
Haemangiomas	9	–	9
Focal steatosis	4	3	7
Total	28	12	40

areas in a fatty liver parenchyma. At US examination, these areas appeared relatively hypoechogenic with respect to the surrounding parenchyma; so they could have been misdiagnosed as liver involvement by lymphoma.

All the 22 detected cysts were biliary simple cysts. In 12 cases, these lesions were submitted to US- guided fine needle aspiration biopsy, which yielded yellow fluid with no neoplastic cells. In all cases of cyst, the size, number and sonographic appearance showed no changes in the follow-up period.

The 3 cases of liver metastases were due to a breast adenocarcinoma (pre-existent to the lymphoma), colon cancer (detected after the diagnosis of liver metastasis) and lung adenocarcinoma (diagnosed during the re-staging procedures).

In the indolent NHL group, we detected 40 focal liver lesions (28 at onset and 12 during the follow-up).

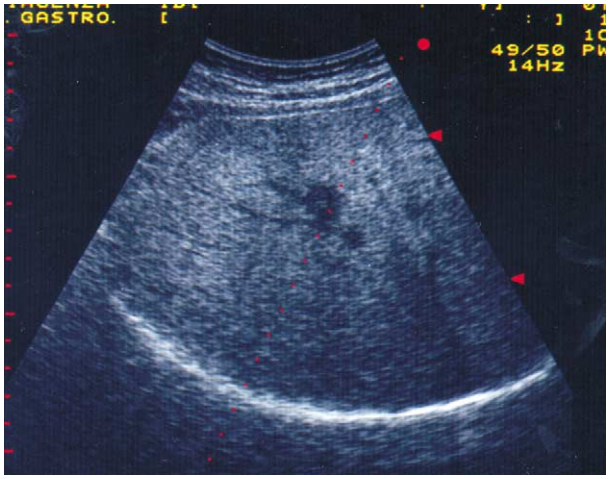

Fig. 2. US image of a skip area in a liver with steatosis. The lesion appears hypoechogenic.

Table 3
Focal liver lesions detected in a subgroup of 100 patients with non-Hodgkin's lymphoma and chronic HCV infection, according to disease histology, type of lesions and time of occurrence

Type of liver lesions	Onset	Follow-up	Total
Aggressive HCV-Positive NHL (54 patients)			
Lymphoma	5	6	11
Hepatocellular carcinoma	1	2	3
Cysts	4	–	4
Haemangiomas	2	–	2
Total	12	8	20
Indolent HCV-positive NHL (46 patients)			
Lymphoma	–	2	2
Hepatocellular carcinoma	1	3	4
Cysts	3	–	3
Haemangiomas	3	–	3
Focal steatosis	1	–	1
Total	8	5	13

Conversely, n the aggressive NHL group we detected 89 lesions (48 at onset and 41 in the follow-up). As expected, the occurrence of focal liver lesions was more frequent in patients with aggressive NHL (38% versus 22%: $P<0.001$: Chi square test) and the difference was entirely due to the hepatic localisation of NHL (26% versus 4%: $P<0.001$: Chi square test). Among these, 3 patients suffering from indolent lymphomas showed evolution to aggressive, large-cell NHL on liver involvement.

In our population, we observed the presence of HCV infection in 100 patients. Among these, 54 had chronic liver disease (35 cirrhosis and 19 chronic aggressive hepatitis), according to the previously described criteria. In this subset of patients, the distribution of the focal lesions was similar in HCV-positive patients when compared with the whole population, both for the lesions detected at onset and for those occurring in the follow-up period (Table 3).

The only difference that we have observed between HCV-positive and HCV-negative NHL patients is in the incidence of HCC (Fig. 3): in fact, the occurrence of this tumour was observed in HCV-positive patients only. All these patients had chronic liver disease.

4. Discussion

The occurrence of liver involvement in patients with lymphoma is of great significance, affecting staging and therapeutic decisions. To this purpose, a variety of diagnostic imaging techniques are employed. Nowadays, CT scanning is regarded as a routine staging procedure for these cases, because of its higher sensitivity in the detection of chest and abdominal enlarged lymph nodes. Nonetheless, its diagnostic accuracy in detecting liver involvement is not high. In a study by Zornoza and

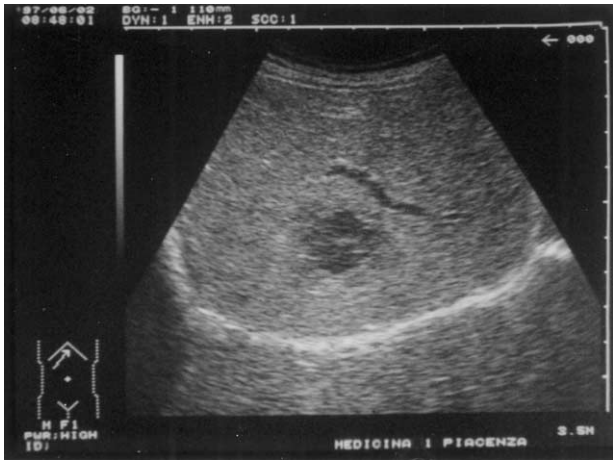

Fig. 3. US image of hepatocellular carcinoma (HCC) in a cirrhotic liver: the patient suffered from a non-Hodgkin's lymphoma and showed chronic HCV infection.

colleagues [16], CT scan showed a sensitivity of 57%, a specificity of 88% and an overall accuracy of 83% for the detection of liver involvement in lymphoma cases. Thomas and colleagues [17] employed EOE 13, a particular contrast medium to enhance the sensitivity of CT scan, but assessed a limited number of cases. Even magnetic resonance studies [18] showed the same sensitivity as CT. In a previous paper from our group [4], we evaluated the accuracy of US for the detection of hepatic lymphoma. We found a sensitivity of 61%, a specificity of 93% and an overall accuracy of 88%. These data were confirmed in a subsequent study on Hodgkin's disease by Munker and colleagues [19]. However, all these studies were designed to assess the detection rate of the focal liver lesions and not to evaluate the type and clinical significance of these lesions. Some ancillary information on this point is given in the study of Wernecke and colleagues [8]. These authors reported the detection of six benign lesions (three haemangiomas, two focal fatty liver changes and one cyst) in 256 patients with lymphoma, but follow-up findings were not available. Therefore, there are currently no significant data concerning the incidence, prevalence and clinical significance of the focal liver lesions detected in patients with lymphoma.

In our population, we detected at the onset of the disease a high percentage of focal lesions that were not due to liver involvement by NHL, particularly in patients with indolent lymphoma. In these patients, the occurrence of hepatic NHL is much less frequent than the detection of a benign lesion.

Some of these, although benign, could be confused with NHL lesions ('skip' areas in fatty liver). These changes in the liver tissue could be induced by chemotherapeutic drugs: their differentiation from liver involvement by NHL is very important in order to assess subsequent therapeutic strategies. In these cases, a US-guided fine-needle biopsy is indicated to obtain a definite pathological diagnosis [20]. However, most cases of cysts and haemangiomas are easily recognisable by US. These data are highly relevant from a clinical point of view, and the relative therapeutic decisions were heavily conditioned in these patients.

Conversely, our data concerning the new focal liver lesions detected during the follow-up period in the same patient populations show that most of these were due to NHL recurrence. Moreover, the occurrence of second tumours was not rare. Therefore, these lesions must be regarded with great suspicion as being malignant. So they must be submitted to a complete diagnostic assessment including US-guided biopsy, with the aim of obtaining a definite pathological diagnosis.

Moreover, we observed 10 cases of second liver tumours (2 at onset and 8 in the follow-up period) in our NHL patients and most of these were HCCs. In one case with HCV and Hepatitis B virus (HBV) co-infection [21], HCC and NHL focal lesions were present in the liver at the same time.

The concomitant occurrence of HCC and NHL was previously described by our group [22–24], but we were unable to explain this phenomenon at the time. Later, HCV was first recognised as an important aetiological factor for the occurrence of HCC [25,26]. More recently, most studies have reported a potential role for HCV infection in some patients with NHL [12,13], and single cases of primary NHL of the liver in patients with HCV-related chronic liver disease have been described [27,28].

When we evaluated the occurrence of focal liver lesions in the subset of 100 HCV-positive NHL patients, we found no differences in the prevalence of lesions overall, NHL lesions or benign lesions, both at onset and in the follow-up. Even its distribution between indolent and aggressive NHLs was quite similar in this subgroup with respect to the overall population. However, the occurrence of HCC was detected in the HCV-positive patients only. Moreover, it is important to note that all cases of HCC occurred in patients with chronic liver disease. Therefore, NHL patients with HCV-related liver damage should be considered to be at a higher risk of HCC occurrence.

Additionally, it must be noted that only 54% of our HCV-positive NHL patients showed laboratory and/or liver biopsy findings consistent with chronic liver disease. In fact, HCV is a lymphotropic virus, which can infect mononuclear blood cells and lymphatic tissue, therefore, some infected patients seem not to develop chronic hepatitis. However, in most patients, chronic liver disease can occur without clinical and laboratory findings of liver damage [29].

We must also discuss some limitations of our study. First, this is a retrospective study based on data retrieval from clinical records concerning patients observed over a long period of time. During this time, the diagnostic quality of imaging techniques (US, MRI, spiral CT) has dramatically improved, both in terms of the detection rate and the diagnostic accuracy for focal liver lesions. Moreover, the improved therapeutic strategies in the field of NHL have changed the clinical history of the disease. This could affect the homogeneity of the findings collected over these years. Finally, our data were collected on an Italian population, in which the prevalence of HCV infection in high: this may have affected the incidence and type of lymphoma. Therefore, our conclusions must be regarded with caution when applied to a population with a low incidence of HCV infection.

In conclusion, our data suggest that the detection of a focal liver lesion in a patient with NHL is a diagnostic problem that should be resolved taking into account some additional clinical findings, like the type of NHL, HCV status, US findings of the lesion and disease history.

The following final remarks can be made:

1. Focal liver lesions observed at the onset of the disease in NHL patients are frequently benign and not related to the underlying disease, particularly in the course of indolent lymphomas.
2. Conversely, new liver lesions detected with imaging techniques during the follow-up period must be considered as potentially malignant and should be submitted to a complete diagnostic work-up, including US-guided fine-needle biopsy.
3. Additional attention must be paid in HCV-positive patients, particularly in those with chronic liver disease because of the relatively frequent occurrence of HCC. This substantially affects the subsequent therapeutic strategy.

Acknowledgements

The work was supported in part by 'Associazione Piacentina per lo Studio delle Leucemie e altre Malattie del Sangue'.

References

1. Castellani R, Bonadonna G, Spinelli P, Bajetta E, Galante E, Rilke F. Sequential pathologic staging of unterated non Hodgkin's Lymphoma by laparoscopy and laparotomy combined with marrow biopsy. *Cancer* 1977, **40**, 2322–2328.
2. Rosemberg SA, Diamond HD, Jaslowitz B, Craver LF. Lymphosarcoma: review of cases. *Medicine (Baltimore)* 1961, **1269**, 40 31–84.
3. Wright PG, Summers C. *Systemic Pathology, vol. 1*. New York, American Elsevier, 1966 253.
4. Cavanna L, Di Stasi M, Foranri F, *et al*. Ultrasound and ultrasonically guided biopsy in hepatic lymphoma. *Eur J Cancer Clin Oncol* 1987, **23**, 323–326.
5. Buscarini L, Fornari F, Bolondi L, *et al*. Ultrasound guided fine needle biopsy of focal liver lesions: techniques, diagnostic accuracy and complications. A retrospective study on 2093 biopsies. *J Hepatol* 1990, **11**, 344–348.
6. Zinzani PL, Colecchia A, Festi D, *et al*. Ultrasound guided core needle biopsy is effective in the initial diagnosis of lymphoma patients. *Haematologica* 1998, **83**, 989–992.
7. Ginaldi S, Bernardino ME, Jing BS, Green B. Ultrasonographic patterns of hepatic lymphoma. *Radiology* 1980, **137**, 427–431.
8. Wernecke K, Peters PE, Kruger KG. Ultrasonographic patterns of hepatic and splenic lesions in Hodgkin's and non Hodgkin's lymphoma. *Brit J Radiol* 1987, **60**, 655–660.
9. Travis LB, Curtis BE, Glimelius B, *et al*. Second cancers among long term survivors of non Hodgkin's lymphoma. *J Natl Cancer Inst* 1993, **23**, 1932–1937.
10. Cavanna L, Sbolli G, Tanzi E, *et al*. High prevalence of antibodies to Hepatitis C virus in patients with lymphoproliferative disorders. *Haematologica* 1995, **80**, 486–487.
11. Zuckerman E, Zuckerman T, Levine EM, *et al*. Hepatitis C virus infection in patients with B cell Non Hodgkin's lymphoma. *Ann Intern Med* 1997, **127**, 423–428.
12. De Rosa G, Gobbo ML, De Renzo A, *et al*. High prevalence of Hepatitis C virus infection in patients with B cell lymphoproliferative disorders in Italy. *Amer J Haematol* 1997, **55**, 77–82.
13. Vallisa D, Berte' R, Rocca A, *et al*. Association between Hepatitis C virus and Non Hodgkin's Lymphoma and effects of viral infection on Hystologic subtype and clinical course. *Am J Med* 1999, **106**, 356–360.
14. Luppi M, Ferrari MG, Bonaccorsi G, *et al*. Hepatitis C virus infection in subsets of neoplastic lymphoproliferations not associated with cryoglobulinemia. *Leukemia* 1996, **10**, 351–355.
15. Shipp M, Mauch PM, Harris NL. Non Hodgkin's lymphomas. In De Vita VT, Hellman S, Rosemberg SA, eds. *Cancer: Principles and Practice of Oncology*, 5th edn. Lippincott-Raven, PA, NY, 1997, 2165–2220.
16. Zornoza J, Ginaldi S. Computed tomography in hepatic lymphoma. *Radiology* 1981, **138**, 405–410.
17. Thomas JL, Bernardino ME, Vermass M, *et al*. EOE 13 in the detection of hepatosplenic lymphoma. *Radiology* 1982, **85**, 629–634.
18. Weinreb JC, Brateman L, Maravilla KR. Magnetic resonance imaging of hepatic lymphoma. *Am J Roentgenol* 1984, **143**, 1211–1214.
19. Munker R, Stengel A, Stabler A, Hiller E, Brehm G. Diagnostic accuracy of ultrasound and computed tomography in the staging of Hodgkin's disease. Verification by laparotomy in 100 cases. *Cancer* 1995, **76**, 460–466.
20. Caturelli E, Rapaccini GL, Sabelli C, *et al*. Ultrasonography and echo guided fine needle biopsy in the diagnosis of focal fatty liver change. *Hepato-Gastroenterol* 1987, **34**, 137–140.
21. Cavanna L, Civardi G, Fornari F, *et al*. Simultaneous relapse of liver cell carcinoma and non Hodgkin's lymphoma in the liver. Report of a case with diagnosis by ultrasonically guided fine needle biopsy. *Acta Cytol* 1994, **38**, 451–454.
22. Di Stasi M, Cavanna L, Fornari F, *et al*. Association of non Hodgkin's lymphoma and hepatocellular carcinoma. *Oncology* 1990, **47**, 80–83.
23. Di Stasi M, Sbolli G, Fornari F, *et al*. Hepatocellular Carcinoma associated with other primary malignancies. *Eur J Cancer* 1990, **26**, 648–649.
24. Di Stasi M, Sbolli G, Fornari F, *et al*. Extrahepatic primary malignant neoplasms associated with hepatocellular carcinoma. High occurrence of B cell tumors. *Oncology* 1994, **11**, 459–464.
25. Colombo M, Dr Franchis R, Del Ninno E, *et al*. Hepatocellular carcinoma in Italian patients with cirrhosis. *New Engl J Med* 1991, **325**, 675–678.
26. Sbolli G, Zanetti A, Tanzi E, *et al*. Serum antibodies to Hepatitis C virus in Italian patients with hepatocellular carcinoma. *J Med Virol* 1990, **30**, 230–232.
27. Rubbia-Brandt L, Brundler MA, Kerl K, *et al*. Primary hepatic diffuse large B cell lymphoma in a patient with chronic hepatitis C. *Am J Surg Pathol* 1999, **23**, 124–130.
28. Mohler M, Gutzler F, Kallinowski B, Goeser T, Stremmel W. Primary hepatic high grade non Hodgkin's lymphoma and chronic hepatitis C infection. *Dig Dis Sci* 1997, **42**, 2241–2245.
29. Silvestri F, Baccarani M. Hepatitis C virus related lymphomas. *Brit J Haematol* 1997, **99**, 475–480.