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Incident Cases of Primary Liver Cancer (PLC): Proposal for the Use of a Standardised Method in Case-definition

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We defined some standardised criteria for classifying incident cases of liver cancer into either Primary Liver Cancer (PLC) or Unspecified Liver Cancer (ULC), on the basis of the diagnostic procedures performed. A pilot hospital-based study (98 cases) was carried out in Verona, northern Italy, in order to assess the feasibility of the method. The same protocol was subsequently applied in a population-based study (349 cases) in Bresica, northern Italy. The percentage of cases with histological verification was 38.7 and 41.8%, respectively, with a wide variation among different hospitals. The percentage of cases we attributed to the PLC category was 78.6% in the hospital-based study and 78.8% in the population-based study. No differences in the proportion of cases attributed to PLC were found according to patients' age, sex or hospital of admission. Repeatability of the method was assessed through a cross-panel review of 198 cases, with a 91.9% interobserver agreement. Implications of this method are discussed and some suggestions for cancer registration and future research are proposed.

Key words: liver cancer, registration techniques, descriptive epidemiology, cancer statistics, cancer registration
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INTRODUCTION

RELIABILITY OF data sources is of great relevance in the interpretation of incidence rates for primary liver cancer (PLC). The proportion of histologically proven cases differs widely among cancer registries, ranging from less than 30% to over 90% [1]. The use of fine-needle biopsy, alone or under ultrasonography (US) guidance or during laparoscopy, makes histological confirmation potentially easier to obtain [2, 3], but, in the absence of histology, both detection of PLC and differentiation from metastases can be difficult, in spite of continuous advancement in modern imaging techniques, i.e. Computerized Tomography (CT) and US [4–7]. Alpha-feto-protein (AFP) determination is widely used, although the cut-off values of 400–500 ng/ml seem to be highly specific but poorly sensitive [8–10] for the detection of liver cancer (LC). Furthermore, the lack of international standardised criteria for case-definition in cancer registries can reduce validity of geographical comparisons of incidence data.

We describe a method for 'case definition' of PLCs, which may be used principally in cancer registration.

SUBJECTS AND METHODS

A pilot hospital-based study was carried out in the two main hospitals in the Verona province (A = university hospital, B = general hospital), as part of a feasibility study for a population cancer registry. All resident patients admitted to either of the two hospitals between 1 January 1985 and 31 December 1988, with a Discharge Code (DC) for liver cancer (ICD IX 155.0–155.2) [11], were identified through the Regional Hospital Discharge Diagnosis Coding System.

Discharge Code 197 (respiratory and digestive metastases), which might include some erroneously coded PLCs, was not selected since a separate survey carried out in the same hospitals showed that no cases of PLCs were uniquely identified by this source. In addition, all patients with an ICD-O [12] topography and/or specific morphology for PLC were selected from the computerised files of the pathology departments.

For each case, the date of first diagnosis was obtained from clinical records, and only incident cases were considered. The results of all diagnostic procedures were also recorded in detail, with particular regard to the level of confidence expressed by the examiner, and each examination was defined as "conclusive" (when terms like "probable PLC", "likely PLC", "consistent with PLC" were reported) or "not conclusive" (all others). Finally, on the basis of standardised criteria (Table 1), each case was attributed to one of the following categories.

(I) PLC certain or highly probable (metastatic lesions extremely unlikely); or
(II) PLC possible or suspected (metastatic lesions cannot be excluded), henceforth termed Unspecified Liver Cancer (ULC).

A population-based study was carried out in the Local Health Unit (LHU) of Brescia (328,245 inhabitants at the 1991 census). All resident patients with a final diagnosis of liver cancer between January 1986 and 31 December 1990 were identified from the registries of the pathology, medicine, surgery and radiology departments of all the hospitals in the area. In order to avoid a possible underregistration, further research was undertaken at the major hospitals in the neighbouring areas. The date of first diagnosis was obtained from clinical records, and only incident cases were included.

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Table 1. Criteria for classifying primary liver cancer (PLC) and unspecified liver cancer (ULC†)*

Major criteria
A. Histology "conclusive" for PLC
B. Cytology "conclusive" for PLC
C. Serum AFP >500 ng/ml
D. One instrumental examination‡ "conclusive" for PLC
E. Two or more instrumental examinations‡ in agreement as to the diagnosis of suspect PLC

Minor criteria
F. Histology or cytology "not conclusive" for PLC
G. Serum AFP 20–500 ng/ml
H. One instrumental examination‡ "not conclusive" for PLC
I. Sufficient exclusion of primary cancer in other sites

*PLC = (PLC certain or highly probable): at least one major criterion or two or more minor criteria.
†ULC = (PLC possible or suspected): all the remaining cases or if serious disagreement among the results of the examinations performed.
‡Instrumental examinations considered sufficiently accurate for a diagnosis of PLC: ultrasonography (US), computerised tomography (CT), magnetic resonance (MR), scintigraphy, angiography, laparoscopy without isto-cytology. The result of any instrumental examination was considered "conclusive" for PLC when one of the following expressions was used in the examiner's report: "probable", "likely", "consistent with". It was considered "not conclusive" when the presence of secondary liver cancer could not be excluded.

Subsequently, the hospital-based study protocol was followed in order to assess the reliability of the method on a population basis.

The repeatability of the method was evaluated by estimating the agreement proportion in a cross-panel review of 198 cases.

RESULTS

98 resident patients with incident liver cancer were identified by a DC = 155 in the hospital-based study. There were 38 histologically verified cases (by biopsy or surgery), all having at least one DC = 155 in either of the two hospitals. The overall proportion of histologically verified cases was 38.7% (38/98), with a significant difference between hospitals A and B (Table 2).

Table 2. Proportion of histological verification (HV) for PLC in the two studies, according to the hospital of admission

Hospital of admission	Hospital-based study (Verona)* Number	HV	(%)	Population-based study (Brescia)† Number	HV	(%)
A	42	21	(50.0)	—	—	—
B	56	17	(30.3)	—	—	—
C	—	—	—	201	66	(32.8)
D	—	—	—	105	65	(61.9)
Others	—	—	—	43	15	(34.9)
Total	98	38	(38.7)	349	146	(41.8)

*Chi-square test A versus B: $P = 0.04$
†Chi-square test C versus D: $P < 0.001$
D versus others: $P = 0.003$
C versus others: P = NS

77 cases (78.6%) were attributed to the PLC category according to the standardised procedure described previously (Table 3).

In the population-based study, 349 cases with a liver cancer diagnosis were identified, 306 of which (87.7%) were admitted to the two main hospitals (C and D) of the Brescia LHU. Histology was available in 146 cases (41.8%), with significant differences between the hospitals of admission (Table 2). 275 cases were attributed to the PLC category (78.8%; Table 3). If incidence had to be estimated using the method described, the crude rate would have fluctuated between 34.2/10^5 (PLC+ULC) and 26.6/10^5 (PLC) in males and between 9.4/10^5 and 7.6/10^5 in females.

A 91.9% agreement in the attribution to PLC and ULC categories was achieved in the cross-panel review.

DISCUSSION

The great variability in the level of histological verification [1] and reliability of clinical diagnosis are inherent aspects in PLC definition. Final diagnosis of PLC is often based on instrumental and laboratory tests alone. However, specific patterns of the disease have not been clearly identified for imaging techniques, and the validity of these procedures has not been sufficiently evaluated in clinical practice. As a result, a PLC diagnosis is

*Table 3. Distribution of cases classified as primary liver cancer (PLC) or unspecified liver cancer (ULC), according to age and hospital of admission**

	Hospital-based study (Verona) PLC Number (%)	ULC Number (%)	Total Number (%)	Population-based study (Brescia) PLC Number (%)	ULC Number (%)	Total Number (%)
Age						
<50	3 (60.0)	2 (40.0)	5 (100)	22 (75.9)	7 (24.1)	29 (100)
50–59	14 (82.4)	3 (17.6)	17 (100)	49 (75.4)	16 (24.6)	65 (100)
60–69	32 (86.5)	5 (13.5)	37 (100)	118 (80.8)	28 (19.2)	146 (100)
≥70	28 (71.8)	11 (28.2)	39 (100)	86 (78.9)	23 (21.1)	109 (100)
Hospital						
A	35 (83.3)	7 (16.7)	42 (100)	–	–	–
B	42 (75.0)	14 (25.0)	56 (100)	–	–	–
C	–	–	–	153 (76.1)	48 (23.9)	201 (100)
D	–	–	–	84 (80.0)	21 (20.0)	105 (100)
Total	77 (78.6)	21 (21.4)	98 (100)	275 (78.8)	74 (21.1)	349 (100)

*Only data from the two main hospitals are reported for the Brescia study.

often ambiguous and affected by widely differing levels of "probability".

In an attempt to introduce some standardised criteria, we proposed an operational method based on the present knowledge concerning diagnostic examinations currently used for liver cancers. The feasibility of the method was first tested in a hospital-based pilot study and second in a population-based study, i.e. in the same context in which cancer registries usually work. The proportion of PLC-defined cases was similar in the two studies, and no differences were observed with respect to the age, sex or hospital of admission of the patients (Table 3).

Our study shows that approximately 20% of routinely diagnosed liver cancer could not be defined as other than "unspecified" (ULC-cases). These ULCs represent a crucial point in cancer registration, since including or excluding them could lead, respectively, to an over or underestimation of the incidence.

Since a definite solution does not seem possible at present, we suggest that cancer registries put some effort into measuring and publishing the proportion of these cases, in order to improve comparability of international data. Further research addressing both validity of instrumental examinations and interobserver agreement would be particularly helpful in the clinical practice context.

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Possible Involvement of Tumour Cell Membrane Gangliosides in Platelet–Tumour Cell Interactions

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The possible correlation(s) between platelet proaggregating activity, and sialic acid content and ganglioside expression of six human colorectal tumour cell lines (CBS, GEO, HT-29, WiDr, MIP and DLD-1) was evaluated. The three cell lines (HT-29, WiDr and DLD-1) capable of inducing remarkable *in vitro* platelet aggregation, had significantly higher amounts of lipid-bound sialic acid than those cell lines characterised by a lower platelet proaggregating activity (GEO, CBS and MIP). High performance thin-layer chromatography demonstrated the presence of one band comigrating with GM3 in all cell lines, while GD1a and GT1b comigrating gangliosides were present only in HT-29, WiDr and DLD-1 cells. Finally, an increased platelet pro-aggregating activity of GEO and CBS cell lines was observed after the incorporation of exogenous gangliosides. The present data support the hypothesis that lipid-bound sialic acid may be involved in platelet–tumour cell interactions.

Key words: platelets, platelet aggregation, metastases, sialic acid, gangliosides, colon cancer
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