EDITORIAL

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Liver Tumours – New Aspects

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Introduction

In 1849, *Rokitansky* (27) was the first to make a clear distinction between primary and secondary liver carcinoma; he considered the former to be the more frequent of the two. The interest of the clinician in primary liver carcinoma (PLC), however, was until recently, on account of the inadequate diagnostic and therapeutic possibilities, only slight. Only in the last few years has renewed interest been shown in this tumour, stimulated by the observed increase in incidence and also exciting new discoveries in the fields of aetiology and pathogenesis, together with the development of more effective diagnostic and therapeutic procedures.

In recent times, the theoretical basis for successful preventive measures has also been discussed.

Frequency and epidemiology

In numerous countries in Asia and Africa, PLC is the most frequently observed cancer: Mozambique (70 % of all carcinomas), Senegal (67 %), Bantu in South Africa (51 %), Hong Kong (45 %), Malaysia (41 %), India, China, Taiwan and the Philippines (20 % each) head the list of these countries. In Europe, PLC is not uncommon in the Mediterranean countries (Greece 13 %, Spain 10 %). (15, 20, 22, 24, 26, 39). In Middle European countries and in the USA, where there is a close coincidence of liver cirrhosis and PLC, a quoted figure of 2.5 % for the relative frequency of this condition is almost certainly too low; with the appropriate awareness on the part of the clinician and pathologist, PLC is found as a late complication in 30 % of all patients with a long standing liver cirrhosis. On the basis of the continously increasing number of cases of cirrhosis, PLC is already counted among the ten most frequent forms of cancer in Austria. Similar observations have also been made in Switzerland, Poland and Hungary (39).

Just as variable as the geographical distribution of incidence is the average age of the patient with a tumour of the liver: The higher the rate of incidence, the lower the age. In Africa and Asia, PLC is found predominantly in patients in the third decade, in Middle Europe, in contrast, in the 6th to 7th decade.

Aetiology

a) Individual (endogenous) factors:

– *Distribution by sex:* In general, PLC is seen four times more frequently in males than in females. Until quite recently, a possible cause for this discrepancy was seen in a protective effect of the female hormones or a greater exposure of males to carcinogens (15, 40). *Drew* et al., (3) have drawn attention to some interesting relationships between parental reaction to hepatitis B virus (HBV) and the sex distribution of their progeny. This observation might possibly be of significance for the selective "preference" of liver carcinoma for the male sex.

Completely unexplained is the observation that in Denmark, Iceland, Chile and Colombia, PLC is found more frequently in females.

– In most cases PLC is preceded by a *chronic hepatic disease.* A chronic hepatic injury appears to offer hepatocarcinogens favourable conditions to develop their effect. Thanks to the improved methods of detecting HBV, in many countries of Africa and South East Asia a formerly unknown high degree of infection of the population with HBV has been documented in recent years. At the same time a remarkable parallelism in the geographical distribution of viral hepatitis and PLC has also been discovered. In countries with a high incidence of PLC, serological HBV markers were found in 80 to 90 % of all hepatoma patients. This would suggest a causal relationship between these two diseases (22). Epidemiological studies carried out in recent years have shown that infection with HBV in the early part of life considerably increases the risk of later contracting PLC. Already by way of perinatal infection of the newborn by HB_sAg-positive mothers (vertical transmission), the ground is often prepared for subsequent chronic, usually insidious, anicteric liver disease. Hepatitis with a peracute course and massive necroses of the hepatocytes represents a smaller risk of subsequent PLC development, probably because the predisposing liver cells are largely eliminated.

In patients with PLC in a liver previously damaged by HBV, low HB_sAg titres and high anti-HBc titres are characteristic findings. The extremely rare detection of anti-HB_s might be a sign of a disordered immune response (22). As a rule, HB_e antigen is lacking while, in contrast, anti-HB_e is not uncommon. The expression of HB_c antigen in tumour tissue is too small to be measured.

The detection of a HBV genome in the DNA of PLC cells has been interpreted as a sign of a direct carcinogenic potency of the HB viruses, although the exact oncogenic mechanism, at least for the time being, remains unexplained (22, 24, 32, 40).

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Small hepato-cellular (hc) PLC in non-alcohol-induced liver cirrhosis and no serological signs of contact with HBV, might be interpreted as a late complication of chronic non-A/non-B hepatitis (22).

Although it is possible that, in Middle Europe and the USA too, HBV diseases and PLC might be associated, they are quantitatively of very little significance (23). In 80 cases of PLC confirmed at autopsy, we established serological evidence for HBV contact in 6.3 %; the figure for chronic liver disorders without PLC was 6.8 % (39); these observations have, in the meantime, been repeatedly confirmed both in Europe and in the USA (12, 23, 33).

The basis for the development of PLC in Europe is predominantly alcohol-induced hepatic cirrhosis. Alcohol leads to an increase in the carcinogen-activating enzymes, which indicates a relationship between alcohol and carcinoma (34). In Austria, PLC is found particularly frequently in wine growing areas. The increasing sale of alcohol is reflected in a continuous increase in the incidence of liver cirrhosis and PLC (39). In Chile, however, despite a high incidence of alcoholic liver cirrhosis, PLC is remarkably rarely observed (26).

It is known that other chronic diseases of the liver, such as haemochromatosis or porphyria cutanea tarda, are associated with a high risk of subsequent PLC, and similar remarks may be made for the rare condition hypertyrosinaemia or hepatic damage due to a lack of α_1 antitrypsin (40).

– *Genetic disposition:* Reports on familial accumulation of PLC and HBV conditions suggest the presence of genetic aetiological factors. *Larouze* (18) is of the opinion that family members of hepatoma patients have an approximately 60 times greater risk of themselves contracting this tumour. Other working groups investigating HLA antigens, however, have found no evidence for a genetic disposition (16).

– In the previous year, attention was drawn for the first time to a new aetiological variant: *chronic typhoid carriers* contract PLC six times more frequently than do healthy controls. A satisfactory explanation for this remarkable observation has not yet been offered (43).

b) Exogenous environmental influences

– The degree of contamination of food with *mycotoxins*, such as aflatoxin B_1 or sterigmatocystin, bears a direct relationship to the frequency of PLC. At the present state of our knowledge, however, a direct carcinogenic effect on the liver seems to be improbable: Rather, mycotoxins appear to have a negative effect on the cell-mediated immunity and, in this way, prepare the ground for HBV pathology. Accordingly, mycotoxins should be considered co-carcinomas (19). The low content of aflatoxin B_1 in the food in Egypt might possibly be the reason for the low incidence of PLC there, although, in this country HBV is extremely prevalent (44).

– In China, extreme differences in the incidence of PLC were found in adjacent areas of the country sharing an equal prevalence of HBV and ingestion of mycotoxins. Only recently it has been established that Chinese who obtain their drinking water from stagnant bodies of water, more frequently develop PLC; to date, however, the *carcinogen in stagnant water* has not been identified (4).

– Such parasites, as for example, Clonorchis sinensi apparently favour the development of cholangio-cellular (chc) hepatic carcinomas, but in Middle Europe, of course, such parasites are certainly without any significance.

– *Iatrogenic injuries*

a) In the USA in areas with a petrochemical industry, a marked accumulation of PLC cases has been registered. Pesticides, such as DDT, also favour the development of malignant tumours of the liver (20).

b) *Chronic arsenic and copper poisoning*, as also exposure to *thorotrast* and *vinyl chloride*, lead to quite characteristic changes in the liver tissue, which frequently reveal a tendency to subsequently develop into an angiosarcoma, but also PLC (25).

c) Attention has already been drawn to the importance of *alcohol* abuse in the development of PLC in Middle European countries. But *smoking* might also have a carcinogenic effect on the liver by way of enzyme induction (5).

d) *Drugs:* An influence on the development of PLC has been confirmed only for drugs with a steroid structure:

– Long-term therapy with *anabolic androgenous steroids*, as employed for the treatment of *Fanconi's* anaemia, or the misuse of anabolic agents by competitive athletes can result in the development of PLC and angiosarcomas (29).

– Today it is believed that the long-term ingestion of *contraceptives* is associated with a dose-dependent and time-dependent risk of contracting hepatic tumours. In the USA, the annual incidence is estimated to be three to five per 100.000. It is probable that the number of undetected cases is disproportionately higher (28, 35).

In the initial phase so-called "focal nodular hyperplasia" and benign adenomas develop. A malignant transformation tends to be rare and is never associated with an increased synthesis of α_1 fetoprotein (AFP). When the oral contraceptives were discontinued, a spontaneous regression of adenomas, but also the continued growth of hepatic tumours have been observed (30).

– Recently, an above-average incidence of adenomas after the establishment of a *porto-systemic shunt* has been reported and the increased serum oestrogen level of these patients has been thought responsible (38).

Pathogenesis (22, 24, 40)

The pathogenesis of PLC is multifactorial and also multiphasic. The close coincidence of liver cirrhosis and PLC suggests that these conditions are two dose-dependent, differing reactions of the hepatic tissue to the same noxae (40). Only a few environmental toxins or drugs have a primarily carcinogenic effect. Only as a consequence of bio-transformation do bioactive metabolites – the so-called "ultimate carcinogens" – develop.

Dietary factors (amount of fat in the food), viral infections, pesticides, drugs such as phenobarbital or steroids, and also alcohol and smoking, have an effect on the hepatic biotransformation system by way of enzyme induction or modulation, and are thus of considerable importance in the carcinogenesis of hepatic tumours.

Proliferating hepatocytes, with their high mitotic rate, represent, as selective cell populations, a vulnerable "target". An interesting alternative pathogenetic model was developed by *Farber* (7). On the basis of the fact that chemical carcinogens usually inhibit cell proliferation and that, initially, the development of a cancer in a given organ is focal, he postulated that hepatocytes which are resistent to carcinogenic effects, react with unbounded proliferation, and that, paradoxically, liver cancer originates in the cells which are *not* susceptible to hepatic carcinogens!

Finally, the bio-active secondary carcinogens are bound to the DNA of the nuclear chromatin, although the possible role of genetic control mechanisms is, at present, still controversial (16, 18).

Nucleases have the task of removing the modified DNA, so that the nuclease capacity of the liver determines the further course of hepato-carcinogenesis. Under normal circumstances, this capacity is large enough to eliminate all carcinogens from the liver. Eliminated carcinogens can, however, give rise to carcinomas in other organs. The liver of the newborn has a lower nuclease capacity and thus reacts more sensitively to the effects of carcinogens.

Morphologically, dysplasia hepatocytes represent the first link in the carcinogenic chain. They are characterized by the lack of stored iron, storage of glycogen and of a modified gamma-glutamyl transpeptidase. Under the electron microscope, changes can be shown at the cell surface and in the organelles even in the pre-neoplastic stage (24). The next stage in the development is focal nodular hyperplasia which gives rise to benign adenomas and, finally, hepatocellular PLC. It is known that in patients with steroid-induced adenomas this course of development is reversible up to a point so far unknown (30).

Diagnosis

While as little as ten years ago, a diagnostic accuracy of the clinician of 10 % with respect to PLC was quoted in collective statistics, today, thanks to more recent examination techniques, the correct diagnosis can be established intra vitam in 90 % of the cases (41).

1) Serological diagnosis

a) At the present time, the determination of α_1 fetoprotein (AFP) is the only serological examination method which, on account of its considerable "organ affinity", has proved its value in practice as a screening procedure for the early recognition of hepato-cellular PLC and embryonic germinal cell tumours.

Eighty to 85% of all hepato-cellular PLC's show an increased new synthesis of AFP and represent the "target group" of serological diagnostic efforts. The remaining hepatocellular PLC's, and also all mixed and cholangio-cellular PLC's, hepatic metastases and non-carcinomatous malignant liver tumours (angiosarcoma, etc.), have *no* increase in AFP production (10, 21, 42).

In so-called "high risk areas" with a high incidence of PLC, the average normal level of serum AFP in the healthy population is three to four times higher than that seen in Middle Europe (42). A possible explanation for this may be the observation, made in recent years, that an increase in AFP can be triggered by viral infections (HBV, cytomegaly) (36).

It is now known that PLC associated with renewed AFP production represents a poor prognosis. Thus, the determination of the AFP titre in the serum is a valuable parameter for assessing the efficiency of therapy. The half-life of the postoperative drop in titre is now considered determinative for the indication, duration and dosage of post-operative chemotherapy (42). For screening purposes we have developed a procedure which provides a positive result only in the presence of AFP values above 100 ng/ml (42).

b) In future, as a valuable supplement to the determination of AFP, consideration might well be given to the serum *level of ferritin*, which has been found to be elevated in 70 to 85 % of all hepato-cellular PLC patients *without* the renewed synthesis of AFP – especially in the early stages of the tumour (13).

c) Whether a combination of *several serological procedures* can appreciably improve the diagnostic efficiency, as recently suggested by *Waka-Bayashi* et al. (37), (AFP, CEA and the iso-enzymes of alkaline phosphatase or gamma-glutamyl transpeptidase were determined) is doubtful, since this approach would appear limited by inadequate sensitivity and considerable costs.

2) Morphological diagnosis

In addition to well proven techniques such as *angiography*, with the aid of which even the smallest tumours – provided that they are adequately vascularized – can be recognized with certainly, or *laparoscopy*, the diagnostic importance of which is largely dependent upon the personal experience of the examiner, *sonography coupled with trageted fine needle biopsy* and *computed tomography* are becoming more and more important clinically (15, 22, 40).

New aspects in the morphological diagnosis of PLC have resulted from *multi-step scintigraphy of the liver* using 99 m-tc colloidal sulphur and *67-gallium citrate* (67-Ga), which examinations have proved an ideal supplementation of the AFP determination. In particular hepatocellular PLC unaccompanied by an increased synthesis of AFP, and cholangio-cellular PLC, manifest an intensive uptake of gallium. In 80 autoptically proven cases of PLC, which had been investigated with AFP and 67 -Ga, the correct clinical diagnosis was established in 99 % (41).

A decisive new impetus may be expected from initial attempts to localize tumours using *monoclonal tumour-specific antibodies* (10).

Therapy

a) The only curative therapy for PLC is *radical surgical removed* of the tumour-infected lobe of the liver. At centres with appropriate experience, the incidence of surgical resection is 20 to 50 %. The post-operative mortality rate is surprisingly low at 7 to 16 %, and the five-year survival rates (SR) at 9 to 19 % are of an order of magnitude comparable to the results of gastric carcinoma surgery. In children subjected to surgery for PLC, indeed, a five-year SR of more than 50 % has been reported (8, 9, 40). With the introduction of special surgical techniques these results may be expected to improve further, as a study that achieved a three-year survival rate of 88 % has shown (9). In view of these results, a "therapeutic nihilism" would no longer seen justifiable in PLC patients. In contrast, the indication for *liver transplantation* in PLC patients is no longer accepted by *Starzl* (31) although this opinion is by no means shared by all the experts (2).

b) Attempted palliative treatment employing *chemotherapy* has, to date, not beeen particularly promising, and is all the more to be rejected in view of the fact that survival rates of 6 years and more are certainly not uncommon in untreated PLC patients (22, 40). The results of a multicentre investigation supports such a point of view: In only 15 of 189 treated PLC cases was a partial remission achieved, 9 of the 15 observed "partial successes" having employed adriamycin as the cytostatic agent (6).

It is possible that, in the future, on the basis of more suitable *prognostic criteria*, the indication for palliative measures may be more accurately established. Thus, for example, *Lai* et al. (17) attaches considerable importance to the histological assessment of hepatocytes, considering the absence of so-called "clear cells" as a reliable sign of a favourable prognosis.

c) We have just received an initial report on good results obtained with *Interferon* (14). For the present, the high costs of such a therapy are not calculated to justify too much optimism. In general, it would appear that *measures to stimulate the immune reaction* in PLC patients are the most worthy of recommendation, if a radical surgical procedure proves impossible (22).

Prevention

a) In Middle Europe and the USA a reliable preventive effect could presumable be achieved by *restricting alcohol abuse.* The chances of realizing such an aim, however, are as illusory as the incurably optimistic hope of being able to achieve a reduction in the consumption of nicotine.

b) In animal experiments it has already proved possible to inhibit the development of liver cirrhosis and hepatomas (11) using the antiallergic agent neurotropine.

c) Since the causal role of HBV infections for the high incidence of PLC in Asia and Africa is well known, effective preventive measure are, at least theoretically, imaginable. On the one hand, by means of a *hygiene clean-up project,* infection with HBV could be reduced, while, on the other hand, the application of *HBV vaccine* in a large-scale vaccination programme would, theoretically, result in a drastic reduction of the PLC incidence in "high risk areas" (18, 45). The realization of such ideas, however, must be viewed with scepticism, not least since the number of HB_sAg-positive people throughout the world is estimated at 176 millions, and the funds needed to vaccinate such an immense number of people are hardly likely to be forthcoming.

References

1 *Ballou, B., T.R. Hakala, G. Levine, D. Solter:* Tumor Location Detected with Radioactively Labeled Monoclonal Antibody and External Scintigraphy. Science 206 (1979) 844
2 *Calne, R.Y.:* Lebertransplantation. Chirurg 51 (1980) 271
3 *Drew, J.S., W.T. London, E.D. Lustbader, J.E. Hesser, B.S. Blumberg:* Hepatitis B virus and sex ratio of offspring. Science 201 (1978) 687
4 *Editorial:* Liver Cancer: Something in the Water? Lancet 1 (1980) 747
5 *Everson, R.B.:* Individuals transplacentally exposed to maternal smoking may be at increased cancer risk in adult life. Lancet II (1980) 123
6 *Falkson, G., C.G. Moertel, P. Lavin, F.J. Pretorius, P.P. Carbone:* Chemotherapy Studies in Primary Liver Cancer. A Prospective Randomized Clinical Trial. Cancer 42 (1978) 2149
7 *Farber, E., D. Solt, R. Cameron, B. Laishes, K. Ogawa, A. Medline.* Newer Insights Into the Pathogenesis of Liver Cancer. Am. J. Path. 89 (1977) 477
8 *Flatmark, A., B. Frethem, O. Knutrud, G. Lande:* Surgical Treatment of Primary Liver Carcinoma. Scand. J. Gastroent. 12 (1977) 571
9 *Fortner, J.G., D.K. Kim, B.J. MacLean, M.K. Barrett, S. Iwatsuki, A.D. Turnbull, W.S. Howland, E.J. Beattie:* Major Hepatic Resection for Neoplasia. Personal Experience in 108 patients. Ann. Surg. 188 (1978) 363
10 *Harada, T., K. Shigeta, K. Noda, Y. Fukumoto, H. Nishimura, M. Mizuta, T. Takemoto:* Clinical Implications of AFP in Liver Cirrhosis: Five Year Follow-up Study. Hepato-Gastroenterology 27 (1980) 169
11 *Ishii, K., H. Shibata, H. Okabe:* Inhibition of liver cirrhosis and liver cell carcinoma in rats by an anti-allergic agent. XI. Int. Kongr. Gastroent., Hamburg 1980
12 *Johnson, P.J.:* Hepatocellular Carcinoma and Hepatitis B Vir Markers in Europe and USA. Lancet I (1979) 434
13 *Kaneto, A., Y. Kubo, T. Koga, T. Tanikawa:* Serum ferritin, a useful indicator in the early diagnosis of hepato-cellular carcinoma. XI. Int. Kongr. Gastroent., Hamburg 1980
14 *Kawanishi, H., W.N. Carter, J.N. Sheagren, J.M. Greenwood, R.P. McDermott, M. Ibrahim:* Effect of human fibroblast interferon on injury of HB_sAG producing human hepatoma cells in vitro. (Abstr.) Gastroenterology 78 (1980) 1192
15 *Kawata, H.:* Retrospective Study on the Evaluation of Diagnostic Procedure for Hepatoma in Patients with Cirrhosi of the liver. Acta hepato-gastroent. 21 (1974) 106
16 *Kew, M.C., A.J. Gear, I. Baumgarten, G.M. Dusheiko, G. Ma* Histocompatibility Antigens in Patients with Hepatocellular Carcinoma and their Relationship to Chronic Hepatitis B Virus Infection in these Patients. Gastroenterology 77 (1979) 537
17 *Lai, C.L., P.C. Wu, K.C. Lam, D. Todd:* Histologic Prognostic Indicators in Hepatocellular Carcinoma. Cancer 44 (1979) 1677
18 *Larouze, B.:* Studies on the prevention of primary hepatic carcinoma. Parental influences on the transmission of, and host response to, hepatitis B Virus. Cancer detect. Prev. 2 (1979) 65
19 *Lutwick, L.I.:* Relation between aflatoxin, hepatitis-B virus, and hepatocellular carcinoma. Lancet I (1979) 755
20 *Mason, T., F. McKay, R. Hoover* et al.: Atlas of cancer mortality for U.S. counties: 1950–1969, DHEW Publication (NIH) 75–80 U.S. Department of Health, Education and Welfare. 1976
21 *Nolan, J.P.:* Significance of α-Fetoprotein in Liver Disease. Gastroenterology 74 (1978) 953
22 *Okuda, K., T. Nakashima:* Hepatocellular Carcinoma. A Review of of the Recent Studies and Developments. In: H. Popper, F. Schaffner (eds.): Progress in Liver Diseases, Vol. VI, Grune & Stratton, New York (1979) 639–650
23 *Omata, M., M. Ashcavai, C.T. Liew, R.L. Peters:* Hepatocellular Carcinoma in the USA, Etiologic Considerations. Localization of

Hepatitis B Antigens. Gastroenterology 76 (1979) 279
24 *Popper, H.:* The Increasing Importance of Liver Tumors in H. Remmer, H.M. Bolt, P. Bannasch, H. Popper (eds.): Primary Liver Tumors, MTP Press, Lancaster, 1978
25 *Popper, H., L.B. Thomas, N.C. Telles, H. Falk, I.J. Selikoff:* Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast and arsenic. Comparison with cases of unknown etiology. Am. J. Path. 92 (1978) 349
26 *Remmer, H., H.M. Bolt, P. Bannasch, H. Popper* (eds.): Primary Liver Tumors, MTP Press, Lancaster, 1978
27 *Rokitansky, C.A.:* Manual of pathological anatomy. Edward Publishing Company, London, 1849
28 *Rooks, J.B., H.W. Ory, K. G Ishak, L.T. Strauss, J.R. Greenspan, A.P. Hill, C.W. Tyler jr., The Cooperative Liver Tumor Study Group:* Epidemiology of Hepatocellular Adenoma: The Role of Oral Contraceptive Use. JAMA 242 (1979) 644
29 *Scheuer, A., H. Gerdes, F.G. Lehmann:* Anabolika und Lebertumoren. Dtsch. med. Wschr. 104 (1979) 779
30 *Sherlock, S.:* Hepatic Tumors and Sex Hormones. In: H. Remmer, H.M. Bolt, P. Bannasch, H. Popper (eds.): Primary Liver Tumors, MTP Press, Lancaster (1978) 201
31 *Starzl, T.E., L.J. Koep, C.G. Halgrimson, J. Hood, G.P.J. Schroter, K.A. Porter, R. Weil III:* Fifteen Years of Clinical Liver Transplantation. Gastroenterology 77 (1979) 375
32 *Theodoropoulos, G.:* The Relationship between Hepatitis Associated Antigen and the Development of Hepatocellular Cancer. Acta hepato-gastroenterol. 21 (1974) 430
33 *Trichopoulos, D., R.J. Geretry, L. Sparros, E. Tabor, E. Xirouchaki, N. Munoz:* Hepatitis B and Primary Hepatocellular Carcinoma in a European Population. Lancet II (1978) 1217
34 *Tuyns, A.J.:* Epidemiology of Alcohol and Cancer. Cancer Res. 39 (1979) 2840
35 *Vana, J., G.P. Murphy, B.L. Aronoff, H.W. Baker:* Primary Liver Tumors and Oral Contraceptives. Results of a Survey JAMA 238 (1977) 2154
36 *Wahren, B.:* Fetal Proteins in Viral Infections: Review Article Acta Med. Scand. 205 (1979) 145
37 *Wakabayashi, T., N. Sawabu, M. Nakagen, L. Ozaki, D. Toya, H. Sendai, N. Hattori, M. Ishii:* Immuno-biochemical diagnosis of hepatocellular carcinoma in which serum AFP is lower or negative. XI. Int. Kongr. Gastroent., Hamburg, 1980
38 *Webster, M.W., D.H. van Thiel, K.M. Bron, E.L. Barnes.* Hepatic Adenoma Associated with Portasystemic Shunting in Young Woman. Digestion 19 (1979) 328
39 *Weiss, W., H. Hanak:* Primary Liver Cancer in Austria. In: H. Remmer, H.M. Bolt, P. Bannasch, H. Popper (eds.): Primary Liver Tumors. MTP Press, Lancaster, 1978, 145
40 *Weiss, W.* Das primare Leberkarzinom. int. prax. 18 (1978) 243
41 *Weiss, W., G. Eder, A. Kroiss, P. Kahn, A. Neumayr:* Clinical Significance of Liver Scintigraphy Using 67-Gallium and AFP-Determination as Screening for Primary Cancer of the Liver. Scand. J. Immunol. 8 (1978) Suppl. 8/417
42 *Weiss, W.:* Klinische Relevanz der AFP-Bestimmung im Serum Onkologie 1 (1978) 6
43 *Welton, J.C., J.S. Marr, St.M. Friedman:* Association between hepato-biliary cancer and typhoid carrier state. Lancet I (1979) 791
44 *Ziegler, J.L.:* National Institutes of Health International Workshop on Hepatitis B and Liver Cancer, Meeting Report. Cancer Res. 37 (1977) 4672

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