

## Regional chemotherapy in primary liver tumors

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In the East and in the southern hemisphere the incidence of hepatocellular carcinoma (EC) is higher than in the West, and it seems more strictly correlated to viral hepatitis, cirrhosis of the liver, nutritional deficiency, specific toxins. In Asia, EC autoptic incidence varies from 1.5% to 3.1% with high peaks in Hong Kong (5.2%), Singapore (45.3%), Taiwan (5.5%). In North America and Europe the incidence is less than 1%.

When EC incidence is considered with reference to every kind of neoplasia, regional variance is still larger. In fact it passes from relative percentage below 2.5% in North America and Europe, to 13.2% in China, 16.9% in Singapore, 19.8% in Taiwan and 50% in some parts of Far East and Southern Africa (4.6).

The annual incidence, in terms of population, fluctuates enormously from 1-3 cases/100.000 males/year in Australia, North America and Europe to 100 cases/100.000 males/year in Mozambique up to peaks of 1158/100.000 positive HbsAg males in Taipei. In fact the risk of being affected by EC in positive HbsAg patients is of 2%, that is 307 times higher than global population. In cirrhotic patients it reaches 7.1%, with a higher risk for male and elderly patients.

In recent years the incidence of this neoplasia in surgical division and simultaneously its surgical or parasurgical treatment have been progressively increasing, not only because of the real increase of its incidence, but also of the diagnostic refinement, of a better surveillance of the patients at risk, of a greater familiarity by the surgeons with resective hepatic surgery even in cirrhotic patients, of the very limited indications about transplant in these cases, except in fibrolamellar hepatoma.

If the indication is given at the right time, the possibility of obtaining a positive result from the operation is more concrete. In fact that makes possible to increase the resectability index, the curability and to reduce operative mortality.

Since cirrhotic and HbsAg positive patients are, as we have already said, at risk for this kind of neoplasia, it is obvious that an early diagnosis can be obtained through their continuous monitoring by using ultrasonography and specific markers, such as alfa-feoprotein (AFP) and, more recently; Desy-Carboxyprothrombin (DCP).

In 1984 Okamoto clearly established the anatomopathological features that an EC must have to be defined as curable: 1) single nodule; 2) fibrous capsule; 3) absence of arterio-venous, portal or biliary spreading; 4) presence of at least 2 cm of sound perineoplastic tissue.

The resectability of these tumors can be estimated at about 33% (average of different case studies) (26% in our experience).

Of course this percentage is higher if neoplasia is asymptomatic and casually discovered. If tumor is symptomatic the resectability rate is not above 5% of the cases.

Since there is usually a combination with the cirrhosis of the liver, the surgical approach must be more careful because of the impairment of some biochemical parameters; however the frequent improvement in the clinical history of cirrhosis itself, in resection, encourages the results which could be obtained by surgical therapy.

In the past parasurgical treatments (ligation of the hepatic artery, embolization, chemoembolization, regional chemotherapy by external catheter or with implantable system) found indication exclusively in the cases, that at diagnostic assessment, resulted not to be treated surgically. Recently, Japanese authors, in particular, drew the attention on loco-regional therapies, instead, which - in their experience, make operable hepatocarcinomas which, at first assessment, had been considered not operable, or rather they obtain the complete necrosis of tumor; so they do not represent a palliative treatment but a final treatment for hepatocarcinoma.

The first attempts were carried out by ligation of the hepatic artery or even by dearterialization. The results were deeply deceptive: in a review made on 130 cases of hepatocarcinoma, treated with hepatic dearterialization, no difference was noticed in median survival in comparison with the controls, (Lee-Y-T, 1978); out of 18 treated

patients Ong (76) had a median survival of 55.5% at 3 months and 5.5% at 12 months; Balasegaram out of 24 patients he discovered a survival of 66% at 6 months and 20% at 12 months with a 50% R.O.

The failure of this method seems mainly linked to the reopening of collateral circles, so an almost normal hepatic arterial stream reforms in a very short time.

Moreover, as it found in Graham and Cannel's experience ('83), the index of mortality by ligation of the hepatic artery can reach 25% even if in a review carried out by Kim and Fortner ('73) on 322 practised ligations, it results an 18.6% mortality (60 pts), only 3.7% of which (12 PTS), directly caused by ligation. These results are likely to be attributed to a non selection of patients. Actually, it seems obvious that tumor staging and the functionality of the remaining parenchyma can condition post-operative complications. From Inokuchi and Nagasue's bibliographical study (1979), in fact, it results an operative mortality of 20% in consequence of ligation of the hepatic artery in hepatocarcinoma with cirrhosis.

Another locoregional method, which is liked best by many authors today, is arterial embolization, which grants a good palliative effect, just like the previous one, particularly in the presence of large hepatomegalies. In recent years the mixed technique of chemoembolization, which combines locoregional chemotherapy with partial embolization of the hepatic arterial system, has been increasingly spreading. The survival by this form of treatment is about 50% at 12 months.

Certainly intraarterial regional chemotherapy is more interesting. It can be carried out either by catheter surgically located in gastroduodenal artery and exteriorized cutaneously, or percutaneously through the femoral, brachial or axillar artery.

In the last case therapy is almost always bolus therapy and catheter is removed at the end of every therapeutic course. With this treatment median survival is about 6 months.

With surgically planted catheters either a bolus or a continuous infusion administration is possible; in the first case the survival is about 8 months, while in the second it results slightly longer (8.8 months).

A more recent application is the use of arterial or venous catheters with portal in the subcutaneous pocket. These systems allows to carry out regional chemotherapy with scanty possibilities of infection. Responses have sensibly improved and median survival can

reach 20 months.

The data we have noticed fully agree with those reported by Ramming in 1980 in a review carried out on 18 groups of patients.

The results obtained by the combination of intraarterial chemotherapy by ligation of the hepatic artery are significant too. In our bibliographical study on 195 cases there has been a median survival of 14.6 months.

Considering the results obtained with the different methods, as a whole: ligation of the portal branch, intermittent occlusion of the hepatic artery, use of intraarterial yttrium and ligation of the hepatic artery combined with resection: on 1827 cases treated in literature with the different methods, median survival is 8.8 months reaching 16.1 months with reference to district chemotherapy by systems which can be completely implanted.

Since 1973, 91 EC have been observed, 86 (94.5%) on cirrhosis and 5 on sound liver. We have operated 46, of which 8 were small E.C.; practising in total 25 resections (11 subsegmentectomies, 9 segmentectomies, 3 left lobectomies, 1 right lobectomy, 1 right trisegmentectomy). 12 cases have been treated with the aid of peroperative echography, which has been used on cirrhosis since 1984. While in remaining 21 cases an hepatic arterial chemotherapy or ligation of the hepatic artery, has been carried out. 4 patients underwent a chemoembolization with lipiodol and mytomycin C, one of these after regional treatment, underwent a resection, because of the disappearance of satellite nodes. In 4 cases the ligation of the hepatic artery has been carried out and in the other 13 patients arterial regional chemotherapy has been used (2 by an extracutaneous catheter according to Seldinger's technique, and 11 by the use of implantable systems).

The habitual use of peroperative echography has excluded operation in patients presenting satellite tumoral nodes, which had not been preoperatively visualized or presentig invasion of the portal or caval venous walls. Moreover peroperative echography has often guided tumoral resection providing precise indicatios about the extension of the hepatic tissue which must be resected.

Operative mortality has been 6.6%, and above all it has been limited to larger hepatectomies. Segmentary resection, in fact, have widely shown a survival similar to that of the larger hepatectomies, with a lower operative mortality, on condition that the resection margin is enlarged at 2 cm from tumoral tissue. The survival at 5 years is assessed around 8% in our case. and it is influenced by

various factors, such as hepatocellular insufficiency, and the onset of ascites, during the postoperative stage, but also by the presence of peritumoral fibrous capsule, which is not always present, and by tumoral microspreading, which cannot be diagnosed.

The longer survival in non operated patients has been 22 months in a case of E.C. spread on cirrhosis. We have adopted the hepatic artery clamping technique at hilum of the liver to limit hepatic bleeding. A balloon catheter, guided by echography, placed through the hepatic surface can temporarily stop blood flux to the segment where tumor is localized. In 4 cases we have resected tumor by a systematic subsegmentectomy, by ultrasonographic indication of the portal branch afferent to the tumor, and the injection of methylene blue inside it. In order to prevent postoperative bleedings we have often carried out an hemostasis by elective ligation of vascular peduncles, or of small sections of parenchyma which were located around the bleeding focuses. For the first postoperative days, SGOT, SGPT, albuminemia, bilirubinemia, hematocrit, plasmatic and urinary electrolytes and osmolarity have been monitored; during the treatment besides to plasma and albumine we have administered diuretics. Moreover we have constantly controlled the patients echographically, in order to diagnose in time a possible liquid collection (suppuration, ascite, bleeding) to be drained percutaneously.

Systemic chemotherapy inefficiency, largely proved in literature, (2 cases in our experience), instead, has moved our attention on intra-arterial chemotherapy, also by administering a Lipiodol and Mitomycin C emulsion, selectively inoculated in liver by Seldinger's transfemoral catheterization. In fact, out of 4 patients treated with lipiodol, the one who had undergone a resection 30 days after regional treatment, has had a 12 months survival from the operation, and 13 months from lipiodol treatment. The other 3 patients who have undergone a chemoembolization without surgery, reported the following survivals: 6, 10 and 11 months; two of them are still alive. All the patients who have undergone regional chemotherapy, by use of fluorodeoxyuridine (FUdR), have had a 40% survival at 12 months with a median survival of 9 months.

The regular determination of serum AFP in cirrhotic patients makes possible the diagnosis of neoplasia in a percentage of cases higher than 50% when all E.C. are considered independently from their size.

This percentage is lower in smaller lesions. Shinagava reports AFP values above 200 ng/ml only in 39.3% tumors with a diameter included between 3 and 5 cm and 26.1% of those with a diameter smaller than 3 cm.

So for the early diagnosis of hepatocarcinoma in cirrhotic patients the use of echography, which has given a positiveness of 61.5% in Kobayashi's case studies, has become increasingly important. These data are similar to our experience and they support the concept that cirrhotic patients' screening must be carried out by combination of AFP and US, which, as a whole, allows to detect more than 60% small hepatocarcinomas.

Early diagnosis and subsequent possibility of attacking EC whose size is below 5 cm, represent the best strings at the bow of surgical therapy. All the cases studied, in fact, agree in attributing a significant better prognosis to tumors whose size is below 5 cm.

EC is a complicative evolution of cirrhosis which can be surgically treated. This is, in fact, the unique therapeutic operation that can alter the natural history of cirrhosis; because, in our experience, the risk of an hepatic resection on cirrhotic liver seemed acceptable in terms of operative mortality.

Regional therapy, in our opinion, and particularly, the technique of chemoembolization with lipiodol and mitomycin, represent the treatment to choose in cases of non operability. In a variable percentage of cases it certainly has prolonged some patients life -when it was not possible to carry out a resection - offering them, of course, a better expectation of life.

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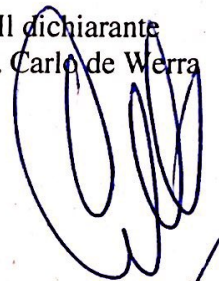
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

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