Peer reviewed article

Treatment of primary and secondary liver malignancy

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The management of hepatic malignancy is one of the most controversial areas in medicine. It is a continuously evolving field which requires a multimodal approach and the inclusion of a medical oncologist, a hepatobiliary surgeon, a radiotherapist, an interventional radiologist and in some cases a transplant surgeon. In addition, the recent development of novel approaches such as neoadjuvant tumour therapy, cryosurgery, thermal ablative techniques as well as biological and immunological manipulation of malignant cells has added to the complexity of this field. Today, the availability of such innovative modalities, in the absence of an extrahepatic localisation of disease, allows the potential to cure many large primary and secondary hepatic tumours. However, the appropriate use of these various treatment modalities should be limited to centers with experience in treating patients with advanced disease where innovative study protocols are available. Experience of the surgeon with difficult hepatectomies is of paramount importance. Currently, mortality following major hepatectomies in non-cirrhotic patients is below 5% in centers of reference. For example, in the series from Duke University Medical Center there were no fatalities in more than 150 liver resections in patients with benign diseases and a 2% mortality in more than 300 patients with malignant diseases. Mortality, however, reached 5% in cirrhotic patients undergoing a resection involving more than 2 segments. This review will attempt to focus on an overview of the diagnosis and treatment of a selection of more common hepatic malignancies.

Keywords: liver tumours; neoadjuvant therapy; adjuvant therapy; resection; transplantation

Primary malignant liver tumours

The two most common primary malignant liver tumours are hepatocellular carcinoma (HCC) and cholangiocarcinoma. Hepatocellular cancer is 10 times more frequent than cholangiocarcinoma and is one of the most common malignant neoplasms in the world [1]. The overall incidence is estimated to be 1 million cases per year with a wide geographic variability and a preponderance in the mediterranean areas of Europe rather than in northern countries [2]. There also appears to be a clear association with cirrhosis with an annual risk of developing HCC in such cases of 1% to 6% [3, 4]. Frequent aetiologies of cirrhosis associated with HCC include hepatitis B (HBV) & C (HCV), haemochromatosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, autoimmune hepatitis as well as alcohol abuse [5–7]. In recent series from the United States and Italy, the relative risk of HCC is quoted as 7% to 11% for HBV-positive patients, 10% to 23% in HCV-positive patients (RNA or anti-HCV positivity) and 5% in heavy alcohol abuse [5–7]. Diagnostic modalities include dynamic spiral or helical contrast enhanced CT-scan and/or MRI, although ultrasound remains the most common screening technique in high risk patients for HCC associated with measurement of the tumour marker alfa feto protein (AFP). On CT-scan, HCC appears as an isodense lesion surrounded by a low density contrast enhancing ring; in the early arterial phase of dynamic CT-scan 60% of lesions are hyperdense due to their predominantly hepatic arterial supply and in the late phase 88% become hypodense as portal flow begins to dominate. In addition, a CT-scan showing a liver mass associated with portal vein thrombosis without venous compression is highly suggestive of HCC as nearly 60% of patients with HCC have evidence of portal vein thrombosis on CT-scan [8–10]. Whole body positron emission tomography (PET) as a modality for the staging and detection of extrahepatic HCC is limited and only 55% as sensitive compared to CT-scan; in addition high cost is a major disadvantage [10].

Untreated HCC carries a poor prognosis and is directly related to tumour stage and degree of cirrhosis. Survival is usually not more than 6 months in patients with a large tumour mass and Child C cirrhosis. Although small HCCs, i.e. <5cm diameter, are considered to have a better prognosis in the presence of stable liver function, survival rates in such patients in the setting of cirrhosis are 81% at 1 year, 56% at 2 years and only 21% at 3

years [11]. Therapeutic approaches in HCC localised to the liver without extrahepatic spread are modulated by the presence or absence of cirrhosis. Surgical resection and liver transplantation remain the mainstay of curative therapy. Resection is recommended for patients without cirrhosis or with limited segmental or lobar HCC and preserved hepatic function, eg, Child A cirrhosis. In the absence of cirrhosis, curative resection can be attempted for most large lesions (figure 1). The main limitation to resection however is the high recurrence rate in the remnant liver which can reach up to 80%, and usually occurs within the first 2 years [12]. Speculation regarding the reasons for this include: undetected microscopic disease at the time of resection, the presence of unrecognised multicentricity as well as tumour portal venous radicle invasion and embolisation; also patients with chronic hepatitis infection or cirrhosis are at risk for metachronous tumour growth in the liver remnant [13]. Repeat resections have been advocated by some groups and recent reports indicate extended survival with such an approach and comparable morbidity and mortality to the initial hepatectomy [14, 15].

Transplantation is mainly recommended when there are multiple lesions (≤3 lesions) or when the location (single tumour <5 cm in diameter) and / or severity of cirrhosis precludes resection [13]. The presence of cirrhosis has a negative impact on long term survival with curative resection when compared to non-cirrhotic livers. Survival in the latter group of patients is 70% to 90% at 1 year,

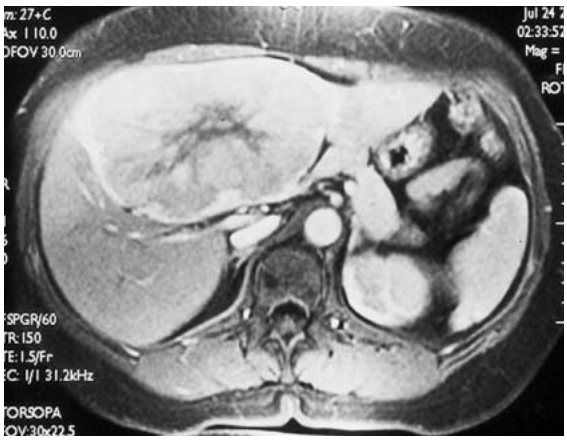
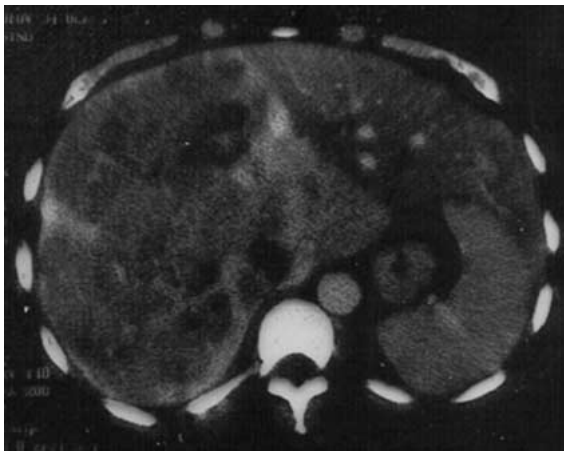


Figure 1

CT-scan showing a large hepatoma without underlying liver disease in a 54-year-old patient. The mass involves segment IV, V and VIII of the liver. The patient underwent a successful curative central resection of the liver using a technique of total vascular exclusion. To date there has been a disease free survival of 18 months.



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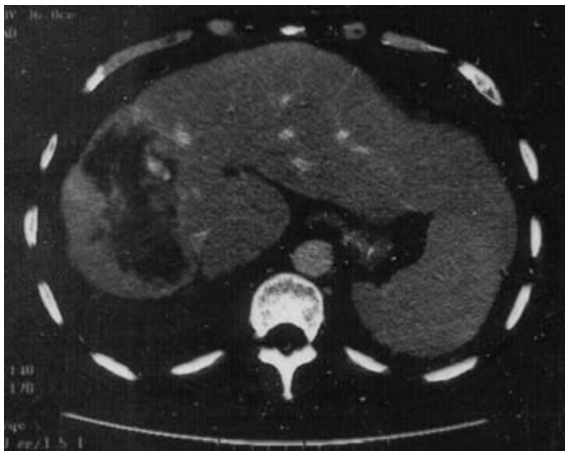

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Figure 2

CT-scan showing a large unresectable HCC in a 47-year-old patient. The mass involves the entire right hemi-liver and segment IV including right portal vein thrombosis (fig. 2a). After 9 months of selective intra-arterial chemotherapy via the gastro-duodenal artery, the tumour shrunk dramatically with subsequent increase in size of the remaining healthy liver (segments II and III, fig. 2b). The patient underwent a curative extended right hemi-hepatectomy.

Table 1

Patient survival after curative resection for HCC in series including more than 50 patients.

Authors / year	number of patients	1 year	2 year	3 year	4 year	5 year
Ohnishi et al. 1987	100	76%	62%	46%	28%	NA
Nagasue 1989	107	77%	57%	45%	33%	25%
Yamanaka et al. 1990	239	76%	NA	44%	NA	31%
Iwatsuki et al. 1991	76	71%	55%	47%	37%	33%
Ozawa et al. 1991	225	70%	60%	35%	NA	NA
Bismuth et al. 1993	60	NA	NA	52%	NA	NA
Sugioka et al. 1993	137	NA	NA	58%	NA	49%
Nagasue et al. 1993	229	88%	NA	53%	NA	29%
Kanematsu et al. 1993	67	89%	79%	75%	68%	55%
Portolani et al. 1996	62	80%	71%	50%	NA	NA
Takenaka et al. 1996	280	88%	NA	70%	NA	50%
Noami et al. 1997	262	80%	53%	33%	20%	13%
Total (average)	1844	80%	62%	51%	37%	32%

NA: not available

40% to 70% at 3 years and 30% to 50% at 5 years (see table 1). The survival rate in cirrhotics treated with resection is approximately 25% less [16]. Although liver transplantation provides good results in patients with limited tumour disease, the shortage of donor organs and the long waiting time, during which HCC progression can occur, tends to limit its overall advantage over resectional therapy. There are no randomised controlled studies comparing these 2 treatment modalities in the same group of patients. However, retrospective three year survival rates with liver transplantation vary between 18% and 69% (depending on the staging of the disease) while with resection the range is 31% to 51% [13]. Living related liver transplantation is a new approach which offers the possibility of a shorter waiting time as well as an elective timing relative to preoperative chemotherapeutic regimens in addition to bypassing the cadaveric organ donor shortage. Donor safety however is the main ethical limitation to this approach and needs to be assured.

Results of liver transplantation for advanced HCC, have been poor with 5 year survival rates of 11% to 18% due to the presence of extrahepatic micro-metastases and the negative influence of immunosuppression on the outcome in such cases [17, 18].

Novel approaches in the treatment of HCC include the development of neoadjuvant therapy. In most series, only approximately one third of HCCs are resectable at the time of diagnosis. Some preliminary data suggest that neoadjuvant chemotherapy may enable resection of approximately 10% of previously non-resectable tumours. Such data have been difficult to analyse as most of the studies are retrospective and tend to involve a conglomeration of approaches: In one series of 571 patients with non-resectable tumours, neoadjuvant treatment including hepatic artery ligation, selective intra-arterial infusion and arterial chemo-embolisation converted 55 patients i.e. 9.6% to a resectable stage [19]. Selective intra-arterial infusion of chemotherapeutic agents is a novel strategy for down-staging non-resectable HCC to resectability. While blood supply to the liver arises from both the hepatic artery and portal vein, most hepatic tumours including HCC and metastatic colorectal cancer are almost exclusively perfused by branches derived from the hepatic artery. Therefore, directing a local infusion of chemotherapy through the hepatic artery should expose the malignant cells to a high drug concentration and spare normal liver tissue. Moreover, new agents such as floxuridine (FUDR), an active metabolite of 5 FU, have the advantage of being rapidly metabolised with a 90% extraction rate within the liver on first pass, thereby limiting systemic toxicity. The effect of selective intra-arterial chemotherapy for down-staging non-resectable HCC have been evaluated in a pilot study of 28 patients with non-resectable primary or secondary liver tumours by our group [20]. Five of the twenty-eight patients included in this study had a diagnosis of hepatocellular carcinoma and underwent selective intra-arterial chemotherapy using an FUDR, Cisplatin and Doxorubicin based regimen provided by a subcutaneous pump device via

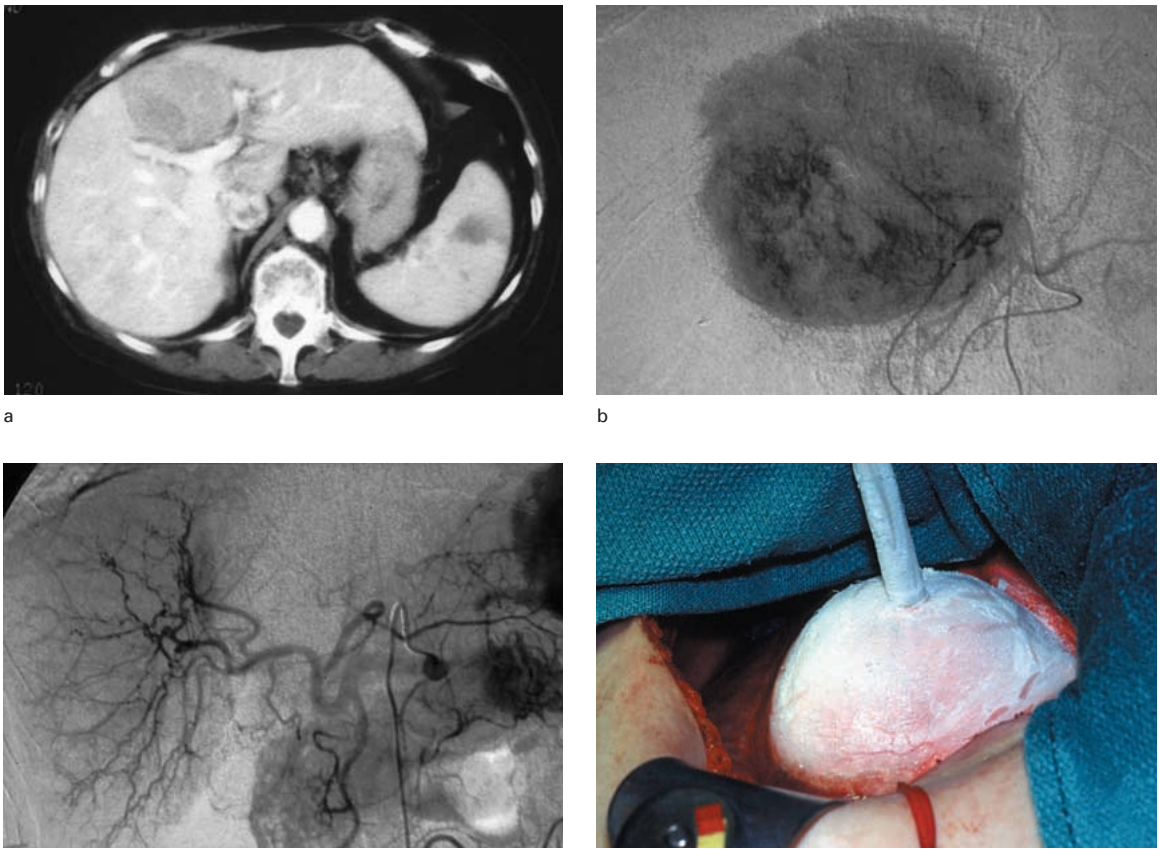

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Figure 3

Protocol of chemo-embolisation followed by cryosurgery in cirrhotic patients with unresectable HCC. CT-scan in a 77-year-old woman showing a large mass in segment IV of liver (fig. 3a). This patient had cirrhosis related to long-term methotrexate treatment for psoriasis. She underwent a chemoembolisation. As the tumour involved only the left lobe of the liver, a selective catheterisation of the left hepatic artery branch was performed, following by selective chemoembolisation (fig. 3b). Control coeliac arteriography following chemo-embolisation demonstrates the success of embolisation (fig. 3c). Patient underwent cryoablation of the tumour, 4 weeks after chemoembolisation with a 4-year follow-up (fig. 3d).

a catheter placed in the gastroduodenal artery. Four of the five patients demonstrated a positive response rate (decrease of >30% of initial tumour volume after a median of 4 cycles of chemotherapy). Curative resection was achieved in three of the 4 cases. The overall actual survival rate at the end of follow up (median 20 months), in patients who underwent a surgical resection was 75%. The actual survival at 1 and 3 years were 100% and 60% respectively. Figures 2a and 2b illustrate a case of non-resectable HCC in whom a curative resection was performed following selective intra-arterial chemotherapy.

Cryoablation has been applied in HCC. Tumour tissue destruction is mediated through insulated probes placed within hepatic tumour lesions and a freezing/thawing mechanism is achieved through the delivery of supercooled liquid nitrogen. Usually this is combined with resectional therapy, or is used in cases of cirrhosis where the tumour is considered unresectable (figure 3). Zhou et al. reported on the use of cryosurgery in 107 patients with HCC of which 56% were considered unresectable due to cirrhosis: patients with lesions of 5 cm diameter or less had survival rates of 49% at 5 years and 17% at 10 years compared to an overall patient survival rate of 22% and 8%, respectively, indicating a better overall result with smaller tumours [21]. Bismuth et al. reported 9 patients with HCC who received either cryotherapy alone or in association with resection. Cumulative survival rates were 63% at 24 months and six patients (67%) were free of tumour [22].

Non surgical treatment of HCC includes modalities such as percutaneous ethanol injection, thermal ablation by radiofrequency, or microwave and by laser, as well as hepatic artery (chemo-) embolisation. Non surgical patients can be categorised in 2 broad groups: those who are asymptomatic with large and/or multinodular HCC without vascular invasion or extrahepatic spread, and those with symptoms and/or invasive tumours. The overall 3 year survival without treatment of the first group is 50% and that of the second group is 10% at 3 years [23].

Percutaneous ethanol or thermal energy achieve best results in HCC lesions ≤3 cm in diameter. The most common technique is repeated ethanol injection until complete infiltration of the tumour has occurred, which results in necrosis. Dynamic CT-scan allows evaluation of treatment response: absence of intra-tumoral contrast uptake is considered to reflect tissue necrosis. Relative contra-indications to this technique include lesions >5 cm in diameter and >3 lesions where it is difficult to uniformly distribute ethanol in the tumour, subcapsular lesions due to the risk of intraperitoneal ethanol spillage, proximity to bile ducts or vessels can result in biliary strictures or vascular thromboses and most groups do not inject patients with Child C cirrhosis, non-correctable bleeding disorders, or those who have extrahepatic spread or portal vein thrombosis. Hisa et al. reported results with ethanol injection on 51 patients and survival rates at 1, 2 and 3 years were 87%, 73% and 63%; the results in the subgroup with <3 cm diameter lesions were better however with 94% at 1 year, 79% at 2 years and 66% at 3 years [24]. Overall, cirrhotic patients with a Child's class A generally achieve a 5 year survival of 50% while those with a Child's class B cirrhosis with the same anti-tumour effect have a worse survival due to the severity of the underlying liver disease [25].

Thermal ablation techniques such as radiofrequency (RF) provide an alternating current in the range of 200 to 1200 kHz. Other thermal ablation modalities include microwave therapy which consists of electromagnetic waves at a variety of frequencies eg, 433, 915 and 2450 MHz, and laser therapy. Such modalities have the advantage of being relatively safe, preclude the use of a general anesthetic and laparotomy, can be easily used to treat marginal recurrences or new tumours, and HCC lesions <3 cm in diameter can be dealt with in 1 to 2 sessions and do not require the mandatory repetitive injections of ethanol therapy. There is insufficient current data to allow comparison of the various thermal ablative techniques. They are however highly effective debulking techniques. Rossi et al. reported 39 patients with HCC treated with RF using 3 to 24 ablations in 1 to 8 sessions: results were 1, 2, 3 and 5 year survival rates of 94%, 86%, 68% and 40%, respectively, with 28 patients alive without evidence of tumour recurrence for >12 months [26]. Seki et al. reported 18 patients with single unresectable HCC of ≤2 cm diameter using microwave repetitive ablations as necessary. There were no recurrences during the 11 to 33 month follow-up, however 3 patients developed new tumours in extrahepatic sites [27].

Transarterial chemoembolisation (TACE) is frequently used in patients with HCC before transplantation. Its use however in early HCC in liver transplant candidates has shown no additional advantage [28, 29]. Its ideal role may be in the control of tumour growth while waiting for a liver graft, but this is difficult to assess.

TACE versus hepatic artery embolisation without the administration of chemotherapy have both been used for control of HCC when all other treatment modalities are considered to be contraindicated. Randomised controlled studies however have failed to show any advantage of TACE or hepatic artery embolisation of HCC compared to no treatment in terms of survival [30, 31]. Thus despite a visible anti-tumoral effect with tumour necrosis there is no clear benefit from either technique.

Cholangiocarcinoma is the second most prevalent primary hepatic tumour, makes up 5% to 30% of malignant liver tumours, and can be classifed as intra- or extra-hepatic; the latter being the most common, making up 94% of cholangiocarcinomas. Predisposing conditions for the development of cholangiocarcinoma include primary sclerosing cholangitis where there is a 6% to 30%

increase in risk of developing carcinoma of the biliary tract, choledochal cysts (2% to 25% increased risk) and hepatolithiasis (5% increased risk). The most frequently used classification of cholangiocarcinoma is the Bismuth system (figure 4).

Only approximately 30% of cholangiocarcinomas are resectable at the time of diagnosis [32]. The overall survival rate with this approach is dependant upon tumour staging, tumour free surgical margins and lymph node status. Since caudate lobe involvement has been documented in 30% to 95% of patients with tumour at the *hepatic* bifurcation or above, caudate lobe resection has been recommended in such cases [33]. Partial pancreatoduodenectomy and radical lymph node dissection has been recommended for tumours involving the middle or distal bile duct especially since negative resection margins and absence of lymph node involvement are strongly associated with a favourable prognosis [34].

Vogl et al. reported a series of 9 out of 13 patients where arterial embolisation of the right liver lobe allowed hilar cholangiocarcinomas initially considered as unresectable to become resectable with a 10% mean volume reduction of the right hepatic lobe and a 37% increase in the volume of the left hepatic parenchyma as assessed by helical CT-scan volumetry [35]. The follow-up of these patients however, is not available.

In early series of transplantation for cholangiocarcinoma there was a very high tumour recurrence rate with the vast majority of patients not surviving more than 3 years. Recently, however, the University of Pittsburgh reported a 1 and 5 year survival rate of 60% and 25% respectively in 38 patients who underwent liver transplantation for cholangiocarcinoma [36]. Although this was a retrospective analysis, it does suggest that the results may not be as poor as initially thought. Gores et al. take this concept further and have reported the results of a neoadjuvant protocol using external beam irradiation plus bolus fluorouracil (5 FU) followed by brachytherapy and a protracted venous infusion of fluorouracil in 12 patients with primary sclerosing cholangitis and an established diagnosis of cholangiocarcinoma lying above the cystic duct and judged as unresectable. Tumour outside the bile ducts and liver was excluded in all patients through an exploratory laparotomy 2 to 6 weeks after transcatheter irradiation. With a mean follow-up of 41 months, only one patient developed tumour recurrence and had a stage IVa carcinoma at the time of transplantation [37].

No benefit has been reported with the use of chemotherapy and/or irradiation alone in cholangiocarcinoma. Neoadjuvant treatment of cholangiocarcinoma has been reported in resectional therapy. One retrospective analysis of 9 patients who underwent preoperative 5 FU and external beam radiation compared to 31 patients who underwent resection alone, showed that a curative resection was possible in the former group (R0) compared to only 54% in the latter group [37]. Adjuvant treatment has been mainly recommended as useful in the category of patients with positive tumour margins after resection. Verbeek et al. reported a retrospective study of 64 patients where there was an improved median survival (27 months versus 8 months) in patients treated with chemoradiation after a non-curative resection [38].

Future therapy in cholangiocarcinoma might include a gene therapy based multimodal approach. For example, cell culture studies indicate that infection of tumour cells encoding for the enzyme cytosine deaminase facilitates the conversion of 5-fluorocytosine to 5-fluorouracil with a subsequent cytotoxicity in the range of 20% to 64%. When followed by irradiation, this cytotoxicity rate increased to 84% to 92% [39]. However, there has been no clinical application of this data as yet.

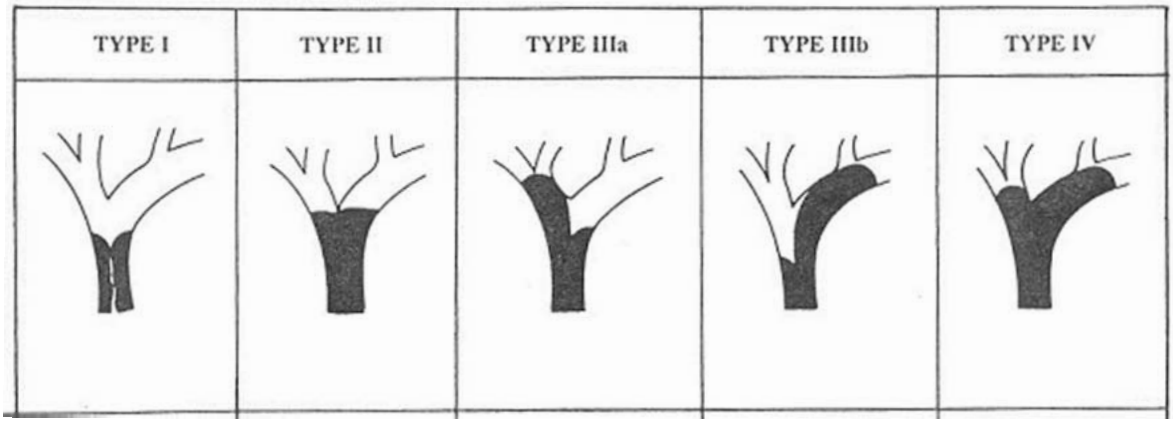

Figure 4

Bismuth classification of cholangiocarcinoma.

Secondary malignant tumours

Metastatic tumours account for 95% of all hepatic malignancies and 50% of malignancies involving the cirrhotic liver [45]. The great majority are manifestations of systemic spread and are usually a sign of end stage disease. Two types of malignancies however present as solitary metastases to the liver and are potentially curable: colorectal adenocarcinoma and neuroendocrine tumours. We will confine this discussion to the more common of the two: metastatic colorectal cancer. Synchronous metastases in the liver at the time of initial diagnosis of colorectal cancer are reported to be present in 15% to 25% of cases, while metachronous metastases after resection of the primary tumour have been found to occur in 40% of cases. Curative resection of metastatic colorectal cancer to the liver is reported to offer a 5 year survival rate of 25% to 38% whereas non-operative therapy only provides a median survival rate of 9 months [16]. Poor prognostic factors quoted in the literature include tumour free margins of <1 cm, the presence of extrahepatic disease, the presence of 3 or more lesions, bilobar disease, a tumour load (in the liver) of greater than 30%, poor differentiation of the primary cancer, the presence of jaundice or weight loss and a wedge rather than anatomic resection. Approximately 20% of patients with colorectal liver metastases are resectable at the time of diagnosis. The 5 year patient survival rate after curative resection has been reported to range between 20% and 40%. Approximately 70% of such patients develop a recurrence after curative resection and in 15% to 25% it is limited to the liver [40]. In addition, it is only recently that repeat hepatectomy has emerged as a viable therapeutic option. Adam et al. reported on a total of 243 patients of whom 64 (26%) underwent a repeat resection and in whom the 3 and 5 year survival rates were 60% and 41%, respectively [40, 41]. This is one of the largest single center series in which a minimum morbidity and mortality was associated with the repeat resection procedure thus emphasising its potential therapeutic viability.

A novel approach to metastatatic colorectal cancer has been the development of neoadjuvant therapy. Bismuth et al. reported 330 patients with non-resectable metastases who underwent neoadjuvant systemic chemotherapy using 5-FU, folinic acid and oxaliplatin. 53 patients were converted to a resectable stage with 3 and 5 year survival rates of 54% and 40%, respectively [16, 42]. Selective intra-arterial chemotherapy for non-resectable colorectal metastases without extrahepatic localisation of the disease, as assessed by CT-scan and PET scan has been evaluated in 23 patients by our group [20]. Nine of 23 patients (40%) had a local positive response to chemotherapy with a decrease of more than 30% of the initial tumour volume: a 26% conversion rate to a resectable stage. Six of the 9 patients underwent a curative resection in a median time of 7 months after initiating the chemotherapy. The overall actual survival rate at the end of follow up of all patients was 50%. Figure 5 illustrates a case of a non-resectable metastasis from colorectal carcinoma in whom a curative resection was performed following selective intra-arterial chemotherapy.

Cryoablation of metastatic colorectal cancer is an option which has been described by several groups. In one prospective study involving 59 patients, 58% underwent cryotherapy alone and 42% benefited from a combination of cryotherapy with resection. The mean number of lesions treated by cryotherapy alone was 4.6 (range 1 to 16) and 42% had bilobar disease. Thirty one patients (52%) were alive and 16 (27%) were disease free (normal CT-scan and CEA levels) at a mean follow-up of 18 months [43]. Cryotherapy has also been used as adjuvant therapy in cases with positive resection margins. Bismuth et al. reported 273 patients of whom 102, (37%). were considered to have resectable colorectal cancer. Of the latter group, 15 patients had positive resection margins and were

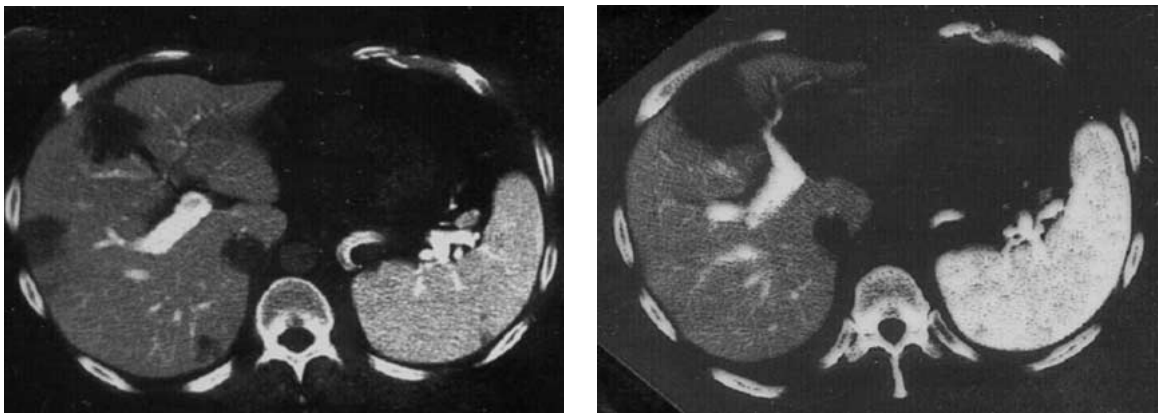

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Figure 5

A CT-scan in a 45-year-old man who underwent a low anterior resection 2 years before for colorectal carcinoma. Multiple lesions were seen in both liver lobes (fig. 5a). After 10 months of selective intra-arterial chemotherapy in the gastro-duodenal artery, only one lesion persisted (fig. 5b). The patient underwent a curative left hemi-hepatectomy. The patient has had a 5-year follow-up and remains disease free.

treated with adjuvant cryotherapy using a flat probe: none had recurrence with a mean follow-up of 17 months [44]. In summary, although initial reports on cryotherapy appear to indicate that it is beneficial, it still requires to be evaluated in a randomised prospective fashion. The same also applies to the use of thermal ablative techniques such as laser, microwave and radiofrequency. If randomised clinical trials show a failure in complete eradication of tumour, all these modalities may still have a role as tumour debulking techniques perhaps in combination with chemotherapeutic agents.

In summary, the treatment of primary and secondary liver malignancies is a highly complex topic which requires a multidisciplinary approach. There is still a great deal which requires to be evaluated in a randomised prospective fashion, especially in view of the availability of many new therapeutic approaches. This review has focused on some of the more common liver malignancies from a surgical perspective and has provided, we hope, an overall synopsis of some of the approaches which are used in these difficult clinical settings.

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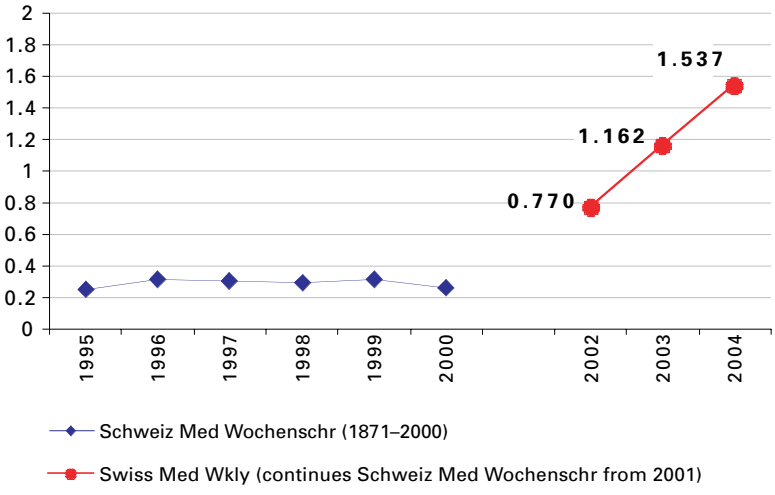

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