Resection of Nonresectable Liver Metastases from Colorectal Cancer After Neoadjuvant Chemotherapy

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Objective
The authors discuss the technique and evaluate the results of an aggressive surgical approach in patients with primarily unresectable colorectal liver metastases that were downstaged by chronomodulated chemotherapy.

Background
Resection is the best treatment of colorectal liver metastases, but it may be achieved in only 10% of patients. In the remaining 90%, survival is poor, even after partial response to chemotherapy. Little is known about the results of curative hepatectomy in patients whose metastases are downstaged by chemotherapy.

Patients and Methods
Fifty-three patients with colorectal liver metastases initially unresectable because of ill-located (8), large (8), multinodular (24) lesions, or because of extrahepatic disease (13) were downstaged by a systemic chronomodulated chemotherapy associating 5-fluorouracil, folinic acid and Oxaliplatin to the point that operation could be performed. This consisted of a major hepatectomy in 37 patients and a minor resection in 16. Associated procedures (including 5 two-stage hepatectomies and 3 pulmonary resections) were performed in 25 patients.

Results
There was no operative mortality. Complications occurred in 14 patients. The cumulative 3- and 5-year survival rates were 54% and 40% (according to the type of lesions: ill-located, 75% and 48%; large, 62% and 62%; multinodular, 54% and 40%; extrahepatic, 43% and 14%). Hepatic recurrence (34 patients, 64%) was amenable to repeat surgery in 15 cases.

Conclusions
Liver resection may be achieved in some previously unresectable patients with the help of an effective chemotherapy. The benefit in survival seems comparable to that obtained with primary liver resection (40% at 5 years). This therapeutic strategy involves a multimodal approach, including repeat hepatectomies and extrahepatic surgery.
Approximately half of all patients with colorectal cancer present at some stage with hepatic metastases.1,2 Hepatic resection currently is the only form of treatment that offers a chance of long-term survival, with rates ranging from 25% to 39% reported in the literature.3-7 However, using current indications for surgery, it is estimated that a curative operation can be performed in only 10% of all patients with colorectal metastases to the liver.1,2 In the remaining patients—the majority—the prognosis is poor and symptomatic treatment or palliative chemotherapy are the only options available. Systemic chemotherapy using conventional cytotoxic agents, mainly 5-fluorouracil, is effective in some cases, but long-term survival is uniformly poor.8 Hepatic arterial chemotherapy has increased the clinical response rate, but its use has been limited by severe complications.9 An incompletely explored benefit of chemotherapy in patients who respond favorably is that it may allow secondary resection of liver metastases in cases in which primary surgery had been considered impossible.

In this study, a group of patients with liver metastases who initially were refused for primary surgical resection responded to chemotherapy to the point that hepatectomy was reconsidered and performed. We present the results of this combined approach, with a special emphasis on the initial causes of unresectability, the methods used to facilitate liver resection, and the possible benefit in survival generated by secondary hepatectomy in this select group of patients.

PATIENTS AND METHODS

Patient Population

From April 1988 to March 1994, 434 patients with liver metastases from colorectal cancer were referred to our hospital. In all patients, a complete clinical, laboratory, and radiologic work-up was undertaken to detect evidence of local and disseminated disease. Of these 434 patients, 104 had metastases confined to the liver that technically were resectable, and the patients underwent primary hepatic surgery (24%). We had no predefined criteria of resectability with regard to either the number or the size of tumors, or to locoregional invasion of perihepatic structures, provided that resection could be complete and macroscopically curative. The other 330 patients (76%) were initially considered unresectable, according to the same criteria. All patients in this group were treated with systemic chemotherapy, according to the description that follows. All were periodically reviewed with regard to modification of the criteria contraindicating primary resection. Of these, 53 responded to chemotherapy to a point that surgical resection was considered possible. These 53 patients represent the study population. There were 30 men and 23 women. Median age was 59 years (range, 32-84 years).

Protocol of Systemic Chemotherapy

All patients were registered in protocols aiming to evaluate the clinical relevance of chronomodulated intravenous infusion (through an implanted venous access port—Port-a-Cath, Pharmacia, Uppsala, Sweden) of 5-fluorouracil (700-1200 mg/m²/day), folinic acid (300 mg/m²/day) and oxaliplatin, a non-nephrotoxic platinum complex (25 mg/m²/day). Courses lasted 4 to 5 days and were repeated every 2 to 3 weeks. The administration of the drugs was done in ambulatory patients through a time/dose programmed multichannel pump (Intellject, Aguetttant, Lyon, France) according to the pattern shown in Figure 1. The details and the toxicity of this chemotherapy regimen have been reported previously.10,11

Reconsideration of Liver Surgery

All patients were followed up by oncologists and surgeons. Response was assessed every three treatment courses and defined according to previously reported criteria.12 All radiologic investigations were reviewed by the same two radiologists highly specialized in hepatic imaging. Abdominal computed tomography scans were preferred for evaluation because they allowed better objective comparison and were less operator dependent than ultrasonography.

Hepatic resection was reconsidered periodically, along with the objective response to chemotherapy, and was attempted when technically possible and when potentially curative. To optimize the chances of curative resection, our policy was to perform the hepatectomy when the reduction in tumor size on repeated computed tomography and of tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9) had reached a plateau. Accordingly, the mean time under chemotherapy needed to downstage the disease so that secondary hepatectomy could be performed was approximately 8 months (Table 1). When liver metastases were associated with pulmonary metastases and both were resectable, our policy was first to perform the liver resection and then, after two to three courses of chemotherapy, the pulmonary resection. This approach seems logical because

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it first removes the potential liver reservoir of neoplastic cells, which can migrate at surgery.

Causes of Primary Unresectability

The characteristics of the metastases and the duration of chemotherapy according to the initial causes of non-resectability are summarized in Table 1. In 40 (75%) of the 53 patients, unresectability was decided on the radiologic investigations, showing that it was not possible to achieve a curative hepatectomy (in relation to the features of the liver metastases or to the presence of extrahepatic disease). In the other 13 patients, curative surgery had been thought possible on the preoperative radiologic findings; however, at laparotomy, either the liver metastases were not resected because of higher tumoral intrahepatic diffusion than expected or because there were unsuspected peritoneal seedings.

Liver Resection

All 53 liver resections were performed with the intent of removing all known neoplastic tissue. Forty-six first hepatectomies (87%) were macroscopically curative. In seven patients who underwent incomplete hepatectomies, chemotherapy was continued until a second-stage hepatic resection could be performed.

The operative technique for liver resection used at our center has been described previously. Frozen-section histology was performed routinely in the presence of any suspect peritoneal nodule that could change the operative decision. A complete examination of the liver was performed by palpation and intraoperative ultrasonography to confirm the number and size of metastases, to define their relationship with intrahepatic vascular structures, and to look for occult liver metastases. We preferentially used resections according to the segmental anatomy of the liver.

Techniques to Improve Resectability

When it was believed that resection could not be afforded because the amount of liver tissue left in place after surgery was likely to be too small, two techniques were used. Portal vein embolization, as described previously, was done to induce atrophy of the liver to be resected and hypertrophy of the liver to be left. For the same principle, two-stage hepatectomies were performed. This procedure, involving delayed rehepatectomy after hypertrophy of the residual liver tissue, was

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<th>Table 1. TUMOR CHARACTERISTICS AND DURATION OF CHEMOTHERAPY ACCORDING TO THE INITIAL CAUSE OF UNRESECTABILITY</th>
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<td><strong>Cause of Unresectability</strong></td>
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<tr>
<td>No. of Patients</td>
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<tr>
<td>Largest tumor diameter (mm)**</td>
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<tr>
<td>No of metastases**</td>
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<tr>
<td>Bilateral disease (%)</td>
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<tr>
<td>No of segments involved*</td>
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<tr>
<td>CEA levels (ng/mL)</td>
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<tr>
<td>No of chemotherapy courses**</td>
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<td>Duration of chemotherapy (mos)*</td>
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CEA = carcinoembryonic antigen

* Value as mean (range)
used for large bilateral lesions in which one-stage resection of all involved segments would have led to liver failure (e.g., segments 5–8 at the first operation and segments 2–3 thereafter).

Postoperative Treatment

All the patients who underwent curative hepatic resection were treated by the same regimen of chronomodulated intravenous chemotherapy for a minimum of 6 months. Chemotherapy was discontinued in the absence of signs of recurrence on ultrasonography and computed tomography examinations, and tumor markers remained normal. Patients were followed up every 3 months with a complete physical, biologic, and radiologic work-up. If a recurrence was found, a new resection was performed, if possible. Chemotherapy was used when the recurrence was not resectable.

Data Analysis

Only patients who underwent surgery up to April 1994 are reported, to allow a minimum follow-up of 2 years. Survival curves are calculated with the actuarial Kaplan-Meier method.

RESULTS

Surgical Procedures

Of the 53 patients, 16 (30%) underwent a minor hepatectomy (less than 3 segments) and 37 (70%) had a major hepatectomy (>3 segments). No difference in the extent of resection was noted between groups (Table 2).

The mean number of blood units transfused during the operation was 2.5 (range, 0–6 units) in the group of patients with large tumors, 2.1 (range, 0–7 units) in the group with multinodular tumors, 2.1 (range, 0–5 units) in the group with ill-located tumors, and 1.3 (range, 0–6 units) in the group with extrahepatic disease. Case reports of patients with large tumors, with ill-located metastases, or with multinodular lesions are illustrated in Figures 2 through 5.

Associated Initial Surgical Procedures

Associated initial surgical procedures are summarized in Table 3.

Before Resection

Portal vein embolization was performed in five patients (9%). Two patients underwent rectal resection, one for anastomotic recurrence of the primary tumor and one for resection of the primary malignancy discovered concomitantly to the liver metastases.

At Time of Liver Resection

Cryosurgery was used as an adjunct to liver resection either to treat residual tumor nodules that could not be resected (4 patients) or to freeze the raw surface of the resection when the margin of security between the tumor and the normal liver was less than 1 cm (2 patients). Associated extrahepatic surgery included one small bowel resection, one splenectomy, one partial resection of the diaphragm, and one desobstruction of the left portal branch occluded by a tumoral thrombus.

After Liver Resection

Five patients underwent the second stage of a two-stage hepatectomy. Three patients underwent planned

| Table 2. TYPE OF HEPATECTOMY ACCORDING TO THE INITIAL CAUSE OF UNRESECTABILITY |
|--------------------------------------|------|--------|--------|----------------|-----|
| Cause of Unresectability             | Large | Ill-Located | Multinodular | Associated Extrahepatic | Total |
| No. of Patients                      | 8     | 8       | 24       | 13              | 53   |
| Minor hepatectomy (<3 segments)      | 3 (37%) | 3 (37%) | 7 (29%) | 3 (23%) | 16 (30%) |
| Major hepatectomy (≥3 segments)     | 5 (63%) | 5 (63%) | 17 (71%) | 10 (77%) | 37 (70%) |
| Anatomic                             | 3 (37%) | 5 (62%) | 7 (29%) | 6 (46%) | 21 (40%) |
| Nonanatomic                          | 3 (37%) | 3 (38%) | 11 (46%) | 5 (38%) | 22 (41%) |
| Anatomic and nonanatomic            | 2 (25%) | —       | 6 (25%) | 2 (15%) | 10 (19%) |
| No vascular clamping                 | 1 (12%) | 1 (12%) | 9 (38%) | 2 (15%) | 13 (25%) |
| Selective clamping                   | 3 (37%) | 4 (50%) | 8 (33%) | 8 (62%) | 23 (43%) |
| Pediclarial clamping                 | 3 (37%) | 2 (25%) | 7 (29%) | 3 (23%) | 15 (28%) |
| Hepatic vascular exclusion           | 1 (12%) | 1 (12%) | —       | —     | 2 (4%) |
| Curative                             | 7 (88%) | 8 (100%) | 19 (79%) | 12 (92%) | 46 (75%) |
| Noncurative                          | 1 (12%) | —       | 5 (21%) | 1 (8%) | 7 (25%) |
Figure 2. Case 1. A 66-year-old man who presented with a colonic tumor and a synchronous liver metastasis in November 1987. Computed tomography scan shows a large unique lesion (110 mm) involving segments 4, 5, and 8, in close contact with the portal bifurcation; the left lobe is small (A). Tumor size reduction following chronomodulated chemotherapy was observed: after 4 courses (B) and after 8 courses (C). Bisegmentectomy 4 and 5 was performed in March 1989, followed by six courses of adjuvant chemotherapy. A 40-mm nodule in segment 3 was found in February 1991 (D), leading to a left lobectomy in April 1991. The patient is disease free in February 1996, 7 years after the initial liver resection.

Figure 3. Case 2. An 84-year-old woman who underwent a colectomy in May 1991 presented with a unique ill-located metastasis involving segments 8 and 1 (40 mm) in May 1993 (A). Tumor size reduction was observed after four courses of chronomodulated chemotherapy (B). A segmentectomy 1 and 8 was performed in September 1993. The patient is alive in April 1996 with a suspected tumor recurrence (right bile duct stenosis).
Figure 4. Case 3. A 50-year-old man who underwent a colectomy in August 1988 presented with multiple bilateral liver metastases in January 1991 (A). Tumor size reduction (with calcification) was observed after 6 courses (B) and 13 courses (C) of chronomodulated chemotherapy. Noncurative metastasectomies in segments 2, 4, and 8 were performed in November 1991. A second hepatectomy was performed in June 1993: right posterior sectoriectomy and resection of three metastases; with persistence of a deep nodule in segment 4. A third hepatectomy was done in October 1995: left lobectomy extended to segment 4a (40 courses of chemotherapy in total). The patient is alive without known tumor recurrence in April 1996 (D), 4 1/2 years after the first liver resection.

pulmonary resection of synchronous lung metastases (2–3 months).

Mortality

There was no intraoperative mortality or postoperative mortality within 2 months.

Complications

Fourteen complications were observed in the 53 patients (26%). There were 11 complications at the site of hepatectomy (5 fluid collections that resolved spontaneously, 3 infected fluid collections treated by percutaneous drainage, 1 reoperation for intra-abdominal bleeding, 2 transient biliary leaks) and 3 general complications (1 thrombosis of the upper vena cava in association with a central line, 1 renal failure in a diabetic patient, 1 septicemia).

Disease Recurrence After Liver Resection

The patterns of recurrence according to the initial causes of unresectability are summarized in Table 4. Hepatic recurrence was observed in 34 patients (66%) after a mean follow-up of 42 months. The rate of hepatic recurrence was lower in patients with metastases whose unresectability was related to extrahepatic disease (46%) than in the other groups (75% for large, 62% for ill-located, and 71% for multinodular tumors). A repeat hepatectomy—not considering two-stage hepatectomies—could be performed in 15 of the 34 patients (44%). A second resection could be performed more frequently in patients with large and multinodular tumors (37% and
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Figure 5. Case 4. A 60-year-old woman who had undergone a colectomy in May 1989 presented with two large (80 mm) metastases in May 1990, one involving segments 8, 4, and 2, the other in segment 7 (A). Tumor size reduction was observed after five courses (B) and nine courses (C) of chronomodulated chemotherapy. A left hepatectomy extended to segments 1 and 8, together with partial excision of segment 7, was performed in March 1991. The patient is alive and disease free in March 1996, 5 years after liver resection (D).

Table 3. ASSOCIATED INITIAL SURGICAL PROCEDURES ACCORDING TO THE INITIAL CAUSE OF UNRESECTABILITY

<table>
<thead>
<tr>
<th>Cause of Unresectability</th>
<th>Large</th>
<th>Ill-Located</th>
<th>Multinodular</th>
<th>Associated Extrahepatic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>8</td>
<td>8</td>
<td>24</td>
<td>13</td>
<td>53</td>
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Before hepatectomy
- Portal embolization
  - Large: 2 (25%)
  - Ill-Located: 3 (37%)
- Liver cryosurgery
  - Large: 1 (12%)
  - Ill-Located: —
  - Multinodular: 4 (17%)
- Alcohol injection
  - Large: —
  - Ill-Located: —
  - Multinodular: 2 (8%)
- Extrahepatic surgery
  - Large: —
  - Ill-Located: —
  - Multinodular: 2 (4%)*

At the time of hepatectomy
- Pulmonary resection
  - Large: —
  - Ill-Located: —
  - Multinodular: 4 (17%)

After hepatectomy
- Second stage hepatectomy
  - Large: 1 (12%)
  - Ill-Located: —
  - Multinodular: 4 (17%)
- Pulmonary resection
  - Large: —
  - Ill-Located: —
  - Multinodular: 3 (23%)

* Desobstruction of the left portal vein, small bowel resection.
† Splenectomy, small bowel resection, diaphragmatic resection.
42%, respectively) than in patients with ill-located tumors or patients with extrahepatic disease (12% and 8%, respectively). A third hepatectomy was performed in three patients with multinodular metastases.

Extrahepatic recurrence developed in 25 patients (47%). Twelve patients had intra-abdominal recurrence (23%), seven of whom underwent reoperation and their recurrence were resected (58%). There were two anterior resections of the rectum, one total colectomy, one abdominoperineal excision, one small bowel resection, one lymphadenectomy, and one resection of the bile duct (invaded by a tumoral thrombus). Pulmonary metastases developed in 14 patients (26%), mainly in the group of patients with multinodular tumors (9 patients) or with extrahepatic disease (3 patients). A pulmonary resection could be performed in 6 of the 14 patients with lung metastasis (43%), and 4 patients underwent repeat pulmonary resections. Overall, among the 53 patients of the study, there were 73 hepatectomies, 13 lung resections, and 29 associated surgical procedures either before hepatectomy (5 portal embolization procedures), at time of liver resection (13 associated hepatic and 4 extrahepatic procedures) or after liver resection (7 abdominal procedures).

### Patient Outcome

Patient outcome is summarized in Table 5. Overall patient survival for the 53 patients is 54% and 40% at 3 and 5 years, respectively (Fig. 6). The survival rate at 3 and 5 years is 62% in patients with large tumors and 75% in patients with ill-located tumors (Figs. 7A–7B). It was higher in these two groups compared with patients with multinodular tumors (44%–37%; Fig. 7C) or extrahepatic disease (43%–14%; Fig. 7D). Twenty-seven patients died after a mean follow-up of 24 months, mainly from recurrence of liver metastases (85%); 26 patients currently are alive with a mean follow-up of 42 months. Of these, 19 are disease free, representing 36% of the series (Table 5). Of the 34 patients with hepatic recurrence, 12 (35%) currently are disease free after repeat hepatectomy; of the 26 patients with extrahepatic recurrence, 2 (8%) currently are disease free after repeat surgery at a mean follow-up of 46 months (range, 25–85 months).

### DISCUSSION

We present the results of potentially curative secondary hepatectomy on 53 patients whose primarily unresectable colorectal liver metastases were downstaged by chemotherapy. The fact that patients with liver metastases initially considered unsuitable for radical surgery can undergo potentially curative surgery after chemotherapy is a recent concept in the management of these patients. This combined approach has been reported recently in smaller series of patients after other chemotherapeutic protocols. Independent from the type of chemotherapy, the main point of our study and of others’ is that there is hope for a curative treatment in a group of patients generally considered incurable. Our study emphasizes the importance of reconsidering liver resection in patients who are at first not candidates for primary surgical excision, but who respond well to chemotherapy. Furthermore, it defines a new role for systemic chemotherapy when used in patients in whom the disease is judged too advanced for primary hepatic surgery.

Among the patients with colorectal liver metastases, resection is the only treatment offering a chance of long-
term survival. Unfortunately, surgery will not be possible in up to 90% of patients, either because of extrahepatic disease, or because the hepatic lesions are not amenable to excision. Furthermore, it is uncommon that a patient whose disease initially is considered beyond operative treatment will be offered a second chance for resection. Survival of patients with unresectable hepatic metastases from colorectal cancer is poor, ranging from 3 to 6 months when both lobes of the liver are involved. Expectant symptomatic treatment and palliative chemotherapy are the most common modalities of treatment. Systemic chemotherapy is used most frequently. The standard drug is 5-fluorouracil, with response rates reported between 15% and 25%. More recently, studies with pharmacologic modulation of 5-fluorouracil have demonstrated partial clinical responses in approximately 45% of patients, and some studies have reported increased survival with chemotherapy compared with no treatment. However, the benefit is small and median survival does not exceed 11 to 16 months. Other modalities of administration, such as regional intra-arterial chemotherapy have obtained a higher response rate in selected patients, but their more widespread use is hampered by their increased toxicity and incidence of complications. Survival is increased moderately but not significantly as compared with systemic chemotherapy.

In this study, we used chronomodulated chemotherapy with 5-fluorouracil, folinic acid, and oxaliplatin. With this mode of administration, the doses of medication that can be given without toxic side effects are larger than those usually administered when these drugs are given as short-term or as fixed-rate infusions. Furthermore, the chemotherapy protocol was administered in an outpatient setting, minimizing the discomfort to the patients. A high response rate was observed, which allowed a subsequent resection in 53 of 330 patients initially considered unresectable by our surgical team (16%).

Surgical treatment of these patients requires all the armamentarium of liver surgery techniques. Intraoperative ultrasound was an indispensable tool for a complete diagnosis of the tumoral disease and for planning the adapted surgical procedure. The objective of liver resection was to remove all tumor tissue, with a margin of security of at least 1 cm. However, in cases in which the tumors arrived in contact with the main vessels, the margins had to be more limited. In multinodular tumors, the margins also were limited by the number of nodules and their proximity to main vascular structures. Particularly in these cases, cryosurgical techniques were used either to increase the safety of narrow margins of resection or to destroy in situ small deep nodules not amenable to excision. In cases in which resection was going to leave
only a small amount of healthy liver tissue, a percutaneous portal embolization or a two-stage hepatectomy allowed us to obtain hypertrophy of the healthy liver tissue before resection. Major hepatectomies could be performed in as many as 70% of patients. Our preferred approach for resection was segmental surgery, which offered the advantage of combining resections economical of uninvolved liver tissue and good control of intraoperative bleeding. The use of adapted techniques of vascular occlusion to decrease intraoperative bleeding also was of major importance. We used mainly selective clamping of the part of the liver to be removed or, when possible, no vascular clamping. However, livers submitted to prolonged chemotherapy often were more fragile and hemorrhagic than healthy livers, and the frequent resort of repeat hepatectomies often required the use of the Pringle maneuver. In these cases, we tried to decrease the risk of ischemic damage by using intermittent rather than continuous clamping and by limiting the period of vascular occlusion to a minimum. Hepatic vascular exclusion was reserved for tumors located in contact with the hepatic veins or the vena cava. The ex situ/ex vivo technique of liver resection29 or the modified ex situ/in vivo technique30 was not used in any case.

Our results show that secondary hepatic resections can be performed with little surgical mortality (none in our series) and that morbidity, although high, is consistent with figures commonly reported for primary hepatectomies. The absence of mortality was an argument to support such an aggressive policy of secondary and subsequent resections. The global survival rate observed in this series was very similar to that of primary liver resections for colorectal metastases in our center, with a 5-year survival rate of 40% (unpublished results) and 19 of the 53 patients in this series (36%) currently are disease free after a mean follow-up of 42.9 months (range, 25–85 months).

However, in contrast with the other groups, a poorer
outcome was seen in patients with associated extrahepatic disease. The risk of extrahepatic recurrence was increased in this group, as well as in the group of multinodular tumors, whereas the risk of hepatic recurrence was less compared with that observed in the other three groups. These patients may suffer from a disease of a different pattern, less amenable to surgical cure. Even if the numbers are small for definitive conclusions, the 14% survival rate observed at 5 years questions the validity of the aggressive management we adopted for patients with extrahepatic disease.

In case of recurrence, independent of the site, our policy was to propose a new resection when it was technically possible and it could aim at removing all macroscopic disease. Accordingly, 15 of the 34 patients with hepatic recurrence in the series underwent a repeat hepatectomy, and 7 of 12 patients with abdominal recurrence and 10 of 14 patients with pulmonary recurrence were submitted secondarily to a new resection.

This attitude, associated with chemotherapy, allowed disease-free survival in more than one third of patients (36%). It may be argued that this proportion represents a minority of patients with regard to the aggressiveness of our strategy. However, these results are comparable with those observed after conventional liver resection of colorectal metastases. The criticism could be made that our policy of treating with chemotherapy all patients with unresectable colorectal metastases casts too wide a net for the small number of patients in whom downstaging occurs and who can benefit from secondary resections. Currently, it is impossible to predict which individual will respond and which will not, and further work is needed in this direction. It also has to be added that systemic chemotherapy is accepted as the standard treatment in our country for patients with unresectable colorectal liver metastases, whether they are considered for secondary surgery or not, and most patients are receiving it regardless of whether secondary resections are considered. Further effort also is needed to obtain still more effective chemotherapeutic protocols, such as intensified chronomodulated chemotherapy, to increase the proportion of patients who can be resected secondarily and to lower the high incidence of recurrence seen after surgery.

Thus, the performance of hepatic resections after tumor response to chemotherapy improved in selected patients the poor prognosis of previously unresectable liver metastases from colorectal cancer. An aggressive surgical approach in these patients may provide a reasonable hope of long-term survival.

References


Discussion

DR. SEYMOUR I. SCHWARTZ (Rochester, New York): I appreciate the invitation to discuss this paper. It represents Professor Bismuth's continuous expansion of the horizons of hepatic surgery. He may well have erased all the aphorisms that we have lived by as far as hepatic resections are concerned.

One of the dicta that I have adhered to in the past, and most of us have, when considering the possibility of resection of metastatic tumors within the liver, including those originating in the colon and rectum, is that it is appropriate if not imperative to obviate a needless celiotomy. To this end we have adopted the use of hepatic arterial and portographic computed tomography (CT) scans and found them to be the most effective.

Our decisions have been based on the studies that were put together by Dr. Hughes—this is a cumulative series, reported first in 1986, substantiated by subsequent addition of data—a 5-year survival rate of 33% and a 5-year disease-free survival rate of 25% for resection of colon and rectal lesions metastatic to the liver. In our own personal experience with slightly more than 100 cases, the figures are mirrored. It is approximately a 30% 5-year disease-free survival rate, as evidenced by normal CT scan results and a normal carcinoembryonic antigen level.

I must stress that this multicenter series and our own personal series focus solely on the optimal patients with no evidence of extrahepatic disease, all lesions relatively contiguous, limited to four in number, and all within a segment of the liver that can be readily excised. We have not, up to this point in time, removed so-called bilobar disease that was not in continuity.

The data that Professor Bismuth presents relate to patients who were without question in the poorest subset, ones in whom we would have anticipated poor results, and yet he presents results that are unquestionably better than have been achieved in our country. I would ask him two questions.

The first relates to the chemotherapy regimen that was used. I would like to know the morbidity of the cisplatin-fluorouracil combination. Then a corollary and more definitive question is, if the results are this good when you incorporate chemotherapy with resectional surgery, should this not be applied to all patients who are undergoing hepatic resection, even the better risk patients, if the morbidity is not poor? That may well turn out to be the case. At this point in time, there actually is a prospective randomized series being conducted by a variety of oncology groups to answer this question.

DR. R. SCOTT JONES (Charlottesville, Virginia): Dr. Bismuth has led the way both in the development of technical aspects of liver surgery, application of liver surgery to a variety of diseases, and now in showing us the value of combined chemotherapy, surgery, and other modalities for patients with advanced metastatic disease.

I think it is interesting to note that in this group of patients that was highly selected for severity of disease and heavy tumor burden, he accomplished a 40% 5-year survival rate. I would like to reflect that until not too long ago, we expected approximately a 50% or 55% 5-year survival rate in colorectal cancer with all comers undergoing operation. As Dr. Schwartz mentioned, we have with a highly selected group of patients a 25% or 30% 5-year survival rate in treatment of metastatic disease with surgery alone in patients with solitary lesions. So Dr. Bismuth's experience is a remarkable accomplishment.

The lesson from this experience is that we have not been particularly aggressive with adjuvant or neoadjuvant therapy in the treatment of patients with hepatic metastases from colorectal cancer primarily because we lack confidence in the efficacy of our regimens. I think Dr. Bismuth has shown us that we only know the answers to these questions after we have tested them. I want to compliment him on showing the way with the application of not only chemotherapy, but cryotherapy and embolization to achieve such remarkable results.

DR. HENRY A. PITT (Baltimore, Maryland): I would like to thank Henri Bismuth and his colleagues for the opportunity to review their manuscript. They have presented 434 patients with colorectal liver metastases in whom they initially operated on 104, or 24%. By routinely treating the remaining 330 patients with infusional chemotherapy, they were able to select an additional 53 patients, or 12% of the original group, for surgical therapy. By using the entire armamentarium of surgical therapies, they were able to achieve a 40% 5-year survival rate in these 53 patients.

First of all, I would like to point out that this strategy is similar to the multimodality neoadjuvant approach that has been used and reported by Dr. Sitzman from our hospital in patients with hepatocellular carcinoma, with surprisingly good results.