Postoperative Adjuvant Chemotherapy After Curative Resection of Hepatocellular Carcinoma

A Randomized Controlled Trial

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Objective: To study the effect of adjuvant chemotherapy after curative hepatic resection in patients with hepatocellular carcinoma.

Design: A randomized controlled trial.

Setting: A tertiary referral center.

Patients: During a 54-month period, 142 patients with hepatocellular carcinoma underwent hepatic resection at 1 institution. Sixty-six patients who survived the operation and had no demonstrable evidence of residual disease on ultrasonographic examination and hepatic angiographic testing at 1 month after surgery agreed to participate in the study. The median follow-up time was 28.3 months.

Intervention: Thirty patients received a combination of intravenous epirubicin hydrochloride (8 doses of 40 mg/m² each at 6-week intervals) and transarterial chemotherapy using an emulsion of iodized oil and cisplatin (3 courses with a maximum dose of 20 mL each at 2-month intervals). Thirty-six patients had no adjuvant treatment.

Main Outcome Measures: Recurrence rate and disease-free survival.

Results: A total of 138 courses of intravenous epirubicin was given to the 30 patients. Sixty-one courses of transarterial chemotherapy were given to only 29 of the 30 patients assigned to the treatment group, because the hepatic artery in 1 patient was thrombosed. Six patients (20%) had chemotherapy-related complications with no mortality. Twenty-three of 30 patients in the treatment group and 17 of 36 patients in the control group had recurrences (P=.01). Patients who received adjuvant chemotherapy had a higher incidence of extrahepatic metastases (11 patients vs 5 patients; P=.03). The respective disease-free survival rates at 1, 2, and 3 years were 50%, 36%, and 18% for the treatment group and 69%, 53%, and 48% for the control group (P=.04).

Conclusion: In a group of patients who underwent curative resection of hepatocellular carcinoma, postoperative adjuvant chemotherapy using the present regimen was associated with more frequent extrahepatic recurrences and a worse outcome.

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Although the safety of hepatectomy for patients with hepatocellular carcinoma has improved,¹ the prognosis of these patients remains guarded as recurrences are frequent. Depending on the size of the primary tumors, recent reports from Japan,² France,₃,₄ and Hong Kong⁵ showed that recurrent disease could be found in 20% to 64% of these patients within the first year and 57% to 81% at 3 years after surgery. While the hepatic remnant was the predominant site of recurrence, involvement of extrahepatic organs such as lung and bone was frequent.⁶ To improve the long-term outcome of these patients after a successful resection, effective measures to reduce the risk for recurrence are mandatory. Preoperative transarterial chemoembolization has demonstrated no significant benefit and may accelerate deterioration of the already compromised liver function in patients with cirrhosis.⁹ Recent retrospective studies showed encouraging results with the use of postoperative adjuvant chemotherapy in the prevention of recurrent disease.²,₁₀,₁¹ Either the transarterial or systemic route was used and various chemotherapeutic agents, including fluorouracil, mitomycin, cisplatin, and doxorubicin and its derivatives had been used in combination or as a single agent. The regimens were extremely varied and questions such as the exact choice and dosage of anticancer agents, optimum timing, duration of treatment, and preferred route of administration remained largely unanswered. We conducted a randomized controlled trial...
PATIENTS AND METHODS

Between January 1991 and June 1995, 142 patients with primary hepatocellular carcinoma underwent an elective hepatic resection at our institution. Our technique of hepatic resection has been described previously. At the time of surgery, intraoperative ultrasonography was routinely performed to verify whether all macroscopic disease had been extirpated. For patients with no residual disease in the liver remnant, repeated imaging studies were conducted about 1 month after surgery. These included a percutaneous ultrasonographic examination and a hepatic angiogram. In the absence of any intrahepatic lesions on angiographic examination, iodized oil (Lipiodol, Lipiodol Ultrafluide, Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected into the hepatic artery and this was followed up by a computed tomographic scan of the liver remnant 10 days later. The hepatectomy was considered curative only when these postoperative imaging studies demonstrated no residual tumors.

Seventy-six patients were excluded from this study for the following reasons: previous preoperative chemoeembolization (8 patients), gross residual disease at the end of hepatic resection (19 patients), hospital mortality (9 patients), residual disease detected by imaging studies 1 month after undergoing an operation (30 patients), and refusal to participate (10 patients). Sixty-six patients who satisfied the criteria for a curative hepatectomy were enrolled in the study.

There were 53 men and 13 women with a mean age of 53.3 years (range, 28-78 years). The diameter of the tumor was more than 5 cm in 43 patients, 2 to 5 cm in 19 patients, and less than 2 cm in 4 patients. Forty-seven (71%) of 66 patients underwent major hepatectomy. Fifty-six patients (85%) were hepatitis B surface antigen–positive and 36 (53%) had cirrhosis of the liver on histologic examination. The mean interval between hepatectomy and randomization was 30 days (95% confidence interval, 40-59 days). All eligible patients had cirrhosis of the liver on histologic examination. The mean interval between hepatectomy and randomization was 30 days (95% confidence interval, 40-59 days). All eligible patients were randomly assigned to receive either no treatment or postoperative adjuvant chemotherapy by drawing sealed consecutively numbered envelopes.

For patients assigned to receive postoperative adjuvant treatment, both systemic and transarterial chemotherapy were started immediately after randomization. Systemic chemotherapy consisted of a maximum of 8 doses of intravenous epirubicin hydrochloride (Pharmacia & Upjohn SPA, Milan, Italy), 40 mg/m² each, administered at 6-week intervals. In addition, 3 courses of transarterial chemotherapy were performed every 2 months via either 1 of the 2 routes. At the end of the operation for 24 patients (12 from each group) undergoing hepatic resection before September 1993, a cannula connected to a subcutaneous port (Implantofix, B. Braun Melsungen AG, Melsungen, Germany) was inserted into the gastroduodenal artery with its tip at the junction with the hepatic artery. This subcutaneous port providedatraumatic access to hepatic vasculature for angiography or transarterial chemotherapy when necessary. Alternatively, the hepatic artery supplying the liver remnant was selectively catheterized via the femoral artery under fluoroscopic guidance. Using the pumping method, an emulsion consisting of 10 mL of iodized oil and 10 mg of cisplatin (1 mg/mL) was prepared by mixing through a 3-way stopcock from one syringe to another. The emulsion was infused slowly into the hepatic artery until retrograde flow was evident. Intravenous or oral amoxicillin–clavulanic acid and cimetidine were administered immediately before the procedure and for 5 days afterward.

The primary endpoint was the occurrence of recurrent disease; the secondary endpoint was survival. The follow-up program was uniform for all patients and included a serum a-fetoprotein assay, chest radiograph, and percutaneous ultrasonographic examination of the liver remnant every 4 weeks for the first year and then at gradually increasing intervals. Suspected recurrent disease was confirmed with appropriate imaging studies and, if possible, histologic or cytologic examination. When recurrence was evident, adjuvant chemotherapy was stopped and the disease treated accordingly with treatment modalities such as reoperation, therapeutic transarterial cheemoembolization, or systemic chemotherapy. No patient was lost to follow-up and all follow-up information was updated to May 31, 1996. The study protocol was approved by the Ethics Committee of the Faculty of Medicine of The University of Hong Kong and informed consent was obtained from each patient.

The necessary sample size required was estimated on the assumption that the incidence of recurrent tumor at the end of the third postoperative year for the control and treatment groups was 70% and 35%, respectively. Thirty-one patients were needed in each group to have a type I error of 5% and a type II error of 20% with a 2-tailed test. Comparisons between groups were on an intention-to-treat basis. The statistical tests used included the Student t test, the Mann-Whitney U test, the χ² test with Yates correction, and the Fisher exact test where appropriate. The disease-free survival and survival rates were measured from the day of operation to the time when recurrent tumor was first localized by imaging studies and to the time of death, respectively. Survival was estimated according to the life-table method and was compared using the Wilcoxon test. Statistical significance was P < .05; all statistical analyses were conducted using a standard biomedical statistical program (SPSS/PC+, SPSS Inc, Chicago, Ill).

RESULTS

Thirty and 36 patients were randomized to the adjuvant chemotherapy and control groups, respectively. The 2 groups were comparable for sex, age, preoperative laboratory data, indocyanine green retention rate, tumor size, extent of resection, and operative blood loss (Table 1).

The pathologic features of the resected specimens were also comparable (Table 2). The mean interval between hepatectomy and randomization was 47 days for the adjuvant chemotherapy group and 52 days for the control group (P = .09).

POSTOPERATIVE TRANSARTERIAL CHEMOTHERAPY

No complications were related to the insertion of the subcutaneous port in all 24 patients (12 from each group).
The port failed to provide vascular access owing to occlusion or malposition in the early postoperative period in 9 patients (38%), 4 of whom were in the adjuvant chemotherapy group. Three of these 4 patients had successful transarterial chemotherapy performed via the femoral artery, but the remaining 1 had a thrombosed hepatic artery precluding any transarterial injection. Thus, 29 of 30 patients received transarterial chemotherapy via the subcutaneous port (8 patients) or the transfemoral route (21 patients). Fifteen patients received all 3 courses of treatment, while adjuvant transarterial chemotherapy was discontinued in the remaining 14 patients because of recurrent disease (12 patients) and refusal to continue (2 patients).

Three patients had local complications after transarterial chemotherapy via a subcutaneous port. Two patients had cellulitis from extravasation around the port and 1 had severe epigastric pain with necrosis of the lesser curve of the stomach shown on endoscopy. All 3 patients were treated conservatively and, except for 1 who had thrombosis of the hepatic artery, were able to continue treatment via the transfemoral route. There were no other serious adverse effects, such as liver failure, from the transarterial chemotherapy and no patient had any local complications as a result of the femoral artery catheterization.

**POSTOPERATIVE SYSTEMIC CHEMOTHERAPY**

One hundred and thirty-eight courses of intravenous epirubicin were given to 30 patients in the adjuvant chemotherapy group. Eleven patients received all 8 planned courses but in 19 patients treatment was stopped because of recurrent disease (15 patients), adverse effects (2 patients), and refusal to continue (2 patients). Adverse reactions were recognized in 3 patients during the administration of systemic chemotherapy. One patient with a previous history of thyrotoxicosis had atrial fibrillation and was treated with digoxin. Another patient had leukopenia (lowest white blood cell count, 1.98 × 10^9/L) and recovered unevenly. In both cases, systemic chemotherapy was stopped. The remaining patient had alopecia, which did not affect the schedule of the adjuvant treatment. Thus the overall complication rate for adjuvant transarterial and systemic chemotherapy was 20% (6 of the 30 patients) and there was no treatment-related mortality.

**RECURRENT DISEASE AND DISEASE-FREE SURVIVAL**

At a median follow-up time of 28.3 months (range, 4.9-77.1 months), 23 of the 30 patients in the adjuvant chemotherapy group and 17 of the 36 patients in the control group had proved recurrent disease (P = .01). Recurrence in the liver remnant alone was found in 24 patients, in extrahepatic organs alone in 8 patients, and in both sites in 8 patients (Table 3). There was no difference in the incidence of intrahepatic recurrence be-

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### Table 1. Clinical, Laboratory, and Operative Findings of 66 Patients Studied by Treatment Group*

<table>
<thead>
<tr>
<th>Finding</th>
<th>Adjuvant Chemotherapy Group (n=30)</th>
<th>Control Group (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>26/4</td>
<td>27/9</td>
</tr>
<tr>
<td>Mean age, y (95% CI)†</td>
<td>54.6 (50.2-59)</td>
<td>53.4 (49.2-57.5)</td>
</tr>
<tr>
<td>Hepatitis B surface antigen–positive, No. of patients</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Preoperative values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median α-fetoprotein titer, ng/mL (range)</td>
<td>246.5 (1-735 000)</td>
<td>181.0 (1-388 800)</td>
</tr>
<tr>
<td>Mean serum total bilirubin, µmol/L [mg/dL] (95% CI)</td>
<td>8.63 [0.5] (7.52-9.75)</td>
<td>13.23 (8.18-45.6)</td>
</tr>
<tr>
<td>Mean serum albumin, g/L (95% CI)</td>
<td>43.7 (42-45.5)</td>
<td>43.8 (42.1-45.6)</td>
</tr>
<tr>
<td>Mean prothrombin time, s (95% CI)</td>
<td>0.49 (0.29-0.68)</td>
<td>0.63 (0.3-0.96)</td>
</tr>
<tr>
<td>Mean indocyanine green retention rate at 15 min, % (95% CI)</td>
<td>11.1 (9.9-12.3)</td>
<td>11 (8.8-13.3)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>8.5 (6.8-10.1)</td>
<td>10.4 (5.2-15.6)</td>
</tr>
<tr>
<td>&gt;5 cm, No. of patients</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Major hepatectomy, No. of patients</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Operative blood loss, L (95% CI)</td>
<td>2.1 (1.6-2.6)</td>
<td>2.3 (1.8-2.8)</td>
</tr>
</tbody>
</table>

*All variables are statistically comparable between the 2 groups.†CI indicates confidence interval.

### Table 2. Pathologic Features of 66 Patients Studied by Treatment Group*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Adjuvant Chemotherapy Group (n=30)</th>
<th>Control Group (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Multinodular lesion</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Mean macroscopic resection margin, cm (95% CI)†</td>
<td>1.39 (0.96-1.82)</td>
<td>1.45 (1-1.87)</td>
</tr>
<tr>
<td>Positive histologic margin</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Venous permeation</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Microsatellite</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Encapsulation</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>III</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

*All variables are statistically comparable between the 2 groups. Stage of tumor is classified according to the description of the Liver Cancer Study Group of Japan.†CI indicates confidence interval.
When considering postoperative adjuvant chemotherapy that aims primarily at preventing tumor recurrence, the distinction between recurrent disease after a curative operation and residual tumor after a palliative resection is crucial. The curability of hepatectomy for hepatocellular carcinoma is difficult to define. The definition based on tumor staging and resection margin recommended by the Liver Cancer Study Group of Japan is so restrictive that few resections included in the present study could be considered curative. In addition, it does not consider tiny intrahepatic metastases that are not detected by preoperative imaging studies or intraoperative ultrasonography. We have adopted the definition, as described by Nagashue et al., that in addition to preoperative findings, a hepatectomy is considered curative only when imaging studies conducted about 1 month after surgery do not reveal any residual disease. Thus, only patients with no demonstrable tumor at the time of randomization are considered suitable for adjuvant chemotherapy, whereas those with residual disease discovered by such screening immediately after operation should be treated therapeutically. Although there are limitations in current liver imaging techniques, a thorough intraoperative ultrasonographic examination followed by repeated investigations using ultrasonography, angiography, and post-Lipiodol computed tomography is regarded as the most sensitive means to confirm the absence of any demonstrable intrahepatic disease before initiation of adjuvant chemotherapy. Even so, more than 50% of the patients in the control group had recurrence at 3 years and the need for adjuvant treatment was justified.

Figure 2. Survival curves after curative resection of hepatocellular carcinoma. The difference in survival between the 2 groups was not statistically significant (P = .10).

**Figure 1.** Disease-free survival curves after curative resection of hepatocellular carcinoma. Patients who had adjuvant chemotherapy had a lower disease-free survival than those in the control group (P = .04).

### Table 3. Sites of Recurrence by Treatment Group

<table>
<thead>
<tr>
<th>Sites of Recurrence</th>
<th>Adjuvant Chemotherapy Group (n=30)</th>
<th>Control Group (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrahepatic</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Extrahepatic</td>
<td>11</td>
<td>5†</td>
</tr>
<tr>
<td>Lung</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Bone</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total (either site)</td>
<td>23†</td>
<td>17‡</td>
</tr>
</tbody>
</table>

*Four patients from each group had both intrahepatic and extrahepatic recurrences.
†P = .03 compared with adjuvant chemotherapy group.
‡P = .01 compared with adjuvant chemotherapy group.

Among the 40 patients with recurrent disease, 12 patients received therapeutic transarterial chemoembolization for intrahepatic recurrence, 22 patients received systemic chemotherapy (with additional external radiotherapy for spinal metastases in 2 patients), and 5 patients were treated symptomatically because of poor performance status. One patient had resection of a solitary pulmonary metastasis followed by intravenous epirubicin treatment and remained disease-free at 3 years after the second operation.

## SURVIVAL

At the time of analysis, 10 of the 30 patients in the adjuvant chemotherapy group and 10 of the 36 in the control group had died. The cause of death was progressive recurrent hepatocellular carcinoma in all patients except 1, who died of an unknown cause in the absence of any evidence of recurrence. The survival of patients assigned to the treatment group was worse than that of the control group (Figure 2), particularly in the first 2 years after the operation, although the difference was not statistically significant (P = .10).
as the lung and bone are frequent. Our previous study of 277 patients who underwent hepatic resections for hepatocellular carcinoma showed that 25.8% had extrahepatic recurrences. The lower rate of extrahepatic recurrence of 13.9% (5 of the 36 patients) in the control group of the present study can be explained by the definition of a curative hepatectomy, which excludes any patient with residual or recurrent disease within the first month of surgery. Transarterial chemotherapy is an effective locoregional therapy for unresectable or recurrent hepatocellular carcinoma and recent nonrandomized studies showed that it might reduce intrahepatic recurrences after hepatic resection. However, this regional therapy is of no value for extrahepatic tumor dissemination. For adjuvant treatment to be effective, it is conceivable that postoperative chemotherapy should be provided transarterially and systemically.

Based on our experience and that of others in unresectable hepatocellular carcinoma, the response rate of transarterial chemotherapy using an emulsion of iodized oil and cisplatin is between 38% and 59% and may be better than that of treatment using iodized oil and doxorubicin. In the absence of any demonstrable tumor, a maximum dose of 20 mL of the emulsion was considered adequate. Takenaka and associates recommended postoperative lipiodolization only once or twice, but in view of the high risk for intrahepatic recurrence, the present regimen was intensified to 3 courses of treatment within 6 months. As for systemic chemotherapy, doxorubicin is one of the most active drugs against hepatocellular carcinoma, with a response rate of 10% to 24% in patients with advanced disease. Hence, its derivative epirubicin was used because of its reduced cardiac toxic effects. Previous experience with 3 doses of intravenous epirubicin hydrochloride every 3 weeks at full strength (75 mg/m²) after hepatectomy for large tumors showed a high incidence of drug-induced toxic effects, particularly hepatic decompensation. We therefore administered epirubicin hydrochloride at half-doses (40 mg/m²) at longer intervals, up to a maximum of 320 mg/m² over 1 year in the present study.

With regard to the timing of adjuvant chemotherapy, Takenaka and associates started adjuvant transarterial chemotherapy for their patients more than 1 year after surgery. In contrast, other investigators would start at 2 to 6 weeks after surgery and repeat every 3 months for 1 year or longer. The rationale of administering adjuvant chemotherapy after curative resection is to prevent recurrence by suppressing microscopic neoplastic foci. Furthermore, it was reported that recurrence after hepatic resection for hepatocellular carcinoma was most common within the first postoperative year, and this is true even in the present series of selected patients with curative resection. Adjuvant chemotherapy for hepatocellular carcinoma therefore should be started soon after resection. Theoretically, the administration of either regional or systemic chemotherapeutic agents after hepatic resection may affect the performance status of the patient and depress the regenerative activity of the liver remnant, particularly if there is underlying liver cirrhosis. We withhold chemotherapy for at least the first 4 weeks after the operation and with the present regimen, combined adjuvant transarterial and systemic chemotherapy seems to be safe with no serious complications when administered to patients starting 6 to 8 weeks after hepatectomy.

Both surgical cannulation of the hepatic artery followed by placement of a subcutaneous port and transfemoral arterial puncture had been used successfully for delivering chemotherapy intra-arterially. The subcutaneous port was used in the early part of our study because of its theoretical advantage of providing an atraumatic means for repeated access to the hepatic vasculature. Nevertheless, the additional operation time, frequent early occlusion, and morbidity associated with these devices had made the transfemoral route our preferred means for intraarterial drug administration. The latter route had been employed successfully in all 21 patients without a functioning subcutaneous port with minimal morbidity.

Recent retrospective studies have shown encouraging results with adjuvant transarterial chemotherapy following hepatic resection for hepatocellular carcinoma. Using a combination of fluorouracil, doxorubicin, and mitomycin in Lipiodol delivered transarterially, Nonami and associates found a better survival rate in 19 patients who were treated after the operation than 18 who were not. According to Nagasue et al., a significant survival benefit was obtained by giving their patients intravenous epirubicin and peroral fluorouracil after hepatectomy. In a prospective nonrandomized study, Takenaka et al. found a significantly higher disease-free survival in patients who received lipiodolization after hepatectomy than others receiving no treatment, although the timing of their initiation of treatment varied widely from less than 6 months to almost 2 years after the operation. Without a proper control group, these studies had a serious drawback of patient-selection bias. In addition, without proper documentation of a curative resection and the absence of residual disease before initiation of adjuvant treatment, it is difficult to know whether the beneficial effect on survival is merely related to early therapeutic intervention for residual or recurrent disease.

A prospective randomized controlled trial showed improved disease-free survival and overall survival with the use of oral 1-hexylcarbomoyl-5-fluorouracil following curative resection for hepatocellular carcinoma. The study, however, involved 26 institutions with a mean of only 2.3 inclusions per institution. The favorable results of this adjuvant chemotherapy trial may be questionable because treatment was suspended owing to adverse effects in 12 (44%) of 27 patients. In contrast, the present randomized controlled study showed that combined transarterial and systemic adjuvant chemotherapy using the present regimen is very promising and the overall survival of a selected group of patients with curative resection of hepatocellular carcinoma is comparable to the disease-free survival obtained in earlier detection of recurrences and hence a shorter disease-free survival is unlikely. Instead of improving the survival by this early detection of recurrences, the survival of the treatment group was lower, largely because of a higher incidence of extrahepatic metastases and cancer death.

The exact reason for the negative result observed is open to speculation. First, transarterial chemoemboli-
zation was associated with a higher incidence and earlier development of extrahepatic metastases in patients with unresectable hepatocellular carcinoma. The defective blood vessels or the ingrowth of new blood vessels in zones of tumor necrosis may facilitate systemic tumor dissemination. Second, definite evidence shows that malignant primary tumors contain subpopulations of cells that are heterogeneous for metastatic potential and susceptibility to cytotoxic drugs. By destroying the subpopulation of drug-sensitive cells, chemotherapy could stimulate the formation of new clonal variants from the surviving subpopulations and permit cells with a higher metastatic capability to proliferate. Finally, immune surveillance in control of tumor dissemination may be incriminated. The antimimetic effect of the present regimen of adjuvant chemotherapy might have depressed the host immunity against tumor metastasis.

The failure of adjuvant chemotherapy in the present study may call for consideration to intensify the therapeutic regimen. Nevertheless, limitations are inherent in any form of chemotherapy for hepatocellular carcinoma not only because many tumors are slow growing and hence cytotoxic drug-resistant, but also because the associated liver cirrhosis limits the maximum tolerated intensity of chemotherapy. Further prospective studies using other regimens are required before the value of postoperative adjuvant chemotherapy can be defined more clearly.

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REFERENCES


**Surgical Anatomy**

The sympathetic trunk is composed of ascending and descending fibers, some of which are preganglionic effenter, and afferent fibers.