

688

# Liver resection for metastatic colorectal cancer

Shunzaburo Iwatsuki, M.D., Carlos O. Esquivel, M.D., Ph.D., Robert D. Gordon, M.D., and Thomas E. Starzl, M.D., Ph.D., Pittsburgh, Pa.

*From 1975 to 1985, 60 patients with isolated hepatic metastases from colorectal cancer were treated by 17 right trisegmentectomies, five left trisegmentectomies, 20 right lobectomies, seven left lobectomies, eight left lateral segmentectomies, and three nonanatomic wedge resections. The 1-month operative mortality rate was 0%. One- to 5-year actuarial survival rates of the 60 patients were 95%, 72%, 53%, 45%, and 45%, respectively. The survival rate after liver resection was the same when solitary lesions were compared with multiple lesions. However, none of the seven patients with four or more lesions survived 3 years. The interval after colorectal resection did not influence the survival rate after liver resection, and survival rates did not differ statistically when synchronous metastases were compared with metachronous tumors. A significant survival advantage of patients with Dukes' B primary lesions was noted when compared with Dukes' C and D lesions. The pattern of tumor recurrence after liver resection appeared to be systemic rather than hepatic. The patients who received systemic chemotherapy before clinical evidence of tumor recurrence after liver resection survived longer than those who did not.*

*From the Department of Surgery, University of Pittsburgh Health Center, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pa.*

THE LIVER IS a major site of metastatic spread of primary colorectal cancer, and it is the sole site of initial tumor recurrence in as many as 30% of patients. With further technical refinements in hepatic surgery and recent developments in sophisticated perioperative management, major liver resection can now be performed with an operative mortality rate of less than 5%.<sup>1-3</sup> Thus surgical removal of hepatic metastases has been used with increasing frequency, particularly with colorectal carcinoma as the primary cancer.

In this article, our experience in 60 patients who had liver resections for metastatic colorectal cancer will be analyzed to identify factors that may influence the outcome of surgery and also to study the patterns of tumor recurrence after potentially curative hepatic resection of metastatic tumor.

## PATIENTS AND METHODS

During a 10-year period from 1975 to 1985, 60 patients with isolated hepatic metastasis from colorec-

tal cancer were treated with various types of liver resection at the University Health Sciences Center of Colorado (16 patients before 1981) and the University Health Center of Pittsburgh (44 patients after 1981). There were 44 men and 16 women. The ages ranged from 25 to 76 years with a mean age of 55 years. The interval between colorectal resection and hepatic resection ranged from 0 (simultaneous resection) to 216 months, with the median interval of 19 months. There were 16 patients with Dukes' B colorectal cancer, 31 patients with Dukes' C, and 13 patients with Dukes' D lesions. The colorectal cancer with synchronous hepatic metastases was classified as Dukes' stage D, regardless of the stage of primary lesion. Thirty-eight patients had solitary hepatic lesion, and 22 patients had multiple lesions. Among the 22 patients with multiple hepatic lesions, seven patients had four or more lesions.

Liver resections for these 60 patients consisted of 17 right trisegmentectomies,<sup>4</sup> five left trisegmentectomies,<sup>5</sup> 20 right lobectomies, seven left lobectomies, eight left lateral segmentectomies, and three nonanatomic wedge resections. The extent and location of the tumor determined the choice of resection. After liver resection, systemic chemotherapy was recommended to all patients and their referring physicians and surgeons. Twenty-two patients followed the recommendations and received systemic chemotherapy before clinical

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Reprint requests: Shunzaburo Iwatsuki, M.D., Department of Surgery, 3601 Fifth Ave., Rm. 218 Falk Clinic, Pittsburgh, PA 15213.

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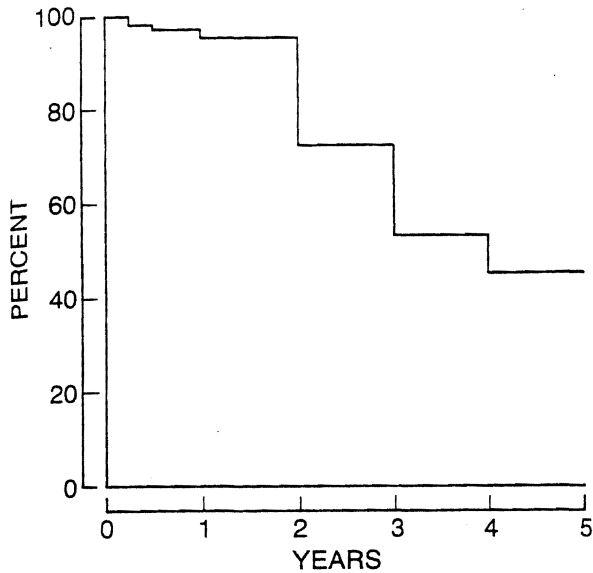


Fig. 1. Overall survival rate of 60 patients after liver resection for metastatic colorectal cancer.

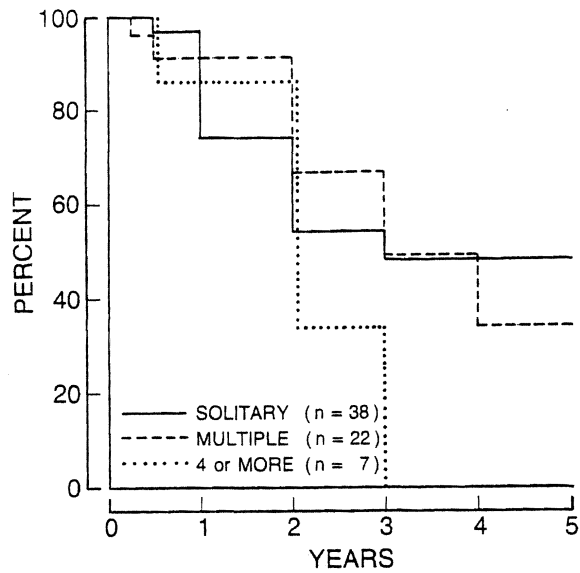


Fig. 2. Survival rate after liver resection for metastatic colorectal cancer by number of lesions.

evidence of tumor recurrence and 28 patients did not. The most commonly used chemotherapeutic agent was 5-fluorouracil for 6 to 18 months.

Survival rates were calculated by the life table method of Kaplan-Meier, and statistical comparisons among the subgroups were performed with the log-rank test.

## RESULTS

**Operative mortality and morbidity.** There were no deaths within a month after 22 trisegmentectomies, 27 lobectomies, eight segmentectomies, and three wedge resections. Thus the 30-day operative mortality rate was 0%. However, there were eight significant postoperative complications. Four patients developed subphrenic abscesses that required surgical drainage, two patients developed deep vein thrombosis, one of which caused a pulmonary embolus, and one patient developed small bowel obstruction. There were no postoperative hemorrhages that led to reexploration.

**Survival.** Overall actuarial survival rates calculated by the Kaplan-Meier method are shown in Fig. 1. One- to 5-year actuarial survival rates of the 60 patients were 95%, 72%, 53%, 45%, and 45%, respectively. When the survival rates of 38 patients with solitary hepatic lesions were compared with those of the 22 patients with multiple lesions, they were nearly identical as shown in Fig. 2. However, the survival rate of seven patients who had four or more hepatic lesions

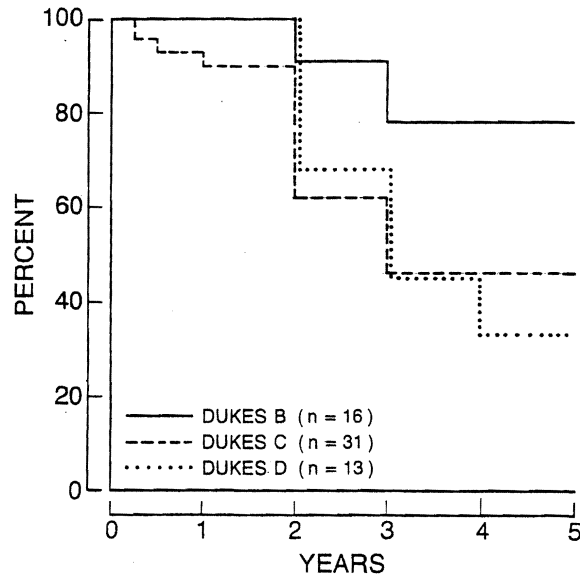


Fig. 3. Survival rate after liver resection for metastatic colorectal cancer by Dukes' staging.

was significantly less than that of 38 patients with a solitary lesion ( $p = 0.05$ ) (Fig. 2).

The influence of Dukes' staging of primary colorectal cancer on survival after liver resection was examined (Fig. 3). The survival rate of 16 patients with Dukes' B primary lesions was significantly higher than that of the 31 patients with Dukes' C primary lesions

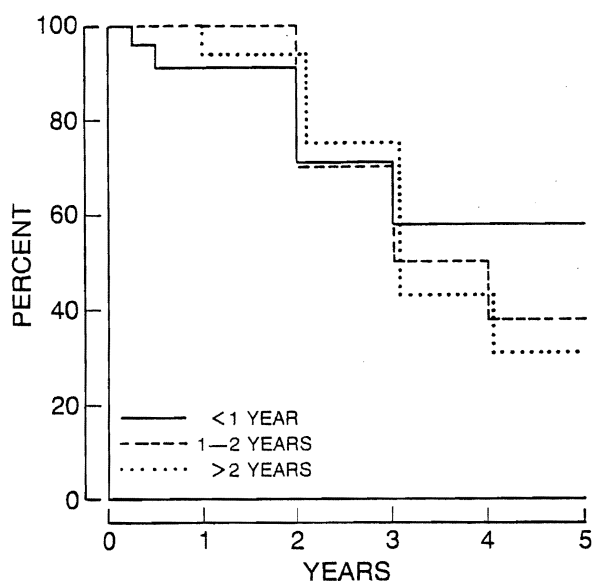


Fig. 4. Survival rate after liver resection for metastatic colorectal cancer by interval between colorectal and hepatic resection.

or the 13 patients with Dukes' D lesions ( $p < 0.05$ ). However, there was no difference in survival rates, after liver resection between patients with Dukes' C lesions and those with Dukes' D stage (synchronous hepatic lesion) colorectal cancers.

The survival rates after liver resection were compared by the interval after colorectal resection (Fig. 4). There was no difference in survival rates between patients with intervals less than 1 year, 1 to 2 years, and longer than 2 years.

The survival rates were compared among 22 patients after trisegmentectomies, 27 patients after lobectomies, and 11 patients after left lateral segmentectomies or wedge resections (Fig. 5). The survival rate of patients whose hepatic metastases could be totally removed only by trisegmentectomies was significantly lower than that of patients whose hepatic lesions could be easily removed by lobectomies or smaller resections ( $p = 0.01$ ). The survival rates after lobectomies and left lateral segmentectomies or wedge resections were essentially identical.

The survival rate of 22 patients who received systemic chemotherapy before clinical evidence of tumor recurrence after hepatic resection was better than that of 38 patients not so treated (Fig. 6) ( $p = 0.05$ ).

Although the survival rate of patients who were 70 years old or older was the lowest, there were no statistically significant differences among the different

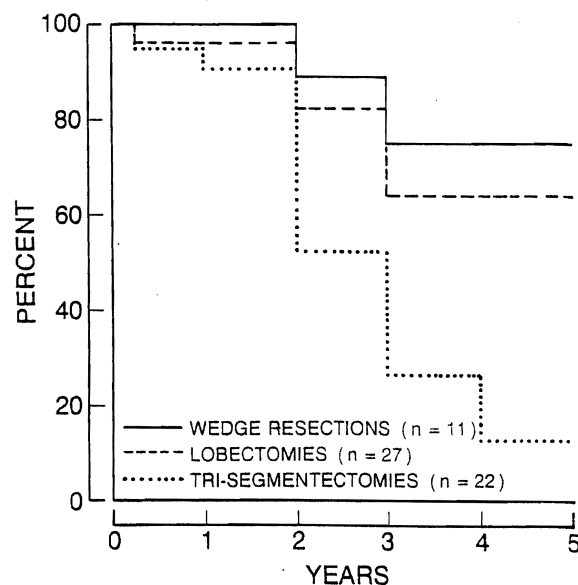


Fig. 5. Survival rate after liver resection for metastatic colorectal cancer by extent of liver resection.

age-groups (Fig. 7). There were no differences in survival rates between 44 men and 16 women.

**Tumor recurrence.** Tumor recurrence was documented in 29 of the 60 patients from 3 months to 7 years after liver resection, most frequently during the second year. The liver was involved in 18 patients, the abdomen outside the liver in 17 patients, the lungs in 15 patients, the brain in five patients, the bones in four patients, and in one patient each, the abdominal wall, chest wall, and pericardium, respectively. It was difficult to determine the first site of recurrence in most of our patients by retrospective study. Most of the tumor recurrences involved multiple organs, and the liver was the isolated site of recurrence in only three patients. The lungs were the isolated site of recurrence in only two patients.

## DISCUSSION

This study has confirmed earlier reports<sup>1-3</sup> that major hepatic resections can be performed with a minimum of risk to the patient. Petrelli et al.<sup>6</sup> reported that right trisegmentectomy had been abandoned at Roswell Park Memorial Institute for metastatic colorectal cancer because of high surgical mortality rates. However, our experience of no operative deaths (death within 1 month) in 22 trisegmentectomies encourages the construed use of trisegmentectomy for extensive hepatic metastasis.

The 1-, 3- and 5-year survival rates of 95%, 53%,

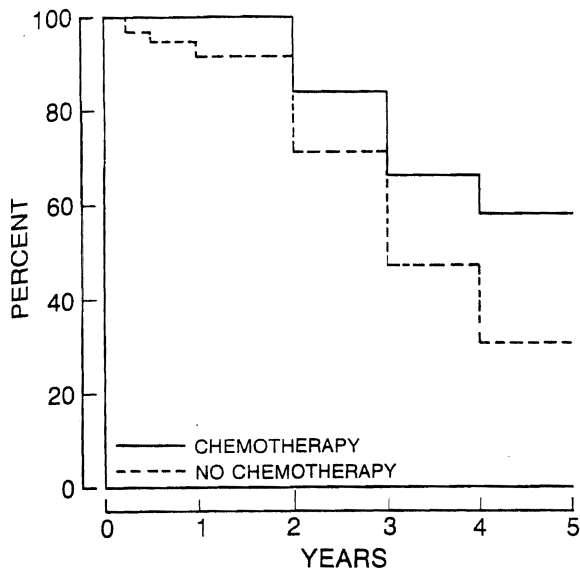


Fig. 6. Survival rate after liver resection for metastatic colorectal cancer with or without systemic chemotherapy before clinical evidence of tumor recurrence.

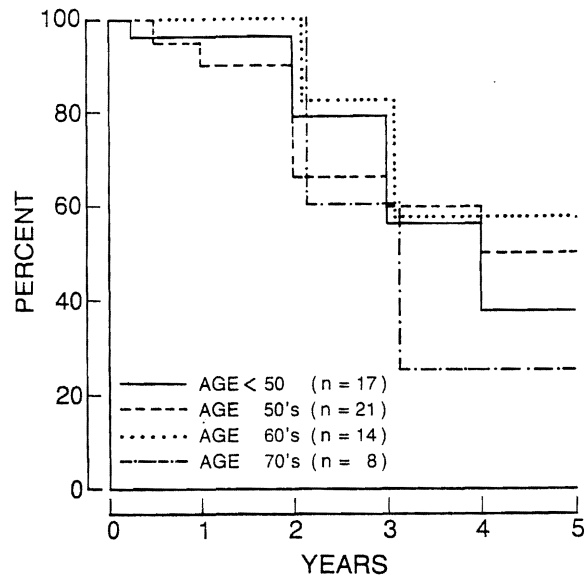


Fig. 7. Survival rate after liver resection for metastatic colorectal cancer by age.

and 45%, respectively, in this study reemphasize that liver resection is the therapeutic modality that offers the best prospect of long-term survival to a small but significant proportion of patients with metastatic hepatic lesions from colorectal cancer. Although it is difficult to compare the survival rates of different series, slightly better results of current series than those of others<sup>2,3,6-8</sup> may reflect the lack of operative deaths and the liberal use of lobectomies and trisegmentectomies in preference to the less radical nonanatomic resections often called "local excisions."

Controversy has existed about the efficacy of major liver resection in controlling multiple hepatic metastasis. It has been reported that multiple hepatic lesions have a poorer prognosis than do solitary lesions after liver resection.<sup>9,10</sup> However, in more recent studies,<sup>2,3,6-8</sup> statistically significant differences in survival rates could not be found after liver resections in patients with solitary versus multiple hepatic lesions. The present study supports the latter conclusion, but it is noteworthy that none of the seven patients with four or more hepatic lesions in this series survived 3 years after liver resection.

The stage of primary colorectal cancer appeared to be a determinant of survival after resection of hepatic metastases. A significant survival advantage was seen for patients with Duke's B primary lesions when compared with patients with Duke's C. Others have reported the same finding.<sup>2,3,7,8</sup> The survival rate of

patients with synchronous hepatic metastasis (Duke's D) did not differ from that of patients with metachronous tumors of Duke's C primary lesions, but it was significantly less than that of patients with metachronous tumors Duke's B lesions. Because only two of the 13 patients with synchronous tumors had primary colorectal cancer of Duke's B stage, the real influence of synchronous hepatic metastasis on survival after liver resection could not be determined. However, the findings of this series and those of others<sup>2,3,7,8</sup> indicate that the interval between colorectal and hepatic resection is not a factor that affects survival after liver resection. Therefore, synchronous hepatic metastases appear to be treated by liver resection as effectively as metachronous metastases.

The extent of liver resection was determined by the degree of tumor involvement of the liver. Trisegmentectomies were applied to the tumors that involved both lobes. Inferior survival after trisegmentectomies merely reflected more advanced stage of metastatic colorectal cancer when compared with lobectomies or smaller resections.

The effect of systemic chemotherapy before clinical evidence of tumor recurrence after liver resection was not examined by a randomized study, but the survival rate of patients who received chemotherapy before tumor recurrence was significantly better than that of those who did not ( $p = 0.05$ ). Well-designed multi-institutional studies involving a large number of

patients will be required to confirm our finding.

The pattern of tumor recurrence or treatment failure after liver resection appeared to be systemic rather than hepatic in this experience and that of others,<sup>6,11</sup> realizing that any retrospective study to determine the first sites of recurrence by clinical tests has limitations. However, even the limited information now available suggests that systemic chemotherapy may be at least as effective in controlling tumor recurrences after liver resection as intrahepatic infusion chemotherapy.

The following multi-institutional study should be considered to determine the effect of systemic adjuvant chemotherapy on survival after potentially curative liver resection of metastases from colorectal cancer. Patients with an elevated carcinoembryogenic antigen before liver resection, which falls to normal levels 1 month after liver resection, would be randomized into either one group receiving systemic chemotherapy or another without this adjuvant therapy. Carcinoembryogenic antigen levels would be measured every 3 months as an indicator of treatment failure. If the treatment were to fail, the sites of recurrence would be investigated extensively every 3 months to determine the pattern of treatment failure. Tumor-free intervals and survival rates would be compared between the two groups. Our group would be compelled to refrain from participation in such a study, since the statistically significant better results in our patients given chemotherapy would not allow us to have a null hypothesis of no treatment difference.

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#### DISCUSSION

**Dr. Jeremiah G. Turcotte** (Ann Arbor, Mich.). Dr. Iwatsuki did not mention it in his presentation, but with their operative mortality rate of 0% for 60 major liver resections it will be some time before another group will duplicate this outstanding result.

The 45% survival rate at 5 years certainly makes one wonder if we are not somehow altering the biology of this tumor with this major intervention. To have such a high proportion of patients alive 5 years after the tumor has metastasized to the liver seems very unusual. Of course, we will never answer the question of whether this is just selection unless a prospective randomized study is accomplished. However, the results from this and other series certainly suggest that resection of metastatic colon cancers is a worthwhile undertaking.

I thought it would be useful to compare the results of this series with the results reported by Flanigan and Foster in 1967. Their communication in 1967 brought the subject to the attention of the surgical world. Their series was a collected series rather than a personal series.

In 1967 operative mortality rates varied from 4% to 30%. The operative mortality rate for most groups was closer to 30%. In Dr. Iwatsuki report the 30-day operative mortality rate was 0%. The 5-year survival rate reported by Flanigan was 24%, while in the present report it is 45%. Much of the improvement in survival is due to a lower operative mortality rate.

Both Iwatsuki's and Foster's report noted a decrease in survival with multiple lesions. With four or more lesions no patient survived 5 years in Iwatsuki's experience. In Foster's report the 5-year survival rate was 12% with multiple lesions, but the term "multiple" was not defined. When more extensive resections, that is, trisegmentectomy, was required, the long-term survival rate was approximately 13% in the Pittsburgh report and 20% in the Flanigan report.

I have three questions. Do you continue to recommend an operation when a trisegmentectomy is required to remove the tumor, since you have experienced only a 13% 3-year survival rate with this operation? Likewise, do you continue to recommend resection with four or more lesions, since there were no long-term survivors in this group? Would you also comment on the use of hepatic resection for other types of tumors, especially sarcomas, since there is evidence that suggests this may be worthwhile.

**Dr. Joaquin S. Aldrete** (Birmingham, Ala.). It is obvious from the article by Dr. Iwatsuki et al. and the one presented by Dr. Gordon, both from the Pittsburgh group, that they

perform liver resections as do most of us in minor cases in between or while waiting for the major cases. In Pittsburgh the major cases are, of course, liver transplants. I personally have witnessed this impressive routine that Tom Starzl and his group have had for a number of years.

I think this is an important article, particularly the conclusions that the actuarial survival curves of these patients are improved. Another meaningful conclusion was that the localized lesions that can be resected with a simple right or left lobectomy have better survival rates than those that require an extensive resection or those with multiple metastases. These observations were also made by the multicenter study that included more than 600 patients and that was done by the surgeons at the National Cancer Institute, presented a few weeks ago at the Society of University Surgeons.

I also think that in the study presented, there may be an element of selection that allowed the observed good results. I noticed, Dr. Iwatsuki, that your mean period of time elapsed between the resection of the primary colonic tumor and the resection of the hepatic metastases was 19 months. This can be interpreted as a valid way of natural selection since patients who can be well after their primary colon resection without having signs of obvious hepatic metastases appear to have a much better prognosis. We have noticed this in our own experience; perhaps there is some wisdom in waiting 2 or 3 months after the hepatic metastasis has been detected, then repeat the computerized tomography, and when there has been little change in the size and number of the metastases, the probabilities for longer survival are better after resection of the slow-growing metastases. This is what I mean when I talk about "natural selection." Therefore my question is: did you analyze the survival curves specifically in relation to the duration between the resection of the primary colonic cancer and the resection of the hepatic metastases?

**Dr. Larry C. Carey** (Columbus, Ohio). I think the group from Minnesota, at this meeting 3 or 4 years ago, presented a review of their initial group of patients on whom Dr. Wangensten had recommended second looks. For my information it provided the first evidence that multiple hepatic metastases were not quite as ominous as we had thought. Dr. Delaney, do you or any of the other Minnesota representatives want to comment about your updated experience with those patients?

**Dr. Delaney.** I have no later update.

**Dr. Carey.** We have had a fairly similar experience in a series of about 50 cases now at Ohio State, also without a death, with a 5-year survival rate of about 35%. I think as more and more centers present these problems, the data

appear to become more and more similar in long-term outcome.

**Dr. Iwatsuki** (closing). Answering the question about trisegmentectomies for metastatic colorectal cancer, we will continue to treat those bilobar tumors by extensive liver resections. The 4-year survival rate is low. However, 1- and 2-year survival rates are excellent. There is no statistical difference in survival rates at the 1- and 2-year level between trisegmentectomies and lobectomies. This means that these tumor-free periods give us an opportunity to treat these patients with adjuvant chemotherapy. Adjuvant chemotherapy after curative resection of colorectal metastases is not well accepted by oncologists or oncologic surgeons, but our data strongly suggest that chemotherapy does something positive after curative resection. Therefore we will continue to perform trisegmentectomies for metastatic tumor if the liver is the only site of metastasis.

There was a question about liver resection for other metastatic liver tumors. We have done approximately 300 liver resections since Dr. Starzl started to collect data on patients with liver resection. There were roughly 100 patients with benign disease, 100 patients with metastatic tumors, and 100 cases of primary liver cancer.

The second most common metastatic tumor was carcinoid tumors, followed by leiomyosarcoma, a few cases of breast cancer, and ovary tumors and melanomas. We have not analyzed these small numbers of cases in detail yet, but I believe liver resections provided significant tumor-free time for those patients.

Both Drs. Turcotte and Aldrete asked about case selection of our patients with liver resection. We do not have any choice in selecting our patients. Most of the patients came to us, as you can see from the extent of the liver resections, after rejection by other institutions. Thus we are not picking up small tumors of a smaller number of metastases. Rather we are treating more advanced metastatic colorectal cancer than do other institutions.

We do not perform the resections if there is obvious distant extrahepatic involvement of the tumors. Many centers do resections with obvious periaortic node involvement but we do not. However, we perform resection on the patient with extrahepatic involvement by extension, such as to the diaphragm or adrenals or kidneys.

We have analyzed and presented that time interval between the colon and liver resection does not influence the survival rates after liver resection. This is also true for synchronous tumors.

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### Reseccion hepatica en casos de carcinoma colorrectal metastasico

*Desde 1975 hasta 1985 se trataron 60 pacientes con metástasis hepáticas aisladas con primario en un carcinoma colorrectal. Se realizaron 17 trisegmentectomías derechas, 5 izquierdas, 20 lobectomías derechas, 7 izquierdas, 8 segmentectomías laterales*

izquierdas y 3 resecciones no anatómicas en cuña. La mortalidad operatoria en el primer mes fue de 0%. La supervivencia actuarial de los 60 pacientes fue de 95, 72, 53, 45, y 45% respectivamente. La supervivencia después de la resección hepática fue similar en los casos con lesiones solitarias que en los casos con lesiones múltiples. Sin embargo ninguno de los 7 pacientes con cuatro o más lesiones sobrevivió más de 3 años. El periodo de tiempo después de la resección colorrectal no influyó en la supervivencia después de realizar la resección hepática, y la supervivencia no mostró diferencias estadísticas importantes cuando se compararon las metástasis sincrónicas con los tumores metácronos. Se observó una importante ventaja de supervivencia de los pacientes con lesiones primarias tipo Dukes B cuando se compararon con las lesiones Dukes C y Dukes D. El patrón de recurrencia tumoral después de la resección hepática parece ser sistémico más que hepático. Los pacientes que recibieron quimioterapia sistémica antes de que hubiese evidencia clínica de recurrencia del tumor después de haber realizado la resección hepática, tuvieron una supervivencia mayor que aquellos que no recibieron quimioterapia.

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