Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival

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Background. *It is unclear whether there is a benefit to resection of primary gastrointestinal carcinoid neoplasm with hepatic metastases. We investigated whether primary tumor resection in this setting led to a significant difference in outcomes.*

Methods. *A retrospective review of patients with abdominal carcinoid neoplasms between 1995 and 2006 was performed. Data collected on patients with proven carcinoid liver metastases at initial diagnosis included whether the primary neoplasm was resected, time to progression of liver metastases, and status at last follow-up. Progression-free survival and survival were calculated by the method of Kaplan-Meier and compared by the log-rank test.*

Results. *There were 84 patients, 60 of whom had their primary neoplasm resected. The resected group had a greater median progression-free survival of 56 months, compared with 25 months for the primary nonresected group ($P < .001$). Median survival time for the resected group was longer at 159 months, compared with 47 months for the nonresected group ($P < .001$).*

Conclusions. *Resection of the primary neoplasm is associated with better progression-free survival and overall survival in patients with abdominal carcinoid neoplasms. Therefore, localization and resection of the primary neoplasm should be considered, even among patients in whom the primary neoplasm is asymptomatic. (Surgery 2006;140:891-8.)*

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Abdominal carcinoid neoplasms are slow-growing neoplasms that arise from enterochromaffin-like cells. The reported incidence is approximately 1 case per 100,000 people. These neoplasms usually follow an indolent course, even when metastatic. Their natural history is characterized by lack of symptoms that are due to the primary neoplasm, followed by nonspecific symptoms induced by different active metabolites released from distant metastases. Because of this particular characteristic, these neoplasms have been notoriously difficult to diagnose.[1,2] It is common to find these neoplasms in stage IV, with metastases frequently found in the liver.

Although there is uniform consensus for the treatment of nonmetastatic neoplasms, there is still debate over how to surgically manage patients with metastatic disease. With the advent of long-acting octreotide treatment, these patients can expect long survival with a reasonable quality of life.[3] The common wisdom in most oncologic diseases dictates to not resect a primary neoplasm once it has already metastasized, unless it is causing specific symptoms (obstruction, pain, etc). Many authors advocate resecting symptomatic primary carcinoid neoplasms in patients with metastatic disease to prevent subsequent complications of malnutrition, and bowel obstruction or infarction.[4-8] They cite the expected long-term survival of these patients as a reason that this intervention is likely to be beneficial.

There is no clear recommendation on how to manage patients with asymptomatic primary neo-

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plasms.[9-11] Makridis et al[6] suggest that liberal indications for celiotomy to resect the primary neoplasm should prevail among symptomatic and possibly be extended to even asymptomatic patients. Boudreaux et al[4] adopted an aggressive approach to advanced abdominal carcinoid neoplasms that included celiotomy to locate and resect occult asymptomatic primary neoplasms in some cases. Their rationale again was prevention of subsequent intestinal obstruction.

These studies have not addressed a possible impact of resection of the primary neoplasm on progression of liver disease and survival. There is a suggestion that resection of the primary neoplasm may have an impact on survival. Hellman et al[12] noted that patients in whom the primary neoplasms were resected had longer survival than patients whose neoplasms were not resected. This observation, however, could be explained by selection bias. Neoplasms that are not resectable may be more aggressive and have worse outcomes.

The present study of patients with carcinoid tumor metastatis to the liver was undertaken to determine the impact of resection of the primary neoplasm on the subsequent progression of liver disease and survival. The aim of the study was to determine whether a recommendation for an operation to locate and resect the primary neoplasm should be made in all cases of carcinoid neoplasms with metastases to the liver.

METHODS

The medical records of all patients with the diagnosis of carcinoid neoplasm referred to a university-based surgical oncologist between 1995 and 2006 were reviewed. Among these, patients with histologically proven carcinoid and hepatic metastases at the time of diagnosis that were not amenable to surgical resection and/or radiofrequency ablation therapy were selected for further review. Data collected were age at diagnosis, gender, date of diagnosis, presenting symptoms, whether or not the primary neoplasms were localized and resected, earliest serum chromogranin A values, Karnofsky status at first visit,[13] date of progression of liver disease, treatments received before and after progression of liver disease, and status at last follow-up. Patients with known bronchial and thymic primary neoplasms were excluded.

Date of diagnosis was defined as the date that the patient received the histologic diagnosis of carcinoid neoplasm. Progression of liver disease was defined as either an increase in the number or size of the hepatic metastases, as determined by imaging studies. Time to progression of liver disease was defined as the interval between date of diagnosis and date of the visit during which liver progression was documented.

Table I. Comparison of the primary resected group with the primary nonresected group

Group characteristics	*Primary resected*	*Primary nonresected*	P *value*
No. of patients	60	24	
Gender (M/F)	31/29	12/12	1.00
Mean age at diagnosis	57	60	.29
Foregut primary	2	2	.13
Hindgut primary	2	2	.13
Median Karnofsky functional level	90	80	.25
Median chromogranin A (earliest level)	104	136	.37

Patients were divided into 2 groups on the basis of whether the primary neoplasm had been resected (primary resected group) or not (primary nonresected group). Patients were included in the primary resected group irrespective of tumor size, length of bowel removed, clearance of nodal disease, or presence of carcinomatosis. Gender distribution was compared between the 2 groups with the use of chi-square analysis. Age at diagnosis was compared with the use of the independent sample *t* test. Treatments given before or after liver progression were compared between groups with the use of the Fisher exact test. Karnofsky functional status and chromogranin A level were compared with the use of the Mann-Whitney test. Liver progression-free survival and survival for various groups of patients were calculated with the use of the Kaplan-Meier time to event analysis and compared by the log-rank test.

RESULTS

Eighty-four patients met the criteria, 60 (71%) of whom were in the primary resected group and 24 (29%) in the primary nonresected group. The 2 groups are compared in Table I. There were no differences between the 2 groups with respect to age, gender, or the number of known foregut and hindgut primary neoplasms, earliest chromogranin A level, or Karnofsky functional status at first visit. Primary tumor sites are unknown for 12 patients in the primary nonresected group. Presenting symptoms are compared in Table II. Significantly more patients presented with diarrhea in the primary nonresected group. Treatments given to the 2 groups before liver progression are compared in Table III. There were no significant differences

Table II. Comparison of presenting symptoms between the primary resected group and the primary nonresected group

Presenting symptom	*Primary resected*	*Primary nonresected*	P *value*
Abdominal pain	14	7	.78
Diarrhea	12	12	.02
Bowel obstruction	12	1	.10
Incidental finding	6	0	.17
Flushing	4	1	1.00
Other	5	2	1.00
Unknown	7	1	.43

Table III. Comparison of the treatments received before liver progression between the primary resected group and the primary nonresected group

Group characteristics	*Primary resected*	*Primary nonresected*	P *value*
Octreotide	56 (93%)	22 (92%)	1.00
Systemic chemotherapy	4	3	.40
Interferon	2	0	1.00

between the 2 groups. Nearly all patients received octreotide, and few patients received any other therapy.

Median follow-up was 90 months. To date, 57 (68%) patients have met the criteria for progression of liver disease and 27 (32%) have stable liver disease. Thirty-eight (63%) of these patients were in the primary resected group, and 19 (79%) were in the primary nonresected group ($P = .20$). Figure 1 shows the liver disease progression-free survival curves for the primary resected group and the primary nonresected group. The median time to progression of liver disease in the primary resected group was 56 months, compared with 25 months in the primary nonresected group. The difference was statistically significant ($P < 0.001$).

Treatment administered for liver progression consisted of hepatic arterial infusion plus chemoembolization.[14] This treatment was given to 24 (63%) patients in the primary resected group and 11 (58%) patients in the primary nonresected group ($P = .63$).

Fifty-one (61%) patients were alive at last follow-up and 33 (39%) have died. The causes of death for patients in the 2 groups are shown in Table IV. Seventy-nine percent of all deaths were due to liver failure. There was no significant difference in the proportion of deaths due to liver failure between the 2 groups. No patient in the primary nonresected group died of bowel obstruction. The

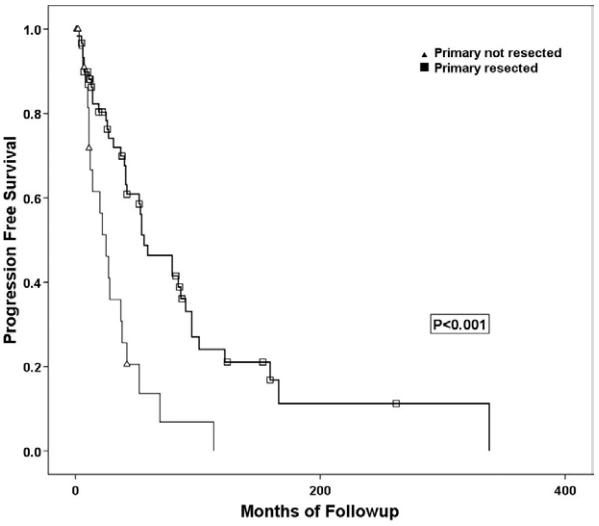

Fig 1. Liver disease progression-free survival curves for the primary resected group (N = 60) and the primary nonresected group (N = 24).

overall survival curve is shown in Figure 2. The median survival time was 90 months; the 5-year survival rate was 63%.

Figure 3 shows the survival curves for the primary resected group versus the primary nonresected group. The median survival for the primary resected group was 159 months and the 5-year survival rate was 81%, compared with a median survival of 47 months and a 5-year survival rate of 21% in the primary nonresected group ($P < .001$).

Six patients were included in the primary nonresected group although they underwent celiotomy; they had no resection because the primary neoplasm was unresectable as a result of neoplastic involvement near the superior mesenteric vessel in 5 patients and massive rectal neoplasm in 1patient. Five of these patients had intestinal bypass and 1 had a colostomy. Because unresectable neoplasms may be associated with a worse prognosis, which could introduce a selection bias, these 6 patients were transferred to the primary tumor resected group and survival was recalculated. This reclassification decreased the observed median time to liver progression to 54 months for the primary resected group but did not change the median time to liver progression of 27 months in the primary nonresected group. The difference between the 2 groups remained statistically significant ($P = .005$). The recalculated survival curves are shown in Figure 4. This analysis decreased median survival from 159 to 108 months in the primary resected group, and increased it from 47 to 50 months in the primary nonresected group. The difference in survival remained statistically significant ($P < .001$).

Table IV. Cause of death in the primary resected group and the primary nonresected group

Cause of death	*Total no. (%) (N = 33)*	*Primary resected (%) (N = 16)*	*Primary nonresected (%) (N = 17)*
Liver failure	26 (79)	12 (75)	14 (82)
Bowel obstruction	2 (6)	2 (12.5)	0
Bowel infarction	2 (6)	0	2 (12)
Other	2 (6)	2 (12.5)	0
Unknown	1 (3)	0	1 (6)

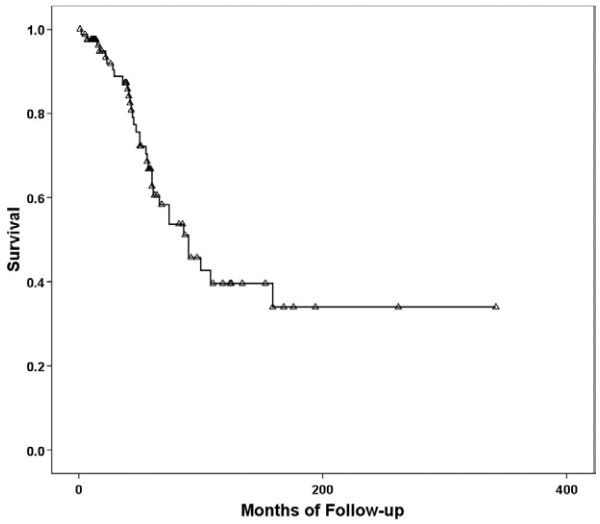

Fig 2. Survival curve for 84 carcinoid patients presenting with liver metastases.

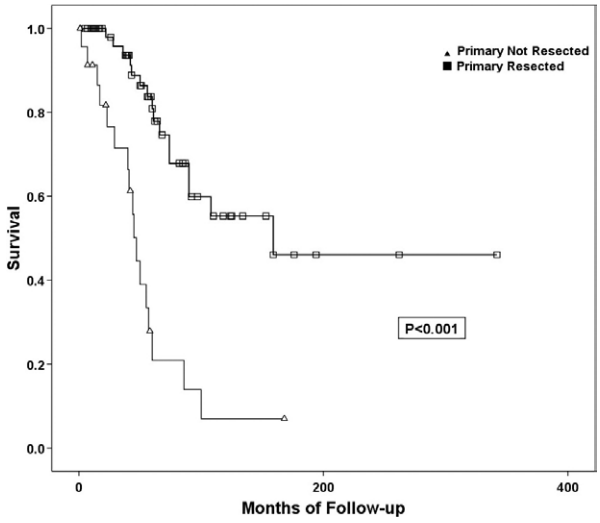

Fig 3. Survival curves for the primary resected group (N = 60) and the primary nonresected group (N = 24).

In an effort to ascertain whether resection of asymptomatic primary neoplasms has an impact on survival, a subsequent analysis was performed in which patients who had operations for symptomatic neoplasms were excluded from the primary resected group. Specifically, 19 patients who presented with bowel obstruction, 13 who presented with other forms of an acute abdomen, and the 6 patients with unresectable neoplasms were censored. The primary resected group then consisted of 2 patients in whom the primary was an incidental finding, 19 in whom the primary had been located during workup, and 7 patients with clinically occult neoplasms found at operative exploration. The survival of these 28 patients was compared with the 18 patients in the primary nonresected group from the previous analysis, which consisted of 6 patients with primary neoplasms found on workup and 12 patients with clinically occult neoplasms. Ten of these patients declined operation, and 8 were not offered an operation by the initial managing physicians. The results of the comparison are shown in Figure 5. The median survival for patients whose asymptomatic primary neoplasms were resected has not yet been reached because the survival rate has not fallen below 56%. The difference between this group

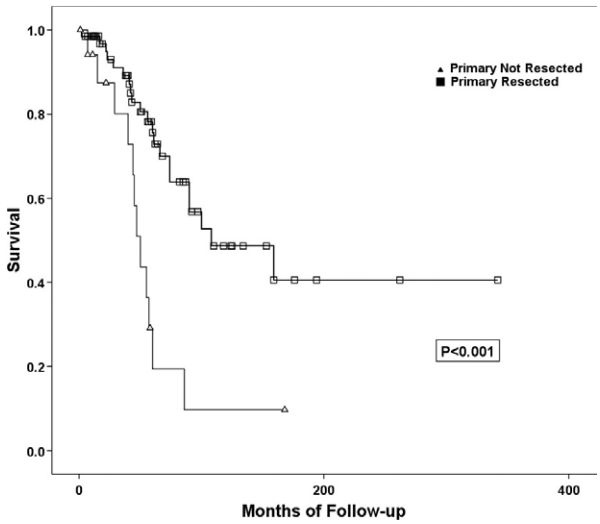

Fig 4. Survival curves for the primary resected group (N = 66) and the primary nonresected group (N = 18) after transferring 6 patients who had unsuccessful attempts at primary tumor resection to the primary resected group.

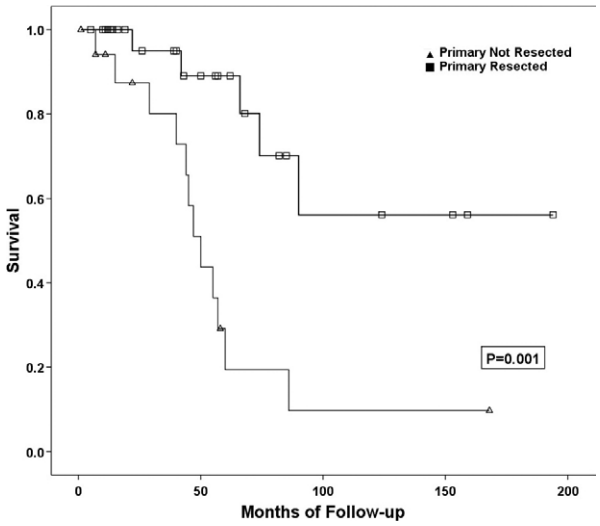

Fig 5. Survival curves for the primary resected group (N = 28) and the primary nonresected group (N = 18) including only patients with asymptomatic neoplasms in both groups.

and the primary nonresected group was statistically significant ($P = .001$).

DISCUSSION

The role of the resection of the primary neoplasm in carcinoid patients who present with liver metastasis has not been completely defined. Resection of the primary is done for patients presenting with bowel obstruction and patients whose liver metastases are resected with curative intent.[10] It is also recommended that symptomatic primary neoplasms be resected to improve quality of life[3] and prevent subsequent obstruction.[4-8] There is no clear recommendation, however, for resection of an asymptomatic primary neoplasm in the presence of unresectable liver metastases.[6,10,11] Furthermore, there is no emphasis on the need for localization of the primary neoplasm in asymptomatic patients with metastatic disease.[9-11]

Recently, Boudreaux et al[4] advocated resection of the primary neoplasm in all patients with abdominal carcinoids, including those with distant metastases. These authors adopted an aggressive operative approach that included exploration of the abdomen in 17% of their patients who had unknown primaries with the intent to locate and resect the primary neoplasm. They were successful in 79% of such cases; however, their rationale was again to prevent intestinal obstruction among patients expected to have long-term survival. This rationale is supported by their median survival of 51 months as well as the median survival of 90 months observed in the present series. This rationale assumes that patients with synchronous liver metastases will, by nature, have long-term survival and that primary neoplasm resection has no impact on liver disease progression and survival.

A report by Hellman et al[12] suggests that resection of the primary neoplasm in patients with liver metastases may have a favorable impact on survival. In that series, patients in whom the primary neoplasm was resected had a median survival of 7.4 years, compared with 4.0 years in patients in whom the primary neoplasm was not resected. These results, however, may reflect the effects of selection biases. Twenty percent of the patients in the series did not have liver metastases. In addition, patients in whom the primary neoplasm is unresectable may have more-aggressive disease, which would be associated with a worse prognosis.

The present study was undertaken to determine whether primary neoplasm resection in the presence of liver metastases has an impact on progression of liver disease and survival. The results indicate that while carcinoid patients with liver metastases can, in general, expect long-term survival, there are major differences in the survival rates associated with whether or not the primary neoplasm has been resected. Patients whose primary neoplasms were not resected had a median survival of 47 months, compared with 159 months for patients whose primary neoplasm was resected—a difference of nearly a decade.

There were no significant differences between these 2 groups with respect to age; gender; treatment with octreotide, interferon, or systemic chemotherapy; or Karnofsky status that might explain the marked difference in survival. Since 12 of the patients were never explored to locate their clinically occult primary neoplasms, there are not enough data for complete comparison of the 2 groups for origin of the primary neoplasm. There were no significant differences, however, between the 2 groups with respect to the number of known foregut and hindgut primary neoplasms, which are considered to be more aggressive than midgut neoplasms.[15-17]

It is unlikely that selection biases can explain the marked observed differences in outcomes in the present series. In contrast to the series reported by Hellman et al,[12] all patients in the present series had liver metastases at diagnosis. It could be argued that a selection bias is occurring if patients with technically unresectable neoplasms, a possible indicator of aggressive disease, are included in the primary nonresected group. To correct for this, all the patients who had unsuccessful attempts at re-

section of their primary neoplasm were transferred to the primary resected group. Despite taking this very conservative approach, analysis still revealed a significant difference in survival. Further subgroup analysis showed that better survival rates are achieved even when asymptomatic primary neoplasms are resected rather than left in place.

The observed difference in survival rates appear to be due to a significant difference in time to progression of liver disease. The primary nonresected group had a median time to liver progression of only 25 months, compared with 56 months in the primary resected group. The majority of deaths in the series were due to liver failure. Interestingly, the only 2 patients to die of intestinal obstruction were in the primary resected group (both due to carcinomatosis). Two deaths in the primary nonresected group were due to bowel infarction. Bowel infarction occurs from encasement and compression of the mesenteric vessels by bulky nodal metastases.[3,10] These deaths might have been prevented or delayed if the primary neoplasms had been resected, possibly in combination with mesenteric nodal debulking as reported by Boudreaux et al.[4]

There are several possible explanations as to how primary neoplasm resection could delay progression of liver metastases. Resection of the primary tumor would remove the source of subsequent liver metastases. Furthermore, carcinoid neoplasms are well-known for their ability to produce amines and peptides that cause carcinoid syndrome, including cardiac and valvular disease,[18,19] and peritoneal fibrosis.[11] Resection of the primary neoplasm may deprive liver metastases of a constant source of hormones and growth factors that accelerate their proliferation.

According to the results of this study, resection of the primary neoplasm may yield better survival rates in carcinoid patients presenting with liver metastases. Liver failure is the chief cause of death in this subgroup of patients, regardless of whether the primary neoplasm is resected. Resection of the primary neoplasm, however, is associated with a longer time to progression of liver metastases, which subsequently translates into a survival advantage of nearly a decade. This survival advantage persists even if unresectable patients are included in the resected group and within the subgroup of patients with asymptomatic primary neoplasms. While a randomized prospective trial would be definitive, it would be difficult to accomplish with this rare disease. On the basis of these retrospective data, resection of the primary neoplasm should be considered for carcinoid patients with liver metastases, even among those whose neoplasms are asymptomatic.

REFERENCES

1. Gore RM, Berlin JW, Mehta UK, Newmark GM, Yaghmai V. GI carcinoid tumours: appearance of the primary and detecting metastases. Best Pract Res Clin Endocrinol Metab 2005;19(2):245-63.
2. Toth-Fejel S, Pommier RF. Relationships among delay of diagnosis, extent of disease, and survival in patients with abdominal carcinoid tumors. Am J Surg 2004;187(5):575-9.
3. Makridis C, Ekbom A, Bring J, et al. Survival and daily physical activity in patients treated for advanced midgut carcinoid tumors. Surgery 1997;122(6):1075-82.
4. Boudreaux JP, Putty B, Frey DJ, et al. Surgical treatment of advanced-stage carcinoid tumors: lessons learned. Ann Surg 2005;241(6):839-45; discussion 845-6.
5. Makridis C, Oberg K, Juhlin C, et al. Surgical treatment of mid-gut carcinoid tumors. World J Surg 1990;14(3):377-83; discussion 384-5.
6. Makridis C, Rastad J, Oberg K, Akerstrom G. Progression of metastases and symptom improvement from laparotomy in midgut carcinoid tumors. World J Surg 1996;20(7):900-6; discussion 907.
7. Partensky C, Landraud R, Velecela E, Souquet JC. [Resection of carcinoid tumors of the small intestine is still indicated in the presence of disseminated hepatic metastases]. Ann Chir 1990;44(1):34-8.
8. Soreide O, Berstad T, Bakka A, et al. Surgical treatment as a principle in patients with advanced abdominal carcinoid tumors. Surgery 1992;111(1):48-54.
9. Clark OH, Ajani J, Benson AB 3rd, et al. Neuroendocrine tumors. J Natl Compr Canc Netw 2006;4(2):102-38.
10. Jensen RT, Doherty GM. Carcinoid tumors and the carcinoid syndrome. In DeVita VT, Hellman S, Rosenberg SA, editors. Cancer, principles & practice of oncology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1559-74.
11. Anthony T, Kim L. Gastrointestinal carcinoid tumors and the carcinoid syndrome. In Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. 7th ed. Philadelphia: Saunders; 2002. p. 2151-68.
12. Hellman P, Lundstrom T, Ohrvall U, et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. World J Surg 2002;26(8):991-7.
13. Karnofsky D AW, Craver L, Burchenal J. The use of nitrogen mustard in the palliative treatment of cancer. Cancer 1948;1:634-56.
14. Diaco DS, Hajarizadeh H, Mueller CR, Fletcher WS, Pommier RF, Woltering EA. Treatment of metastatic carcinoid tumors using multimodality therapy of octreotide acetate, intra-arterial chemotherapy, and hepatic arterial chemoembolization. Am J Surg 1995;169(5):523-8.
15. Kirshbom PM, Kherani AR, Onaitis MW, et al. Foregut carcinoids: a clinical and biochemical analysis. Surgery 1999;126(6):1105-10.
16. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. Cancer 1997;79(4):813-29.
17. Williams ED, Sandler M. The classification of carcinoid tum ours. Lancet 1963;1:238-9.
18. Robiolio PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation 1995;92(4):790-5.
19. Moller JE, Connolly HM, Rubin J, Seward JB, Modesto K,

Pellikka PA. Factors associated with progression of carcinoid heart disease. N Engl J Med 2003;348(11):1005-15.

DISCUSSION

Dr Janice L. Pasieka (Calgary, Alberta, Canada). Thank you for an excellent presentation. You have to admit, though, the retrospective nature in these very diverse and complex patients it is very difficult to tease out whether our surgical intervention truly makes a difference. So I caution on your conclusions, since we all know the bias and the problems with drawing conclusions due to retrospective nature of this study.

What I was surprised to see is that your data on mortality, in particular, that the major mortality was liver failure. I didn't see anybody die of carcinoid heart disease. Do you have the percentage of carcinoid heart disease in each of the groups? And is it true that nobody died of their cardiac disease?

Dr Babak Givi. We have obtained echocardiograms from most of the patients in this study. Some of them do have carcinoid heart disease, but none of them has died of this.

Dr Anders Bergenfelz (Lund, Sweden). One very important thing about determining survival for carcinoid patients which is known to be of great importance is the biochemical markers when you diagnose them. Do you have any data that was that different between the 2 groups?

Dr Babak Givi. Because most of these patients were referred to us after the initial diagnosis, I do not have the exact data on all of them at the time of diagnosis. But as part of our work-up, we monitor all of these patients for those, yes. We do have data for that.

Dr Anders Bergenfelz. Because patients with very high levels of a variety of biochemical markers have the worst prognosis. So that could be a very important factor to analyze.

Dr Babak Givi. Patients with higher serum chromogranin A levels do have a worse prognosis. We did compare serum chromogranin A values between the two groups of patients. The mean chromogranin A value in the primary not resected group was somewhat higher than the mean value in the primary resected group, but the difference was not statistically significant. Therefore, we do not believe this explains the marked difference in outcomes.

Dr H. Richard Alexander, Jr (Baltimore, Md). To resect a small primary tumor in the context of widespread hematogenous metastases and have that translate into an improved survival is almost unprecedented in oncology. Clearly there is an association between taking the primary tumor out and improved survival in this series. I believe this was perhaps being done in the context of a suspected clinical benefit for that particular patient, that is, the decision to operate by a particular surgeon was made because of an understanding of the tumor biology, that favored looking for an asymptomatic primary tumor and taking it out.

What we really don't know here is, what is the real cause of the improved survival? So my question would be whether or not you looked in some detail at potential differences in the tumor biology of the liver metastases between the groups, the number of metastases, the size of metastases, the rate of tumor progression in the groups that had received surgery and those that did not.

You can look at that group that had the unresectable tumors at the time of laparotomy and view them as your control group for the fact that perhaps surgery was of no benefit. You showed that in five individuals the decision to operate was made but they had unresectable primary tumors at the time of laparotomy. Interestingly, they did as well as the others who had their tumor resected and apparently better than those who did not undergo resection. If you had operated on all of the people and not taken the tumors out, they might have done just the same as those five did who underwent operation with intent to resect but were found to have unresectable disease. So I just wanted your comments on the stage of disease in the liver and whether or not they were truly comparable between those who underwent surgery and those who did not?

Dr Babak Givi. We used the serum chromogranin A level as a surrogate for the volume of liver disease because serum chromogranin A levels do correlate with disease burden in patients. Again, we found no significant difference between the two groups, so we think the two groups are comparable in terms of liver disease and overall tumor burden.

Dr H. Richard Alexander, Jr. You may want to evaluate size of tumors, number of metastases, and percent hepatic replacement between the 2 groups. I just didn't see it. If it was there, I may have missed it. But did you look at the tumor burden between the 2 groups to see if they were comparable?

Dr Babak Givi. I don't know if I have enough data for that. Sometimes I do not have the imaging studies before.

Dr Sanziana Roman (New Haven, Conn). I found this very interesting because the is certainly a lot of data on resections of primary tumors which then lead to progression of the metastatic disease at accelerated rates which led some to postulate and look for suppressor tumors that the primary tumors might actually secrete.

The question I have is, did you look at what kind of a resection people had, meaning were people having an oncologic resection or were they simply having a local resection to prevent complications?

Dr Babak Givi. Not all of the patients had oncologic resections. Some had just local resection to remove only the primary tumor.

Dr Sanziana Roman. Just a quick follow-up. I think one might postulate if you simply take out the disease in the bowel but you are leaving lymphatic disease so you still have intraperitoneal disease, it sort of doesn't really make sense why this would make a difference.

Dr Babak Givi. All I can say is that this retrospective data is very provocative. Why take a small primary tumor out when there are liver metastases? How will this change the biological behavior of the tumor? This is open to debate. The primary tumor may be a source of new hepatic metastases and it may be a continuing source of hormones that influence the growth of hepatic metastases. We should not make assumptions about the effect of leaving behind disease in lymph nodes. For breast cancer, it was always believed that positive lymph nodes were a source of subsequent distant metastases until the National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 study showed that they were not.