

Giant Cavernous Liver Hemangiomas

Effect of Operative Approach on Outcome

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Hypothesis: The choice of operative technique for resection of giant cavernous hepatic hemangiomas has an effect on outcome.

Design: Case series.

Setting: Tertiary hepatobiliary surgery–liver transplantation service.

Patients and Interventions: Fifty-two adult patients who underwent resection of symptomatic hepatic hemangiomas (38 [73%] in the right lobe; average diameter, 10.9 cm) by means of lobectomy or enucleation, with or without Pringle inflow occlusion.

Main Outcome Measures: Blood transfusion, morbidity, mortality, and length of hospitalization.

Results: Patient age and sex and the size of hemangiomas were similar for patients who underwent lobectomy and enucleation. Right-lobe lesions were more often treated by enucleation, and inflow occlusion was used more frequently; transfusion requirements and length of hospitalization were similar for both techniques. Complications were more frequent after lobectomy. There were no deaths. In the latter years of the series, enucleation was used in 22 (63%) and inflow occlusion in 24 (69%) of 35 patients.

Conclusions: Outcome is related to the operative approach used for resection of giant cavernous liver hemangiomas. Although lobectomy and enucleation are curative, enucleation offers greater preservation of normal hepatic parenchyma and fewer complications and is the preferred technique for suitable lesions.

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CAVERNOUS HEMANGIOMAS are the most common benign tumors of the liver.¹ The lesions, which may be single or multiple, are thought to be vascular malformations that enlarge by means of ectasia rather than neoplastic growth.² Lesions of greater than 4 cm have been referred to as giant hemangiomas.³

Although most hemangiomas are asymptomatic and may be managed safely with observation alone, larger lesions may produce a variety of symptoms and signs, including pain (abdominal, back, or shoulder), fullness, early satiety, nausea, vomiting, and fever. Kasabach-Merritt syndrome, with thrombocytopenia secondary to platelet trapping within the hemangioma, also may occur. Surgical resection provides the only consistently effective method of treatment and is indicated for symptomatic lesions in patients with an acceptable surgical risk and lesions for which a diagnosis is equivocal despite appropriate preoperative evaluation.²

Before the late 1980s, resection of hemangiomas was performed by means of wedge excision or anatomic lobectomy. Enucleation was first described by Alper et al⁴ in 1988 and is based on the macroscopic observation that the lesions are well circumscribed, with a sheath of compressed liver tissue clearly defining the border between the cavernous tissue and normal liver parenchyma.⁵ The purported benefits of enucleation include less operative blood loss and a reduced risk of biliary leaks.⁶ The present study was undertaken to compare the results of surgical excision of cavernous hemangiomas by means of enucleation or lobectomy in a tertiary hepatobiliary center.

METHODS

We performed retrospective review of the records of all patients who underwent operative resection of hepatic hemangiomas by a single surgical team at the Dumont-UCLA Transplant Center, University of California–Los Angeles, between January 1, 1990, and October 17, 2003. Indications for operation included ab-

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dominal pain, enlarging hemangioma, uncertainty of diagnosis, and Kasabach-Merritt syndrome. Variables selected for analysis included age, sex, size and location of lesion, operative approach, operative time, intraoperative transfusion requirement, pathological examination findings, duration of hospitalization, morbidity, and mortality. Patients were then divided into 2 groups, depending on the operative approach (lobectomy vs enucleation) for further analysis. Data were collected in accordance with requirements of our institutional review board.

Statistical analyses were performed using the *t* test for continuous variables and χ^2 test with the Yates correction for categorical variables. Continuous variables were expressed as mean \pm SD. A *P* value of less than .05 was considered significant.

OPERATIVE TECHNIQUES

Our group uses a standard operative approach for all hepatobiliary procedures. The abdomen was explored through a chevron incision. The liver was mobilized by division of ligamentous attachments; care was taken to preserve the left triangular ligament in cases of right lobectomy. The hemangioma was identified, and a decision as to the type of resection was made, based on the location of the lesion(s) and size in relation to the volume of normal parenchyma. To reduce bleeding in larger resections or enucleations, a Pringle maneuver was performed by placing a noncrushing vascular clamp across the porta hepatis. Inflow was occluded for no more than 20 minutes, at which point the clamp was released and the liver perfused for 5 minutes; if necessary, the clamp was then reapplied. Inflow occlusion to allow for ischemic preconditioning was not used, nor were total vascular isolation, *ex situ* excision, and transplantation.

After completion of the operative resection, an omental pedicle was often placed in the resection bed, and a closed suction drain was inserted to monitor for bile leakage. Prophylactic antibiotics were administered for 24 hours perioperatively.

LOBECTOMY

We applied a standard technique in which inflow vessels were ligated, followed by ligation of hepatic veins and transection of parenchyma. For transection, we used a variety of devices including electrocautery, a cavitation ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, Colo), and dissecting sealer (TissueLink Medical Inc, Dover, NH). Silk or polypropylene ligatures were used for identified blood vessels. After the hepatic parenchyma was removed, residual bleeding sites were controlled with sutures or the hemostatic devices used during parenchymal division. A half-strength solution of hydrogen peroxide was applied to the parenchymal surface to identify leaking biliary radicles.

ENUCLEATION

As for lobectomy, Pringle occlusion was used selectively. The capsule of the liver was incised with electrocautery to demarcate the extent of the resection and to initiate the development of a plane between the hemangioma and the hepatic parenchyma. The cleavage plane was developed further with electrocautery and blunt dissection. Vessels were controlled with silk or polypropylene ligatures. On completion of enucleation, the vascular clamp was removed from the hilum, and the residual cavity was packed and compressed manually. The cavity was then treated in a fashion similar to that used for the parenchymal bed after lobectomy.

RESULTS

During the study period, 52 patients underwent surgical removal of cavernous hepatic hemangiomas. Aver-

Table 1. Characteristics of Patients and Hemangiomas*

	Operative Groups		<i>P</i> Value
	Enucleation (n = 27)	Lobectomy (n = 25)	
Female	26 (96)	20 (80)	.09
Male	1 (4)	5 (20)	
Age, y, mean \pm SD	45 \pm 9.2	51 \pm 10.5	.08
Lobe			.01
Right	24 (89)	14 (56)	
Left	3 (11)	11 (44)	
Single lesion	21 (78)	24 (96)	.10
Multiple lesions	6 (22)	1 (4)	
Diameter, mean \pm SD, cm	10.1 \pm 5.3	11.6 \pm 4.3	.28

*Unless otherwise indicated, data are expressed as number (percentage) of patients.

Table 2. Operative Variables and Outcome

	Operative Groups		<i>P</i> Value
	Enucleation (n = 27)	Lobectomy (n = 25)	
Cholecystectomy, No. (%)	11 (41)	13 (52)	.58
Inflow occlusion			<.001
No. (%) of patients	21 (78)	4 (16)	
Duration, mean \pm SD, min	23 \pm 12	15 \pm 9	.18
Operative time, mean \pm SD, min	174 \pm 72	198 \pm 65	.22
Transfusion			.32
No. (%) of patients	4 (15)	7 (28)	
Mean No. of units	3.3	4.4	.22
Complications, No. (%)	3 (11)	11 (44)	.01
Hospitalization, mean \pm SD, d	6.9 \pm 2.2	8.7 \pm 4.1	.06

age age was 48 years (range, 31-79 years), and 46 patients (88%) were women. The lesion was located in the right lobe in 38 patients (73%) and in the left lobe in 14 patients (27%). Hemangiomas were single in 45 patients (87%) and multiple in 7 (13%). Average diameter was 10.9 cm (range, 3-23 cm).

Resection was performed using enucleation in 27 patients and lobectomy in 25 patients. We compared patients and lesions by operative technique in **Table 1**. Age and sex were similar in both groups. Right-lobe lesions were more frequently treated by means of enucleation and left-lobe lesions by means of lobectomy. Choice of operative technique was unrelated to the number or size of lesions.

Operative variables and outcome are compared in **Table 2**. Pringle inflow occlusion was used far more frequently for enucleations than for lobectomies, whereas cholecystectomy was performed with similar frequency in both groups. Duration of Pringle occlusion, operative times, use of blood transfusion, and duration of hospitalization also were similar for both operative techniques. No enucleations were converted to lobectomies.

There were no deaths. Complications, which occurred in 14 patients (27%), were significantly more com-

mon after lobectomy than enucleation. Complications of enucleation included ileus, pleural effusion, and urinary tract infection in 1 patient each. Complications of lobectomy included bile leaks in 2 patients (requiring reoperation in 1), ileus in 3, elevated coagulation values requiring phytonadione (vitamin K₁) administration in 3, and wound infection, anginal attack, and fever in 1 each.

When analyzed by location of hemangioma in the right or the left lobe, rather than by operative technique, complications and operative times were not significantly different. Complications were found to occur in 11 patients with right-lobe lesions and 3 patients with left-lobe lesions (29% vs 21%; *P* = .73). Operative times were longer for the right lobe, but the difference did not achieve statistical significance (194 ± 68 vs 161 ± 68 minutes; *P* = .13).

Analysis by the period in which the operations were performed showed significant evolution in operative techniques during the 14 years of the series (**Table 3**). When we compared the second 7-year period with the first, enucleation replaced lobectomy as the dominant method of resection. Similarly, inflow occlusion was used once in the earlier period and in more than two thirds of patients in the later.

COMMENT

Cavernous hemangiomas occur with a prevalence of 0.4% to 7.3% in autopsy series.¹ The lesions have female predominance and are seen in all age groups but most fre-

Table 3. Evolution of Technique*

	1990-1996 (n = 17)	1997-2003 (n = 35)	<i>P</i> Value
Enucleation	5 (29)	22 (63)	.04
Lobectomy	12 (71)	13 (37)	
Inflow occlusion	1 (6)	24 (69)	<.001

*Data are expressed as number (percentage) of patients.

quently in the third, fourth, and fifth decades of life. Diagnosis is confirmed by results of noninvasive radiological studies. Dynamic contrast-enhanced magnetic resonance imaging is the best study, as it will identify smaller and/or multiple lesions.⁷ Radionuclide-labeled red blood cell scintigraphy identifies larger lesions and those not immediately adjacent to blood vessels. Dual-phase computed tomography also is an acceptable test but may not distinguish hemangioma from a malignant tumor. Operative resection is indicated for symptomatic lesions and for those in which a diagnosis cannot be made.

Resection of a hepatic hemangioma was first reported by Hermann Pfannenstiel in 1898 and remains the only consistently effective method of treatment.⁸ Irradiation therapy has been reported to provide partial reduction in size and relief of symptoms, but has risks, including radiation hepatitis, veno-occlusive disease, and hepatoma.⁹ Hepatic artery embolization has been used rarely for poor operative candidates, with some success in reducing the size of the lesion.¹⁰

In 1980, Starzl and coworkers¹¹ reported 15 resections for liver hemangiomas (10 anatomic and 5 wide excisions) with no mortality and little morbidity. These authors recommended operative exploration rather than needle biopsy when the diagnosis was equivocal. They also discouraged use of palliative arterial embolization or ligation in favor of definitive excision by experienced liver surgeons. In a retrospective review, Trastek et al¹² studied the natural history of a group of 49 lesions larger than 4 cm and showed that nonoperative management was safe for asymptomatic hemangiomas. Successful excision by means of anatomic resection or wedge excision was reported in other series as well.^{8,13,14}

In 1988, Alper et al⁴ described a new technique for hemangioma enucleation by means of dissection in a fibrous cleavage plane between the capsule of the hemangioma and surrounding normal liver tissue. This technique avoided the need to resect normal liver parenchyma and minimized damage to blood vessels and bile ducts.

The present series analyzed the outcome for 52 patients who underwent surgical excision of giant cavern-

Table 4. Collected Series Comparing Enucleation and Lobectomy for Hepatic Hemangiomas

Source	No. of Patients	No. Undergoing			No. of Complications	Mortality, %
		Operation	Enucleation	Lobectomy		
Alper et al, ⁴ 1988	9	9	9	0	2	0
Lise et al, ¹⁵ 1992	51	25	15	10	2	0
Baer et al, ⁵ 1992	10	10	9	1	1	0
Petri et al, ¹⁶ 1993	50	50	29	21	13	0
Kuo et al, ⁶ 1994	20	20	10	10	2 (Lobectomy)	0
Farges et al, ¹⁷ 1995	163	7	2	5	1	0
Duron et al, ¹⁸ 1995	6	6	6	0	2	0
Pietrabissa et al, ¹⁹ 1996	78	16	11	5	1 (Lobectomy)	0
Weimann et al, ²⁰ 1997	69	69	26	43	13	0
Demiryurek et al, ²¹ 1997	23	23	21	2	3	0
Gedaly et al, ²² 1999	28	28	23	5	12	0
Ozden et al, ²³ 2000	171	42	33	9	9	1
Popescu et al, ²⁴ 2001	57	57	38	19	6	0
Yoon et al, ²⁵ 2003	115	52	31	21	13	0
Present series	52	52	27	25	3 (Enucleation) 11 (Lobectomy)	0

ous hemangiomas by means of enucleation (27 patients) or lobectomy (25 patients) during a 14-year period. There were no deaths. Complications, which occurred in 14 patients (27%), were significantly more common and more serious after lobectomy. Operative times were shorter and transfusion requirements were lower in the enucleation group, but these differences did not reach statistical significance. In the second half of the study, enucleation replaced lobectomy as the dominant method of resection, and Pringle inflow occlusion was used in most cases.

Operative series comparing enucleation and lobectomy are shown in **Table 4**. The first comparative report by Kuo et al⁶ found less blood loss and fewer complications in the enucleation group. Subsequent series have confirmed that enucleation can be performed with no mortality, less blood loss, elimination of the need for hepatic venous outflow occlusion, and preservation of normal hepatic parenchyma.²⁵ Large lesions occupying most of a lobe or located deeply within the hepatic parenchyma can be difficult to enucleate and are better managed by means of anatomic lobectomy.¹⁹

A recent report from a hepatobiliary and liver transplantation center in Japan analyzed experience with 1056 consecutive hepatic resections in 915 patients.²⁶ There was no mortality, but overall morbidity (39%) and major morbidity (5.6%) suggest that less radical procedures should be used for benign tumors if possible.

Although our data show that hemangiomas may be treated by lobectomy or enucleation with excellent results, our current practice favors enucleation in most cases, as we find the need for lobectomy to be rare, even with right-lobe lesions in posterior locations. Pringle occlusion minimizes operative blood loss during dissection. Anatomic resection is now reserved primarily for lesions that occupy most of segments 2 and 3 and for those in which diagnosis is uncertain.

Our experience and that of others identifies a modern strategy for management of cavernous hepatic hemangiomas. Most are asymptomatic, without malignant potential or propensity for rupture or other complications, and may be treated safely with observation alone. For symptomatic lesions or when diagnosis is equivocal, operative resection is advised and may be accomplished by means of simple enucleation or anatomic lobectomy. Enucleation is preferred when feasible, as it preserves hepatic parenchyma and minimizes complications. Lobectomy is reserved for lesions that cannot be enucleated safely.

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DISCUSSION

Steven C. Stain, MD, Nashville, Tenn: As expected, the authors from the UCLA Transplant Center have reported excellent clinical results. To briefly review this series, they treated 52 patients with giant hemangiomas over 14 years without mortality. They have been very demanding in the analysis of their own complications, which was 27%, and have included such complications as ileus or the need to administer vitamin K postoperatively. Over the length of this series, they have evolved to their current practice of favoring enucleation over lobectomy and utilizing Pringle occlusion to minimize operative blood loss. Total vascular exclusion was never utilized.

It is difficult to be critical of their techniques, their results, or the recommendations that come out of this analysis. I have several questions for Dr Hiatt to address. In the manuscript you list 4 indications for operation: abdominal pain, enlarging hemangioma, uncertainty of diagnosis, or the Kasabach-Merritt syndrome. What were the proportions of the patients who were treated because of an expanding lesion or uncertainty of diagnosis? How much of an increase in size do you require before you recommend resection? Are you recommending observation of all asymptomatic patients irrespective of size? Lastly, although it was not the emphasis of this series, can you give us an idea of the denominator? How many asymptomatic patients were not operated upon?

Theodore X. O'Connell, MD, Los Angeles, Calif:

Number one is regarding the indications. When they mentioned that most hemangiomas are asymptomatic, that certainly is true. Even though we talk about 4 cm as being giant, that is just by common acceptance. That doesn't mean that 4-cm ones need to be resected. Most of them are asymptomatic and don't bother the patients. On the asymptomatic patients, how hard do you look for other causes of their symptoms? In how many of the patients after they had their hemangioma removed did their symptoms abate? Was it something else that was causing their symptoms but was blamed on the hemangioma?

Second, even though this is interesting, it is an apples-and-oranges type of comparison. This is not a randomized prospective study. First of all, you have the problem with time. Most of the lobectomies were done early on, when techniques were different, postoperative care perhaps was different, and so forth. Later on, the enucleation came into being, so time has an impact. The other thing is that I don't think any of us try to do a formal lobectomy in any kind of hemangioma. This is not a malignancy. We don't need to have a margin. Maybe we may call it lobectomy, but it truly is a very limited resection, ie, enucleation. However, not all hemangiomas can be treated with enucleation due to size and location. Obviously, when a formal lobectomy is performed, it is often because the hemangioma is so large that it really requires a lobectomy, since the hemangioma fills the entire lobe. There are a lot of apples-and-oranges type of comparisons here.

The next question is regarding complications. Even though there is a difference in complications, a lot of these don't look like they are related to the liver surgery. They are related to surgery in general, ileus, wound infection, etc, so it's not a complication of lobectomy per se. The bile leaks may be a complication of the liver surgery, but certainly the other ones could be a complication of any operation, so how can it be blamed on lobectomy vs enucleation?

The fourth item is that there was a 3- to 4-U transfusion requirement in both lobectomies and enucleations. Do you use a cell saver to cut down on blood from the bank, because obviously this is not a malignancy and this could be a place where cell savers could be used.

Robert C. Lim, MD, San Francisco, Calif: Would the authors comment on the role of selective embolization in preparing the patient for surgery to minimize blood loss? As surgeons, when we operate on the liver, one of the major problems is bleeding. If one can selectively embolize the hemangioma, enucleation or lobectomy might be a bit safer.

Lawrence D. Wagman, MD, Duarte, Calif: It occurs to me that many times when you are evaluating patients for benign disease, like right upper quadrant pain, they turn out to have gallstones. You then inadvertently find a 3- or 4-cm hemangioma. I wonder how the authors would deal with this particular patient where the symptoms could be from either or from both.

Nancy L. Ascher, MD, PhD, San Francisco: I also had a question about the pain issue and follow-up in these patients. When pain is the main indication for enucleating these le-

sions, I have seen a number of patients who have had large right-lobe lesions and small left-lobe lesions. Patients undergo resection of the right-lobe lesion, and the left-lobe lesion starts to grow a little bit. What is your follow-up with these patients, and what happens when the same patient comes back to you complaining of, once again, abdominal pain?

Bruce E. Stabile, MD, Torrance, Calif: The authors have well demonstrated the safety and efficacy of enucleation over lobectomy, but I think we could look at this whole problem from a slightly different perspective and that would be more from the basis of intention to treat. The question then would be were there any lesions that were enucleated that in retrospect should have been treated by lobectomy because of an incorrect preoperative diagnosis, and were any such patients inadequately treated by enucleation?

Paul D. Hansen, MD, Portland, Ore: Granted, most of these lesions in this paper were quite large and a technique like radiofrequency ablation wouldn't play much of a role, but do you see a potential role for ablation in the symptomatic patient with the smaller lesion?

Dr Hiatt: I would like to point out also that this is Dr Busuttil's series. I take responsibility for the scientific presentation but cannot take credit for the operative results.

To Dr Stain's questions first, which I'll answer in a group. Regarding indications for operation and the problem of pain, there is an old adage that if you operate for pain, that is what you will find. Dr Stain asked about a percentage of patients who were treated because of an expanding lesion or uncertainty of diagnosis. We don't have the exact numbers, but the great majority were referred because of abdominal symptoms, most often abdominal pain. Uncertainty of diagnosis was uncommon. Ours is a referral practice; most patients were screened by hepatologists and often surgeons and sent for strong consideration for operative exploration. It doesn't mean we operated on every patient, but that is the slant of the series, rather than a sampling of a large group of patients who happen to have hemangioma.

Dr O'Connell made a very important point related to Dr Stain's question about increase in size required before recommending resection. Dr O'Connell's point was that although 4 cm is defined as giant, in point of fact the mean diameter in our series was almost 11 cm, and a 4-cm lesion picked up as an incidental finding in most instances is best left untouched. Lesions reported are symptomatic and 10 cm or more in size in most instances.

We recommend observation of asymptomatic lesions irrespective of size. Lesions may expand because of bleeding into the tumor but have minimal risk of rupture. In the lesions that are expanding and approach 10 cm in size, we would recommend exploration.

Some patients are operated for what we call "peace of mind," obviously an indication that should be used very selectively. There are patients who are referred because they have been told that they have a liver tumor and are fixated on the idea that this is something that may become cancer. That is not the case; malignant degeneration does not occur, but sometimes they can't be dissuaded from that notion.

Dr Stain asked how many asymptomatic patients were observed without operation. I don't have that number.

Dr O'Connell had a number of questions about operative indications. He made the important point that you have to look very judiciously for other causes of abdominal pain in these patients and be absolutely assured that you have ruled out all other identifiable or treatable causes before resection of a hemangioma.

The patients are all followed by us, and persistence of symptoms has been rare. Occasional patients have been seen with new hemangiomas.

Dr O'Connell, these were anatomic lobectomies, as described in detail in the manuscript. Regarding complications,

we tried to be as inclusive as possible. The critical point is that bile leak is a complication of lobectomy. We have not had a bile leak after enucleation and, to my knowledge, none has been reported in the literature. So there is a distinction that can be drawn between complications of lobectomy and enucleation.

Regarding transfusion, the units shown were in the patients who received transfusion. Overall, a small number of patients were transfused. We have not used the cell saver in these patients. There may be an occasional patient, for example, a reoperation, where one might anticipate a large blood loss and use the cell saver. It has not been our practice to do that routinely.

Dr Lim asked about the role of selective embolization. While there may be a place for this in a large hemangioma, perhaps multiple hemangiomas, we have not utilized it in our series.

Dr Wagman asked about a small lesion found incidentally in a gallbladder patient. Most often we would treat the biliary problem and leave the hemangioma alone. But if the le-

sion is on the capsule of the liver, even if small, we have tended to favor enucleation because we believe that these have the propensity to produce symptoms.

Dr Ascher asked about the problem of a patient who has had resection of a right-lobe lesion and returns with a left-lobe lesion and abdominal pain. I refer to my comments about size of the lesion and a judicious attempt to identify other causes of abdominal pain.

Dr Stabile asked about intention to treat and whether any enucleations in retrospect should have been resected by lobectomy. We haven't seen such a patient in this series; it shouldn't occur with proper operative selection and technique.

Finally, a question from Dr Hansen about radiofrequency ablation. We do RFA in cancer patients but have no experience with the technique for hemangioma. Any kind of a needle biopsy of these lesions has been discouraged because of a risk of bleeding.

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ARCHIVES OF INTERNAL MEDICINE

A Randomized Controlled Trial of Test-and-Treat Strategy for *Helicobacter pylori*: Clinical Outcomes and Health Care Costs in a Managed Care Population Receiving Long-term Acid Suppression Therapy for Physician-Diagnosed Peptic Ulcer Disease

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Background: Guidelines recommend *Helicobacter pylori* (HP) testing and treatment for patients with a history of peptic ulcer disease (PUD), assuming that PUD has been documented and that successful HP eradication would eliminate the need for further therapy and medical utilization.

Methods: An open-label, randomized controlled trial in a managed care setting evaluated the clinical outcome and costs of an HP test-and-treat (T & T) strategy in 650 patients receiving long-term acid suppression therapy for physician-diagnosed PUD. Patients were randomized to T & T for HP (n=321) or to usual care (n=329). Outcome measures included presence and severity of PUD symptoms, use of acid-reducing medication, and acid-peptic-related health care costs during 12-month follow-up.

Results: Only 17% of study participants had PUD confirmed by radiography or endoscopy; only 38% of the T & T group tested positive for HP. At 12 months, patients in the T & T group were less likely to report ulcerlike dyspepsia or use of acid-reducing medication; however, 75% of the T & T group used acid-reducing medication during the second half of the 12-month follow-up. In the 12 months after randomization, the T & T group had higher total acid-peptic-related costs than the usual care group.

Conclusions: Most patients receiving long-term acid suppression therapy for physician-diagnosed PUD in community practice settings are likely to have HP-negative, uninvestigated dyspepsia. Routine testing and treating for HP will not reduce acid-peptic-related costs and have only a modest (though statistically significant) effect in reducing clinical symptoms and use of acid-reducing medications. (2003;163:1165-1171)

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