Background: Accurate staging of malignant tumors in the liver has major implications in defining prognosis and guiding both surgical and nonsurgical therapy. Intraoperative ultrasound in open surgery compares favorably with computed tomography (CT) in the detection of liver tumors; however, there is little experience with laparoscopic ultrasound (LUS).

Hypothesis: Laparoscopic ultrasound is more sensitive than triphasic CT for detecting primary and metastatic liver tumors.

Design: Prospective study.

Setting: University hospital.

Patients: Fifty-five patients with a total of 222 lesions, including primary and metastatic liver tumors, who underwent both CT examinations and LUS as a part of a tumor ablation procedure.

Interventions: Triphasic spiral CT scans of the liver were obtained within 1 week before surgery. Liver LUS was performed with a linear 7.5-MHz side-viewing laparoscopic transducer.

Results: The LUS detected all 201 tumors seen on preoperative CT and detected 21 additional tumors (9.5%) in 11 patients (20.0%). These tumors missed by CT ranged in size from 0.3 to 2.7 cm. Smaller tumors tended to be missed by CT scan (28.6% of the lesions <1 cm, 15.8% of those 1-2 cm, 4% of those 2-3 cm, and 0% of those >3 cm), as did those in segments III and IV. There was good correlation between the size of lesions imaged by the 2 modalities (Pearson $r$=0.86; $P$<.001).

Conclusion: Laparoscopic ultrasound offers increased sensitivity over CT for the detection of liver tumors, especially for smaller lesions. This study documents the ability of LUS in detecting liver tumors and argues for more widespread use in laparoscopic staging procedures.
PATIENTS AND METHODS

Between December 1996 and March 1999, 55 patients with either primary or metastatic liver tumors underwent laparoscopic inspection and LUS as a part of a tumor ablation procedure. Most of these patients were enrolled in an institutional review board–approved phase II safety and efficacy trial. All patients had liver-predominant disease and a life expectancy of greater than 6 months. Preoperative triphasic (noncontrast, arterial, and portovenous) spiral CT examinations were obtained on all patients within 1 week of surgery. Scans were performed on a CT scanner (High Speed Advantage or CTi; General Electric Co, Milwaukee, Wis) with a tube voltage of 120 kV and a tube current of 250 mA. The following standard protocol for image acquisition and contrast injection was used in all cases to obtain images during the arterial and portovenous phases. Seven-millimeter slices were obtained throughout the liver without contrast injection. After the noncontrast images were obtained, 150 mL of 30% iopamidol (Isovue 300) was injected at a rate of 3 mL/s by means of a mechanical injector. Scanning for contrast-enhanced images was started 25 seconds (for hepatic arterial phase) and 70 seconds (for portovenous phase) after initiation of contrast injection. On the High Speed Advantage CT scanner, arterial-phase scanning was performed with 1.3 to 1.6 pitch, while portovenous and noncontrast-phase scanning was done with 1 pitch. With the CT1 scanner, all of the phases were obtained with 1.5 pitch. The maximal diameter of each visible lesion was measured on the CT image by means of on-screen cursors in the CT suite. The location of the lesion was determined with the Couinaud segmental anatomic mapping system.12

Laparoscopic inspection and LUS were performed under general anesthesia with endotrachial intubation. Patients were placed on the operating table in the supine position. One gram of cefazolin sodium was administered as surgical prophylactic antibiotic. A 12-mm camera port was placed to the right of midline between the umbilicus and the costal margin under direct vision by means of a port system (Optiview; Ethicon Endo-Surgery, Cincinnati, Ohio). After pneumoperitoneum was established, a second 10-mm port was placed under direct vision for the ultrasound probe. Adhesions resulting from previous abdominal procedures, including anastomotic liver resection in some cases, were taken down laparoscopically when necessary to expose the surface of the liver. A third 3-mm port was placed under direct vision only when an additional operating port was needed. Liver ultrasound was performed with a rigid linear 7.5-MHz side-viewing LUS transducer (Aloka Co Ltd, Wallingford, Conn). All ultrasound examinations were performed and interpreted by a single surgeon (A.E.S.). A systematic ultrasonographic inspection of the liver with the hepatic and portal veins used as anatomical landmarks was performed on all patients before any ablative procedure. Biopsy of one or more of the lesions was performed for histological confirmation by frozen section before ablation of tumors by means of a spring-loaded needle (Tru-Cut; Micravasive, Natick, Mass). Lesions visible on LUS were mapped in a similar fashion to the CT mapping by means of the Couinaud segmental anatomy defined by the hepatic and portal venous anatomy.12 The maximal diameter of each lesion was measured on the LUS image directly with an on-screen cursor and printed for documentation purposes. For lesions apparent on both preoperative CT and LUS, we compared the maximal diameter. Those that were only visible on LUS were assigned 0 for the CT diameter for the analysis. Postoperative CT scans at 1 week were obtained to confirm that ablation zones successfully encompassed the lesions as well as a 1-cm rim of normal liver. The patients were followed up with triphasic CT scans every 3 months.

Statistical analysis was carried out for both individual lesions and individual patients. Correlation of size determined by CT and LUS was analyzed by linear regression analysis to calculate the Pearson product moment correlation coefficient. Other statistical analysis was carried out with analysis of variance or a paired t test. Differences were considered significant at P<.05.

RESULTS

During a 2-year period, 55 patients with a total of 222 tumors in the liver underwent laparoscopic inspection and LUS. There were 20 women and 35 men in the study. The average age of the patients was 56.9 years, with a range of 26 to 86 years. The majority of patients had previous abdominal procedures, including 3 patients who had previous liver resection. Biopsy confirmed the presence of hepatic malignant neoplasms in all patients. The histological findings of the tumor were adenocarcinoma (predominantly from a colorectal primary tumor) in 25 patients, metastatic neuroendocrine tumors (with or without symptoms from hormone secretion) in 15 patients, primary hepatocellular carcinoma in 9 patients, and metastatic sarcoma in 5 patients. One patient had a melanoma metastatic to liver (Table 1). Most patients were participants in a phase II safety and efficacy trial and were determined to have unresectable disease by preopera-
tive imaging studies because of known bilobar disease or anatomical invasion of major vascular structures. Some patients with unilobar hepatic tumors or a single tumor were determined not to be resection candidates because of major medical comorbidities.

The average number of tumors treated per patient was 4 and varied from 1 to 14. All of the additional tumors found by LUS were ablated, as were the tumors targeted for treatment on the basis of the preoperative CT scan. The average size of the lesions on CT scan was 2.27 cm and ranged from 0.50 to 10.00 cm. The average size of the lesions on LUS was 2.41 cm and ranged from 0.30 to 8.00 cm. Twenty-one (9.5%) of the 222 hepatic tumors were seen only by LUS (Table 2). The extent of disease was staged upward in 11 (20.0%) of 55 patients. The LUS examination resulted in a finding of additional tumors in 40.0% of patients with sarcoma, 33.3% of patients with adenocarcinoma, and 11.1% of patients with hepatocellular carcinoma (Table 1). The tumors seen only on LUS ranged in maximal diameter from 0.3 to 2.7 cm. These lesions were distributed throughout the liver, but significantly more tumors were missed in segments III and IV than the other segments (P = .007). Fourteen (67%) of the 21 missed lesions were adjacent to the falciform ligament or on the surface of the liver.

The sensitivity of triphasic spiral CT scan for detection of hepatic tumors varied with the size of the tumor. The sensitivity for tumors less than 1 cm in maximal diameter was 71.4%, for those between 1 and 2 cm it was 84.2%, and for those between 2 and 3 cm it was 96.1%. For tumors measuring more than 3 cm in maximal diameter, the sensitivity of triphasic CT scanning was 100% (Figure 3, Table 3). Laparoscopic ultrasound of the liver was used both to screen the liver for additional tumors and to guide precise biopsy and placement of the therapeutic radiofrequency ablation catheter. In most cases, the additional lesions that were identified with LUS were deeply embedded in the liver.

Table 1. Histological Findings of Liver Tumors*

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Total No. of Patients</th>
<th>No. (%) of Patients With New Lesions Found by LUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>25</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>NE</td>
<td>15</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>5</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HCC</td>
<td>9</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>11 (20.0)</td>
</tr>
</tbody>
</table>

* LUS indicates laparoscopic ultrasound; NE, neuroendocrine; and HCC, hepatocellular carcinoma.

Table 2. Lesions Detected Only on LUS*

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Total No. of Lesions</th>
<th>No. (%) of Lesions Seen Only on LUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>77</td>
<td>7 (9.1)</td>
</tr>
<tr>
<td>NE</td>
<td>93</td>
<td>9 (9.7)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>30</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HCC</td>
<td>21</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Total</td>
<td>222</td>
<td>21 (9.5)</td>
</tr>
</tbody>
</table>

* LUS indicates laparoscopic ultrasound; NE, neuroendocrine; and HCC, hepatocellular carcinoma.
nant neoplasms. Although intraoperative ultrasound is
essential in staging of potentially resectable hepatic malig-
nancy, and is currently considered an essential compo-
nent of laparoscopic inspection and palpation clearly provides the necessary precision and
meticulous performed LUS shows great promise as an
accurate staging procedure for potentially resectable pri-
mary and metastatic liver tumors. All visible lesions can
be subjected to biopsy under real-time ultrasound imag-
ing, making the false-positive rate low. Patients who are
determined to have resectable disease by laparoscopy and
LUS would go on to undergo open exploration and screen-
ing with open intraoperative ultrasound and palpation be-
fore proceeding with hepatic resection. However, pa-
tients whose disease is clearly not resectable, as determined
by laparoscopic inspection and LUS, will have avoided an
unnecessary laparotomy.

To our knowledge, ours is the largest series of pa-
tients who have undergone laparoscopic inspection and
considered the criterion standard for detecting liver tu-
mors, it must be realized that the long-term follow-up
of patients who have undergone resection for colorectal
metastases (thus considered free of additional disease on
intraoperative ultrasound) have a recurrence rate as high
as 60%. In a study of patients who had hepatic resec-
tions performed for colorectal metastases, for example,
94% of the recurrences were within the abdominal cavi-
ty, with 36% of the recurrences limited to the residual
liver. The implication in the patients with liver recur-
cence is that the disease was present at the time of the
resection, but below the threshold (microscopic) of de-
tection by ultrasound and palpation.

In the current series, 27% of patients had devel-
oped new foci in the liver at 6 months of follow-up. These
patients would be expected to have an even higher re-
currence rate than that seen in patients having under-
gone resection, as they were patients with nonresect-
able disease that was often multifocal and recurrent.

There is obligatory morbidity associated with open
exploratory surgical procedures that affects the risk-
benefit analysis, particularly in a group of patients who
have limited life expectancies despite maximal therapies.
The prolonged convalescence and increased length of hos-
pital stay associated with an open exploration combined
with the high percentage of nontherapeutic laparotomy
make a minimally invasive alternative particularly attrac-
tive for patients with hepatic malignant neoplasms. The
combination of a systematic examination of the liver with
LUS with laparoscopic inspection has enabled us to iden-
tify additional hepatic tumors in 20% of our patients. Some
of the tumors identified at operation were not com-
mented on in the original CT report but, on retrospec-
itive review, were apparent on the initial CT scan. The local-
izing information from LUS and/or comparison with fol-
low-up CT scans after the ablation procedure was used to
help find these lesions on the initial CT. To make our anal-
ysis as conservative as possible, these were not scored as
lesions missed by CT scan. Although our patient group
included a broad range of tumor types, they were for the
most part unresectable because of the presence of bilobar
disease and multiple lesions. Our patients may not be rep-
resentative of the patients who are being considered for
resection and who are, by definition, at an earlier stage of
their disease. Because we were able to identify additional
small lesions and to precisely define anatomical relation-
ship of tumors to vascular and major biliary structures,
we believe that laparoscopic inspection combined with a
meticulously performed LUS shows great promise as an
acceptable staging procedure for potentially resectable pri-
mary and metastatic liver tumors. All visible lesions can
be subjected to biopsy under real-time ultrasound imag-
ing, making the false-positive rate low. Patients who are
determined to have resectable disease by laparoscopy and
LUS would go on to undergo open exploration and screen-
ing with open intraoperative ultrasound and palpation be-
fore proceeding with hepatic resection. However, pa-
tients whose disease is clearly not resectable, as determined
by laparoscopic inspection and LUS, will have avoided an
unnecessary laparotomy.

To our knowledge, ours is the largest series of pa-
tients who have undergone laparoscopic inspection and
parenchyma and would not have been detectable by lapa-
roscopic inspection alone.

At 6 months of follow-up, 50 of 55 patients had CT
scans available to be reviewed for the development of new
foci in the liver. Six (12%) of these 50 patients had re-
didual, multifocal nonablated foci of tumor and were there-
fore excluded. In the remaining 44 patients, 12 (27%)
were found to have developed new foci in the liver that
were not apparent on LUS. In all of these cases, recur-
rence was multifocal.

**COMMENT**

Preoperative imaging studies do not have the necessary
precision at this time to accurately stage disease in pa-
tients with known hepatic malignant neoplasms. This is
illustrated by the large percentage of patients who are
taken to the operating room for potential resection, only
to be found not to be candidates because of the presence
of disease undetected by preoperative screening. Useful
procedures for the accurate staging of hepatic malig-
nant neoplasms should provide for the inspection and
biopsy of all suspicious lesions that may indicate local
infiltration, nodal involvement, or extrahepatic metastas-
tases. Laparotomy with intraoperative ultrasonography
and palpation clearly provides the necessary precision and
access, and is currently considered an essential compo-
nent in staging of potentially resectable hepatic malignant
neoplasms. Although intraoperative ultrasound is

![Figure 3. Percentage of lesions missed on computed tomographic scans but seen on laparoscopic ultrasound. Ultrasound provided an increased sensitivity vs computed tomography for visualization of liver tumors less than 3 cm in diameter. This sensitivity was greatest for lesions less than 1 cm in diameter, as 28.6% of such tumors were missed by computed tomography but detected with ultrasound.](https://archsurg.jamanetwork.com/content/135/8/773.full)
LUS directed specifically at detecting hepatic malignant neoplasms. Different physical properties make a lesion visible in different radiological imaging methods. Tissue density and vascularity are the important factors in CT imaging, while the acoustic impedance of the tissue is crucial in ultrasonography. Although laparoscopic CT imaging and LUS did prove to be very sensitive in our hands, we do not propose that these examinations replace preoperative imaging studies. The CT scan has proved usefulness as a screening examination in patients at risk for hepatic malignant neoplasm. Both CT and magnetic resonance imaging are rapidly improving, with improved image quality and the development of specific liver contrast agents. Both CT scanning and magnetic resonance imaging are able to provide information on extrahepatic disease with more precision than LUS. For both hepatic resection and some of the new local treatment modalities, such as radiofrequency ablation, the ability to detect even small tumors with high sensitivity is critical. Laparoscopic inspection and LUS provide the access and precision necessary to detect small lesions, to target them for biopsy, and potentially to guide treatment.

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REFERENCES


DISCUSSION

Lee Swanson, MD, Portland, Ore: Laparoscopy is an old modality for the staging of abdominal malignancies. Its traditional weakness has been its inability to assess deep lesions and retroperitoneal findings. In the past it has also been a rather passive intervention offering little beyond peritoneal washings and biopsies of superficial lesions. Recently this has changed with the introduction of video endoscopy, which allows other members of the operating team to participate and contribute to the surgery, and developments in monitors, cameras, and laparoscopes have improved the illumination and resolution available to a remarkable degree. Finally, there is increasing comfort on the part of surgeons with the performance of complex therapeutic maneuvers such as solid organ manipulation and palpation, retroperitoneal and lesser sac exposure and exploration, and advanced biopsy techniques including lymphadenectomy and wedge biopsies. Intraoperative ultrasound has long been recognized as an excellent staging modality. It requires, however, extra training and experience to achieve these benefits. Such training is increasingly available through surgical societies, including the American College of Surgeons, and practitioner experience is increasing as ultrasound becomes more widely applied for trauma, breast, biliary, and transplant surgery. The combination of laparoscopy with laparoscopic ultrasound represents a powerful, patient-friendly tool. Multiple investigators have documented the efficacy of laparoscopic ultrasound for the staging of many foregut cancers.

CT scanning has also been improved by technologic advances. In particular, the addition of high-speed spiral techniques has improved the accuracy and readability of these studies. In general, it is cheaper and less invasive to stage patients with imaging studies as opposed to surgery. This paper seeks to compare the relative accuracy of preoperative spiral CT to laparoscopy with intraoperative ultrasound in a particular subset of patients with nonresectable hepatic malignancies confined to the liver. Dr Siperstein has been a pioneer in the development of radiofrequency ablation (RFA) techniques to offer palliation and a hope of cure for this unfortunate group of patients. The success of this therapy depends on the accurate location and sizing of these lesions as well as the general staging of the patient with regards to the presence of extraneoplastic cancer and the location of the liver lesions to critical structures. I have several questions for the authors regarding their presentation.

1. Many of these patients probably had standard abdominouls ultrasound as well as CT. In the patients with missed lesions on CT, was there a better correlation with the standard US, implying that it was the patient’s tissue characteristics that made the lesion “invisible”?

2. I presume that patients with CT evidence of extraneoplastic disease were excluded from consideration of RFA. Was laparoscopic abdominal exploration for extraneoplastic disease performed? Was US used as well? What percent of patients were found to have unexpected extraneoplastic disease?

3. We have performed RFA on 44 patients to date and have used preoperative PET [positron-emission tomography] scans to stage the last 25. Do the authors have any experience with the accuracy of other imaging studies such as PET scans in the staging of these patients?

4. Of the 18 patients with “residual” or “new” tumors on follow-up CT, how many of these could be described as missed lesions on both CT and laparoscopic US? Does this give us an...
estimate of the false-negative rate of laparoscopic US? Or is it better described as failures of RFA or disease progression?

5. Do you have any information on survival rates beyond 1 year? How many of these patients were placed on postoperative chemotherapy? And doesn’t that explain your relatively good early results?

6. What is the learning curve for both the laparoscopic exposure and the laparoscopic ultrasound? How would you recommend that surgeons obtain training for this procedure?

Richard H. Bell, MD, Seattle, Wash: In obtaining histological assessment of the small lesions that were detected by ultrasound, what method did you use and what was the sensitivity of the method?

Lawrence D. Wagman, MD, Duarte, Calif: We also have been very interested in the imaging of the liver prior to surgical intervention, as the failure to be able to proceed through a surgical procedure by finding disease either too extensive in the liver or outside is very significant.

I think one point that came to mind as we heard the presentation is that, in fact, we have brought these patients to the operating room before we had actually made the diagnosis of this additional disease. I think that looking at issues such as MRIs [magnetic resonance images] and more accurate preoperative diagnosis is a very critical issue that has been an interest of ours, and we will be presenting some of that data later this year.

The other issue I think is important is, when we are doing this evaluation and finding more lesions, what does this do in terms of absolute management changes? If Dr Siperstein has already decided to ablate 12 lesions and finds 14, that may not be as significant as if he is planning to do a resection and then finds more. So the issue of management also has to be fed into the analyses of new diagnostic modalities.

Finally, I am not sure that the gold standard is only intraoperative ultrasound and that the surgeon’s hand can now be removed from this equation. It seems to me that, in an analysis of this kind—imaging techniques without palpation—there needs to be a comparison to the palpation skill of the surgeon.

Steven C. Stain, MD, Nashville, Tenn: Are you able to separate the importance of laparoscopy from the importance of laparoscopic ultrasound? How many of these patients had lesions that were visualized just by visual inspection with laparoscopy, before the ultrasound?

Dr Pearl: Was standard ultrasound used, and could that be then compared to laparoscopic ultrasound? Only a few of the patients had preoperative standard ultrasound, and it really isn’t going to help to look back at those patients. Several studies have demonstrated that transabdominal ultrasound is less sensitive than CT or MRI and therefore is not used routinely in the preoperative staging in patients with known or suspected liver metastases. Another question is whether extrahepatic disease, either known or found at the time of surgery, excluded the patients from our study, and it did not. We were asked whether other forms of imaging might be perhaps better for staging, ie, MRI or PET scans. In our experience, there aren’t a lot of PET scans being done, but comparing MRI, we prefer triphasic spiral CT so far.

Were any patients given chemotherapy after our radiofrequency ablation? The answer is approximately 60% did receive chemotherapy. This is sort of a small basket of patients who are looking for all kinds of hope.

The learning curve is there, but I believe, as was mentioned, there are a number of courses available that can shorten the learning curve, and, for anyone interested, the Nafsinger conference given here offers a course this year just for that reason.

We appreciate the question of new member, Dr Bell. We use a core No. 18 gauge biopsy gun, and all of the patients had at least one of these missed lesions biopsied. In cases where more than one additional lesion was seen on ultrasound, a representative lesion was biopsied. I am not sure if I know what Dr Wagman’s question was, but we appreciate his comments, and, Dr Stain, we also appreciate your comments.

**Surgical Anatomy**

The renal arteries arise from the abdominal aorta at the level of L1 to L2. The right renal artery is posterior to the inferior vena cava. Accessory renal arteries exist in 25% of the population.