cannula. Examination begins with the telescope in the umbilical port and then the right-sided port. If no visual sign of incurability is found, the ultrasound probe is passed through the right-sided port. Laparoscopic ultrasonography consists of obtaining systematic views from both the anterior and posterior surfaces. The instruments may be switched between ports, or an additional left-sided port may be placed for detailed examination of the left lateral segment. If adhesions from previous operations preclude easy access to the lateral segment, most of this structure can be viewed ultrasonographically by placing the transducer against the falciform ligament and rotating the transducer to view obliquely through the lateral segment.

Ultrasonography of the liver done at laparotomy may detect an additional 10% to 40% of tumor deposits not visualized by conventional preoperative imaging methods or not palpable by a surgeon. The addition of hepatic computed tomographic arterial portography improves the accurate determination of the extent of hepatic tumor preoperatively; however, this method may overestimate the extent of extrahepatic or hepatic tumor in more than 10% of cases. Laparoscopic ultrasonography in one study defined hepatic tumors that were not visible by laparoscopy in a third of patients. With the use of laparoscopic ultrasonography only, 16% of patients were found to have disease that was not curable by conventional hepatic resection. Our experience suggests that the addition of laparoscopic ultrasonography to laparoscopy for the staging of primary and secondary hepatic tumors defines an additional 15% to 20% of patients to be incurable by treatment with either hepatic resection, cryoablation, or a combination of both. Patients found incurable by laparoscopic methods are generally returned home the same day.

Should the laparoscopic staging operation be done synchronously with laparotomy or as a separate procedure? The former approach is desirable in centers with competence in hepatic surgical procedures that are prepared to proceed with definitive treatment in the same setting. The latter is appropriate for surgeons who may refer cases on after determining possible curability.

GREGORY VAN STIEGMANN, MD
Denver, Colorado

REFERENCES

Goletti O, Buccianti P, Cavina E: Laparoscopic sonography: Basics and equipment, *In* Laparoscopic Sonography. Pisa, Italy, Editoriale Grasso, 1994, pp 11-31

John T, Greig J, Crosbie J, Miles WFA, Garden JO: Superior staging of liver tumors with laparoscopy and laparoscopic ultrasound. Ann Surg 1994; 220:711-719

Karl RC, Morse SS, Halpert RD, Clark RA: Preoperative evaluation of patients for liver resection—Appropriate CT imaging. Ann Surg 1993; 217:226-232

Machi J, Sigel B, Zaren HA, Kurohiji T, Yamashita Y: Operative ultrasonography during hepatobiliary and pancreatic surgery. World J Surg 1993; 17:640-646

Biomarkers for Breast Cancer

BIOMARKERS ARE most helpful in the management of breast cancer in its earliest stages—that is, node-negative breast cancer—when we must identify patients who are at the lowest or highest risk for recurrent or metastatic disease with early mortality. Apart from lymph node status (N), tumor size (T), and grade (G), the only breast cancer markers having proven clinical usefulness are estrogen receptor (ER), progesterone receptor (PR), and S-phase fraction (SPF). With these six well-established prognostic variables, clinicians still treat virtually all patients with stage I or stage II breast cancer with parenteral adjuvant therapy. This treatment for all is necessary to reduce the chance of metastases in those few patients—20% to 50%—who are truly at risk. Thus, there remains considerable incentive to discover new prognostic markers that will identify the few persons at risk, thereby sparing the majority who do not need parenteral adjuvant therapy. As well, biomarkers would be helpful in identifying patients less likely to respond to conventional chemotherapy or hormonal therapy.

Despite great interest and intense searching, there is no ideal prognostic indicator under development or on the horizon. Nor is there a suitable combination of markers that, for any given patient, can predict the natural course of the disease. Increasing optimism that a measure of breast tumor angiogenesis (microvessel density as detected by factor VIII staining) can at least discriminate between high- and low-risk, node-negative patients has now been muted by a recent large clinical study demonstrating the assay's unacceptable variability and failure to predict patients' outcome.

Critical among the established guidelines for the clinical development of any new prognostic marker is that the marker have biologic relevance to the disease process. In this regard, all measures of tumor angiogenesis remain on sound footing. Just as the best use of the estrogen receptor is to select patients for antiestrogen therapy, the ultimate clinical usefulness of a biomarker for microvessel density might be its ability to select candidates for antiangiogenesis therapy. Such is the emerging promise of other previously touted breast cancer prognostics, including the oncogenes c-*erb* B-2 (HER-2/*neu*) and p53. Gene therapies designed to correct mutations in the p53 tumor-suppressor gene have now entered clinical trials. Likewise, various therapeutic approaches are being developed to target the 25% of breast cancers that overexpress the c-*erb* B-2 oncogene; one approach, in particular, uses a tumor-inhibiting anti-HER-2 monoclonal antibody that in phase II studies produced complete and partial clinical responses without substantial toxicity in patients refractory to conventional breast cancer chemotherapy. These examples should help reinforce our interest in and continued search for new biomarkers that will serve as targets for the development of novel therapeutic agents, even if they fail to live up to our expectations as breast cancer prognostic factors.

CHRISTOPHER C. BENZ, MD
San Francisco, California

REFERENCES

Axelsson K, Ljung BM, Moore DH II, et al: Tumor angiogenesis as a prognostic assay for invasive ductal breast carcinoma. J Natl Cancer Inst 1995; 87:997-1008

Benz CC, Brandt BH, Zanker KS: Gene diagnostics provide new insights into breast cancer prognosis and therapy. Gene 1995; 159:3-7

Gasparini G, Pozza F, Harris AL: Evaluating the potential usefulness of new prognostic and predictive indicators in node-negative breast cancer patients. J Natl Cancer Inst 1993; 85:1206-1219 (165 refs)

Levine MN, Browman GP, Gent M, Roberts R, Goodyear M: When is a prognostic factor useful?—A guide for the perplexed. J Clin Oncol 1991; 9:348-356

McGuire WL: Breast cancer prognostic factors: Evaluation guidelines (Editorial). J Natl Cancer Inst 1991; 83:154-155

Liver Transplantation—Treatment Option for Selected Liver Tumors

SURGICAL RESECTION for primary liver cancer, mainly hepatocellular carcinoma, remains the only treatment proved capable of cure. Many patients cannot undergo partial resection, however, because of decreased liver function due to either cirrhosis or a centrally located tumor. For these patients, total hepatic resection followed by liver transplantation offers an alternative. It was this type of patient that became the first long-term survivor after liver transplantation: a 19-month-old girl with an unresectable hepatoma. She had a transplantation in 1967 and, unfortunately, died of recurrent hepatoma 14 months after the operation. In 1983 the National Institutes of Health Consensus Conference on liver transplantation stated that liver transplantation was no longer an experimental therapy, thereby proliferating the number of liver transplant centers in the United States. Primary hepatic carcinoma not amenable to resection was one of the indications for transplantation. Total hepatic resection and liver transplantation allowed a wider resection margin and would hopefully result in an improved cure rate. Unfortunately, like the little girl in 1967, many patients who survived the liver transplantation later died of recurrent cancer. Thus, many liver transplant centers consider a primary hepatic malignancy a contraindication to liver transplantation, even if the tumor is totally confined to the liver.

Some centers have continued to perform liver transplantation in these patients, however. The survival rate after liver transplantation in patients with liver cancer had been approximately 25% at three years, yet more recent reports in similar patient populations have described three-year survival rates of 46% to 66%. The reasons for the improved results are not clear, but they are probably due to at least three factors: improved surgical technique, more refined patient selection criteria, and the availability of combined modality therapy.

Advances and refinements in the surgical technique of liver transplantation and postoperative management have led to an overall improvement in patient survival. The expected one-year survival rate in liver transplant patients with benign diseases was 60% to 70% and is now 80% to 90%.

We have refined our patient selection criteria. Any patient with an extrahepatic tumor, including lymph node metastases, has an extremely poor prognosis and should not undergo either partial resection or total resection with liver transplantation. No other factors have been shown to reliably predict failure, but other preoperative characteristics that have demonstrated increased relative risk of tumor recurrence—in some but not all clinical series—are tumor size greater than 5 cm, bilobar involvement, and macroscopic vascular invasion. It is difficult to decide which risk factors should be "relative" and which "absolute" contraindications to total resection with liver transplantation. Our center excludes patients with portal vein invasion, but does consider patients with tumors larger than 5 cm or bilobar involvement.

Finally, centers are now treating patients with combined modality therapy. All the recent reports describing clinical series of patients undergoing liver transplantation for primary liver cancer use either adjuvant or neoadjuvant therapy in their treatment plan. The implementation of chemotherapy has been the only notable therapeutic change when compared with historical controls. At this time, no randomized, prospective, controlled trials have been done to determine the effectiveness of radiation therapy or adjuvant or neoadjuvant chemotherapy in these patients. Our center currently uses neoadjuvant fluorouracil and chemoembolization with doxorubicin hydrochloride, as well as postoperative adjuvant chemotherapy with doxorubicin and fluorouracil for four months.

The possible liver transplant recipients far outnumber the possible donors. This mismatch between supply and demand creates difficulty in allocating organs. The use of donor livers in patients with liver tumors will shift organs away from patients with benign liver diseases, who have a better predicted long-term survival. Therefore, even though there is some evidence that liver transplantation is superior to partial resection in certain patients with small tumors and cirrhosis, most centers recommend partial resection (if feasible) in these patients, to conserve the availability of donor livers.

Patients with chronic hepatitis should be screened for the presence of liver cancer. Early referral before the cancer spreads outside the liver will increase the number of patients who can be effectively treated. Because the organ supply is limited, patients with cirrhosis who can tolerate a partial resection should have it. In cases where the tumor cannot be removed with a partial liver resection, total liver resection with liver transplantation is the only proven curative alternative. While a patient is waiting for a donor liver, which may be six months or longer, our center uses chemoembolization and neoadjuvant chemotherapy to control disease. Multicenter trials are under way to evaluate the effectiveness of adjuvant chemotherapy in these patients. These trials should provide necessary information as to the best combination of surgical therapy and chemotherapy in the management of liver tumor cases.

JOHN P. McVICAR, MD
Seattle, Washington

REFERENCES

Olthoff KM, Rosove MH, Shackleton CR, et al: Adjuvant chemotherapy improves survival after liver transplantation for hepatocellular carcinoma. Ann Surg 1995; 221:734-743

Schwartz ME, Sung M, Mor E, et al: A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. J Am Coll Surg 1995; 180:596-603

Tan KC, Rela M, Ryder SD, et al: Experience of orthotopic liver transplantation and hepatic resection for hepatocellular carcinoma of less than 8 cm in patients with cirrhosis. Br J Surg 1995; 82:253-256