MEDICINE ELSEWHERE

Manuk Manukyan, M.D.

Department of General Surgery,
School of Medicine, Marmara University,
Istanbul, Turkey.

Terkivatan T, de Wilt JHW, de Man RA, et al. Indications and long-term outcome of treatment for benign hepatic tumors. Arch Surg 2001;136:1033-1038.

In contrast with hemangioma, focal nodular hyperplasia (FNH) and hepatocellular adenoma are uncommon benign liver tumors that are detected more frequently because of improvements in radiological modalities and the widespread use of ultrasonography (US). In this study, the authors summarize a single-center experience with the diagnosis and management of benign hepatic tumors. This study reviews the indications for surgery and the outcome of long-term follow-up in the treatment of these tumors.

A total of 208 patients with benign liver tumors were analyzed between January 1, 1979 and December 31, 1999. A total of 74 patients underwent surgery and 134 were observed at the authors' clinic.

In the case of an incidentally detected tumor (32%, or 24 of 74 patients), the inability to differentiate between FNH, hepatocellular adenoma, or carcinoma was an indication for surgery. In 64% (47 of 74 patients) of the surgically resected patients, abdominal symptoms were the reason for resection even when there was a clear diagnosis of FNH or hemangioma. The tumor diameter was significantly greater in patients with abdominal pain than in those with an incidental finding (median, 8.0 vs 5.5 cm; p=01).

As the diagnostic workup, computerized tomography detected 37% of FNH, 56% of hepatocellular adenoma, 70% of hemangioma. Needle biopsy results were justified postopertively in 50% of FNH, 67% of hepatocellular adenoma, all of hemangioma. Sensitivity of US was 33% for FNH and adenoma as well as 50% for hemangioma. Magnetic resonance imaging yielded 100% sensitivity for hemangioma.

The postoperative hospital stay was median 11 days. The overall morbidity was 27%. Two patients died due to continuous bleeding and severe coagulopathy. Reoperation was indicated in five patients due to intraabdominal bleeding and in one because of inferior vena cava thrombosis. Mean follow-up was 39 months. Of the patients who presented with complaints (n=35) symptoms resolved in 28 after surgery. However, in 7 patients (3 with FNH and 4 with hemangioma), symptoms persisted. Tumor recurrence was not detected during radiological follow-up of all patients.

A total of 134 patients (42 with FNH, 14 with hepatocellular adenoma, and 78 with hemangioma) were managed by observation. Abdominal pain was noted in 33%, 14%, and 12% of those with FNH, a hepatocellular adenoma and a hemangioma, respectively. When the tumor was an incidental finding during laparotomy, the diagnosis was confirmed by incisional biopsy preoperatively. In all other patients, imaging methods led to the diagnosis. Patients were observed for a mean of 45 months. The mean greatest diameter of the hepatocellular adenoma was 3.2 cm. Six (43%) of the 14 patients showed regression of the tumor after cessation of oral contraceptive use, and 2 of these tumors were not detectable during the last follow-up.

The results of this study indicate that liver surgery for benign liver tumors may relieve complaints in a high percentage of symptomatic patients (80%). However, in many patients, symptoms persist after resection of the tumor and surgery-related complications might occur. Regarding the considerable long- and short-term morbidity and even mortality, careful patient selection is warranted, especially in view of the benign nature of these lesions. Conservative management of solid benign lesions such as

focal nodular hyperplasia and hemangioma can be performed safely, irrespective of their size. The authors only advise surgery for liver lesions when there is an inability to exclude malignancy or in the case of severe complaints related to the tumor.

Bahadır M. Güllüoğlu, M.D.

Department of General Surgery,
Breast and Endocrine Surgery Unit,
School of Medicine, Marmara University,
Istanbul, Turkey.

Meijers-Heijboer H, van Geel B, van Putten WLJ, et al. Breast cancer after prophylactic bilateral mastectomy in woman with a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:159-164.

The identification of the breast-cancer-susceptibility genes BRCA1 and BRCA2 evoked widespread interest in genetic testing among women at risk for a mutation in these genes. Women with a BRCA1 or BRCA2 mutation have a cumulative lifetime risk of invasive breast cancer (up to the age of 70 years) of 55 to 85 percent and of invasive epithelial ovarian cancer of 15 to 65 percent. In these women the risk of breast cancer begins to increase near the age of 25 years, and their overall survival once breast cancer does develop is similar to that of age-matched patients with sporadic cases of breast cancer. Current risk-reduction strategies for women with a BRCA1 or BRCA2 mutation include regular surveillance; prophylactic mastectomy, oophorectomy, or both; and chemoprevention. Meijers-Heijboer et al. investigated the efficacy of prophylactic mastectomy in women with a proven pathogenic BRCA1 or BRCA2 mutation. Because a randomized trial is impossible for ethical reasons, they performed a prospective cohort study of women at a single institution who chose either prophylactic mastectomy or regular surveillance.

Beginning on January 1, 1992, the authors studied all women with a BRCA1 or BRCA2 mutation who were being monitored for breast cancer because of familial clustering of breast cancer, ovarian cancer, or both at the Daniel den Hoed Cancer Center in Rotterdam, the Netherlands. They included all women who had been given a molecular diagnosis before January 1, 2000. A total of 139 women fulfilled the criteria. Eventually, 76 of these women chose to undergo prophylactic bilateral mastectomy before the end of the follow-up period (March 1, 2001), whereas the other 63 women chose to remain under regular surveillance. No women were lost to follow-up after prophylactic mastectomy. Of the women in the surveillance group, three died of ovarian cancer and two chose to be monitored at another hospital for practical reasons.

There were no significant differences between the two groups with respect to age, average duration of follow-up after entry into the study, follow-up after premenopausal oophorectomy, and type of mutation. The 26 distinct mutations — 23 in BRCA1 and 3 in BRCA2 — were distributed in a similar fashion in the two groups. The 139 women were from a total of 70 families; the number of women from each family ranged from 1 to 5. The mean (±SE) duration of follow-up was 2.9±1.4 years (219 woman-years) in the mastectomy group and 3.0±1.5 years (190 woman-years) in the surveillance group. After prophylactic mastectomy no case of invasive breast cancer was observed in any of the 76 women during 219 woman-years at risk. In the surveillance group eight invasive breast cancers were detected during 318 woman-years at risk, for a yearly incidence of 2.5 percent. The ratio of observed cases to expected cases was 1.2 (8 vs. 6.7; 95 percent confidence interval, 0.4 to 3.7; P=0.80). All the affected women were from different families. The actuarial mean five-year incidence of breast cancer in the women in the surveillance group was 17±7 percent. Cox proportional-hazards analysis showed that mastectomy significantly (P=0.003) decreased the incidence of breast cancer (hazard ratio, 0;95 percent confidence interval, 0 to 0.36).

As compared with the incidence in the surveillance group, the incidence of breast cancer in the prophylactic-mastectomy group was significantly reduced (P=0.003), but the mean follow-up of three years calls for a cautious interpretation of these results. In conclusion, the data in this study of Meijers-Heiwboer et al indicate that prophylactic bilateral total

mastectomy substantially reduces the incidence of breast cancer among women with a BRCA1 or BRCA2 mutation. Nevertheless, longer follow-up and studies of more patients are required to establish the protective effect and determine the long-term complications of this procedure.

Pınar Mega Tiber, M. Sc

Department of Biophysics,
School of Medicine, Marmara University,
Istanbul, Turkey.

Davis M, Kawai Y, Arinze I. Involvement of $G_1\alpha 2$ in sodium butyrate- induced erythroblastic differentiation of K562 cells. Biochem J 2000;346:455-461.

The K562 cell line, which is derived from a patient with chronic myelogenous erythroleukaemia, is triggered in culture with stimulatory agents such as sodium butyrate. During this event, these cells differentiate to erythroblasts and acquire the capability to synthesise haemoglobin. The aim of this study was to explore changes in the cellular levels of selected G protein subunits during the erythrocytic differentiation of K562 cells. Using Western blot analysis, Davis et al. demonstrated the presence of $G_i\alpha 2$, $G_s\alpha 1$, $G_q\alpha$ and Gß2. $G_i\alpha 3$, $G\alpha_{13}$, $G\alpha_{16}$, $G_0\alpha$ and $G_z\alpha$ however were not detected in these cells. In addition, they also found that the levels of $G_i\alpha 2$ were increased during the differentiation process. Adding *Bordetella Pertussis* toxin to the culture, which inactivated $G_i\alpha 2$, resulted in 62% inhibition of erythroblastic differentiation. A 50% decrease in the $G_i\alpha 2$ levels and in erythroblastic differentiation, was observed due to addition of an oligonucleotide antisense to $G_i\alpha 2$. The authors conclude that the increased levels of $G_i\alpha 2$ contribute to the sodium butyrate- induced erythroblastic differentiation of K562 cells.

Devrim Öz, M. Sc

Department of Biophysics,
School of Medicine, Marmara University,
Istanbul, Turkey.

Janetopoulos C, Jin T, Devreotes P. Receptor-mediated activation of heterotrimeric G-proteins in living cells. Science 2001;291:2408-2411.

Chemotactic responses appear to be mediated via a common set of G-protein-linked signalling events. G-protein-coupled receptor activation allows exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) and dissociation of the G-protein heterotrimer. Phagocytic cells, including leukocytes and free-living amoebae such as *Dictyostelium discoideum*, although evolutionarily distant, share remarkable similarities in behavior as well as in the molecular components involved in chemotaxis. In order to determine the kinetics and to localize the activation site of the G-proteins in cells and tissues, $G\alpha_2$ and Gβ subunits of *D. discoideum* were tagged with cyan and yellow fluorescent protein and were transformed into $g\alpha_2^-$ and $g\beta^-$ (null) cell lines. The state of the G-protein heterotrimer was visualized by monitoring Fluorescence Resonance Energy Transfer (FRET). Treatment of the cells with increasing concentrations of the chemoattactant cylic adenosine monophosphate (cAMP) led to a decrease in FRET fluorescence in a dose-dependent manner, whereas removal of the chemoattractant triggered an increase in FRET intensities, reflecting receptor-mediated activation and dissociation of the G-protein heterotimer. Prolonged stimulation of *D. discoideum* cells with the chemoattractant induced adaptation in a number of physiological responses, such as actin polymerization and PH-domain recruitment to the plasma membrane. On the other hand, persistent stimulation of the cells with cAMP did not return the G-protein back to the heterotrimeric state. The authors thus conclude adaptation does not directly involve the G-protein cycle. They also state that construction of similar energy-transfer pairs of mammalian G-proteins should enable direct *in situ* mechanistic studies and identify ligands of newly found G-protein-coupled receptors.