Hepatocellular carcinoma (HCC) annually causes about one million deaths. Because of advanced stage at diagnosis, HCC carries a five-year survival rate of less than 5% in patients diagnosed with unresectable disease. Incidence for HCC is higher in men and individuals of Asian descent, where viral hepatitis, a leading cause of HCC, is endemic. This article will provide an overview of the complex symptom management of patients with HCC. The occurrence of multiple symptoms, including pain, fatigue, weight loss, and obstructive syndromes (e.g., ascites, jaundice) in patients with HCC is common. Because of limitations in the efficacy of current treatment options, aggressive symptom management is key to preserving physical functioning and quality of life in patients with HCC. A multidisciplinary team approach to symptom management of patients with HCC is critical, with oncology nurses playing an integral role.

At a Glance
- Common signs and symptoms, such as pain, ascites, and jaundice, are potentially distressing in patients with hepatocellular carcinoma (HCC) because of advanced disease and guarded prognosis.
- Aggressive symptom management using an interdisciplinary model is key to maintaining quality of life in patients with HCC and should be initiated at diagnosis.
- Oncology nurses must be aware of the impact of multiple symptoms in patients with HCC.

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of HCC in the United States prior to the 1980s were relatively low (2.1%–2.5%); however, the annual incidence rate has increased about 80% since the late 1980s (El-Serag & Mason, 1999). Overall, HCC tends to occur earlier in life (20–35 years of age) for those in countries with the highest incidence (Di Bisceglie). Mortality rates follow a pattern consistent with incidence rates; the yearly fatality ratio is about one, indicating that most patients do not survive more than a year (Bosch et al.).

Incidence rates in the United States are lowest in Caucasians, but increasing rates are found in Japanese, African American, Hispanic, Filipino, Chinese, and Korean populations (Bosch et al., 2004). In the United States, HCC occurs more frequently in males, with incidence rates among African American men twice as high as Caucasian men (Monto & Wright, 2001). In North America and Europe, Asian males have a 1.3–10.9-fold increase in HCC mortality, which is the highest compared to all other ethnicities (Hanley, Choi, & Holowaty, 1995; Rosenblatt, Weiss, & Schwartz, 1996).

Current Management

Most treatments for HCC (e.g., surgical resection, chemoembolization, percutaneous ethanol injection, radiofrequency ablation, cryosurgery) are palliative in nature and require extensive follow-up patient care. To date, the only potentially curative treatment for HCC is partial hepatectomy, but only 20% of patients are considered eligible for surgical resection (Zhu, 2003). For more advanced and unresectable diseases, overall median survival is about eight weeks (Leung & Johnson, 2001).

In addition, local recurrence will occur despite curative intent resection (Little & Fong, 2001). Although the perioperative mortality for partial hepatectomy is less than 5% in specialized centers because of advances in surgical technologies (Carr, 2004), potential postoperative complications (e.g., portal hypertension, ascites) warrant extensive postoperative monitoring (Little & Fong). Complications associated with other local ablative therapies include hemorrhage, acute cholecystitis, liver infarction, bile duct necrosis, abscess formation, pleural effusions, and acute pancreatitis (Song, Ip, & Fong, 2004).

Surgical resections of varying degrees remain the standard treatment for HCC. Although postsurgical recurrence rates have decreased and survival has increased since the late 1980s, most patients still have only a 50% five-year survival rate (Carr, 2004). The most important parameter to consider when choosing patients for partial hepatectomy is baseline hepatic function (Song et al., 2004). The most common evaluation tool for patients being considered for partial hepatectomy remains the Child-Pugh Classifcation (Child & Turcotte, 1964; Pugh, Murray-Lyon, Dawson, Pietroni, & Williams, 1973) (see Table 1). The prognostic tool is useful in predicting perioperative and postoperative mortality in abdominal surgery patients with cirrhosis (Garrison, Cryer, Howard, & Polk, 1984; Mansour, Watson, Shayani, & Pickleman, 1997). A numeric score is assigned for patients in each parameter (albumin, bilirubin, prothrombin time, ascites, encephalopathy); then patients are categorized into Child A (5–6 points), B (7–9 points), or C (10–15 points), with class C patients presenting the most abnormalities within each parameter. Other factors that dictate resectability include absence of extrahepatic lesions, size of residual liver, and expertise of the surgical team (Song et al.). Perioperative mortality and postoperative morbidity largely depend on the presence or absence of cirrhosis. Patients with HCC and cirrhotic livers have thrombocytopenia, coagulopathy, and varices, which increase the likelihood of operative bleeding. An increasing array of localized semisurgical treatments has become accepted widely, including percutaneous ethanol injection, radiofrequency ablation, and cryotherapy (Carr). Local ablative therapies generally are useful in patients with multiple lesions and as a method to preserve residual liver function when used with surgery. Liver transplantation is a final option for patients with inoperable HCC, but rigorous eligibility criteria must be fulfilled for patients with HCC to compete for healthy livers.

Transarterial chemoembolization is the localized intra-arterial delivery of chemotherapeutic agents that are emulsified in an oily medium and combined with embolic material. The rationale behind this localized treatment arose from the observation that healthy liver tissue receives as much as 80% of its blood supply from the portal vein, whereas liver tumors receive blood entirely from the hepatic artery. Therefore, the hepatic artery is a logical means to target liver tumors while preserving normal liver function (Ramsey, Kernagis, Soulen, & Geschwind, 2002). The partial or complete occlusion of the hepatic artery induces tumor necrosis but will not affect normal liver tissue because of the different blood supply route. The goal of chemoembolization treatment is to deliver a highly concentrated dose of chemotherapy directly to the tumor cells. A second objective is to preserve as much functional liver tissue as possible. Significant

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**Figure 1. Hepatocellular Carcinoma, a Malignant Tumor of the Epithelial Cells in the Liver**

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**Figure 2. Causes of Treatment Uncertainty in Men With Prostate Cancer**

*Note. Based on information from Yu & Yuan, 2004.*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cause</th>
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<tbody>
<tr>
<td>Aflatoxin exposure</td>
<td>Excessive alcohol consumption</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>(&gt; 80 g per day or 6–7 drinks per day for 10 years)</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>Heavy smoking (&gt; 40 cigarettes per day for 10 years)</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>Hereditary hemochromatosis</td>
</tr>
<tr>
<td>Chronic liver disease (cirrhosis)</td>
<td>Obesity</td>
</tr>
<tr>
<td>Diabetes</td>
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improvements in long-term survival have been demonstrated but are not supported by randomized trials. A meta-analysis demonstrated that four randomized clinical trials comparing patients undergoing transarterial chemoembolization with untreated controls have failed to show an effect on patient survival (Geschwind, Ramsey, Choti, Thuluvath, & Huncharek, 2003). Systemic chemotherapy has been studied extensively in HCC, but limited published data have shown a response rate higher than 20% with no survival benefit compared to supportive care alone (Carr, 2004).

Selective internal radiation therapy using radiolabeled microspheres is a current therapeutic option for patients with HCC. The microspheres are administered intra-arterially, resulting in high radiation doses delivered to the arterial-fed tumors while sparing normal liver parenchyma (Geschwind et al., 2004). The one-year survival rate for patients treated with the microspheres is about 63%, which is similar to rates reported in patients receiving transarterial chemoembolization (Geschwind et al., 2004). The side-effect profile is similar to those seen in other localized procedures such as transarterial chemoembolization, including mild abdominal pain, nausea, and fever (Popperl et al., 2005).

To date, the search for novel agents in the treatment of HCC has focused on targeted therapies. One agent, sorafenib, is an oral multikinase inhibitor of the Raf kinase and receptor tyrosine kinases that has been approved for renal cell carcinoma. A phase II study tested the efficacy of sorafenib (400 mg BID) in patients with HCC, inoperable disease, no prior systemic treatments, and Child-Pugh class A or B. Sorafenib showed modest efficacy, with 33.6% of patients (n = 137) achieving stable disease for at least 16 weeks and median overall survival of 9.2 months (Abou-Alfa et al., 2006). In the study, grade 3 or 4 toxicities included fatigue (9.5%), diarrhea (8%), and hand-foot skin reactions (5.1%) (Abou-Alfa et al.). A subsequent randomized, placebo-controlled phase III study called the Sorafenib HCC Assessment Randomized Protocol was conducted to evaluate the efficacy and safety of sorafenib (400 mg BID) versus placebo. Inclusion criteria were patients with advanced measurable HCC and no prior systemic treatments, Eastern Cooperative Oncology Group performance status of 0–2, and Child-Pugh class A. Results suggested that sorafenib was superior in median overall survival (10.7 versus 7.9 months), presenting a 44% overall survival improvement (Llovet, Ricci, & Mazzaferrro, 2007). The most frequent grade 3 or 4 toxicities included diarrhea (11% versus 2%), hand-foot skin reactions (8% versus 1%), and fatigue (10% versus 15%) (Llovet et al.). The placebo group had higher percentages of fatigue (15% versus 10%) and bleeding (9% versus 6%). Although sorafenib was the first agent in decades to have demonstrated statistically significant improvements in survival for patients with advanced HCC, nurses must take caution. The agent was tested only in patients with Child-Pugh class A and high performance status; therefore, the agent’s efficacy for patients with lower performance status and higher Child-Pugh scores is unknown.

### Signs, Symptoms, and Management

Table 2 provides a list of the common HCC symptoms and treatment strategies. Patients with HCC usually are asymptomatic during the early stages of disease. However, 80% of patients with HCC will be diagnosed with advanced-stage disease (Cahill & Braccia, 2004). About 90%–95% of patients with HCC will present with the triad of right upper-quadrant pain, palpable mass, and weight loss (Bartlett, Carr, & Marsh, 2005). Patients typically present with an enlarged, irregular, and nodular liver. Other physical findings include hepatic bruits (25%), ascites, splenomegaly, jaundice, wasting, and fever. Liver function tests and jaundice may not appear until late in the disease trajectory because of the organ’s functional reserve capability (Cahill & Braccia).

Patients with terminal HCC may present with various symptoms related to decompensated cirrhosis, including ascites, variceal bleeding, peripheral edema, and hepatic encephalopathy (Lin et al., 2004). In a cohort of Taiwanese patients with HCC, the most common symptom was abdominal pain (75.5%), originating from an enlarged tumor mass and characterized by dull visceral pain (Lin et al., 2004). Other common symptoms included fatigue or weakness, peripheral edema, cachexia, ascites, dyspnea, anorexia, and vomiting (Lin et al.). Patients diagnosed with HCC had the third-highest level of psychiatric distress among patients with eight other types of cancer (Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Patients with cancer experience a significant number of symptoms as a direct or indirect result of disease, treatment, and comorbidities that are often complex, multifactorial, and challenging to manage. To date, the majority of symptom-related research focuses on a single symptom. However, symptom presentation includes multiple symptoms, and the relationship among those symptoms, their underlying mechanisms, and impact on patient outcomes still are being explored. In addition, unrelieved symptoms have a negative effect on patient outcomes, including functional status, mood states, and quality of life (Miaskowski, Dodd, & Lee, 2004).

The concept of symptom clusters has gained momentum in current symptom-related research. Although the occurrence of multiple symptoms has been studied previously (Sarna, 1993), the phenomenon was not labeled “symptom clusters” until the 2000s. To date, several working definitions for symptom clusters exist in nursing research. Dodd, Miaskowski, and Paul (2001) defined symptom clusters as three or more concurrent, related symptoms that may not share a common etiology. Kim, McGuire, Tulman, and Barsevick (2005) developed a more comprehensive definition by reviewing the research and ultimately defining symptom clusters as two or more related symptoms...
that occur together (Kim et al.). The clusters are composed of stable symptom groups, are relatively independent from other clusters, and may uncover specific underlying symptom dimensions. Symptoms within a cluster may or may not share a common etiology, and the relationship among symptoms within a cluster is associative rather than causal (Kim et al.).

The exploration of potential symptom clusters is critical to the development of effective symptom management strategies for patients with HCC, particularly those with unresectable, metastatic disease. The identification of clusters specific to the specific symptom management needs of patients with HCC based on treatment modalities.

### Pain

Pain is one of the most common and distressing symptoms in patients with cancer. Abdominal pain is common in HCC because of visceral involvement that originates from a primary or metastatic lesion in the abdominal or pelvic viscera (Mercadante, 2002). Treatment-related pain also is common in patients with HCC. Postembolization syndrome occurs in 80%–90% of patients with HCC treated with transarterial chemoembolization (Ramsey et al., 2002). Postembolization syndrome often includes abdominal pain, ileus, fever, nausea, and vomiting, and can last from hours to days (Ramsey et al.).

#### Table 2. Management of Common Symptoms in Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Opioid analgesics (moderate to severe), non-steroidal anti-inflammatory drugs (mild)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Treatment of contributing factors, if indicated: anemia (erythropoietin), depression (antidepressants), sleep disturbance, nutritional deficiencies, deconditioning (exercise), and decreased energy level (psychostimulants)</td>
</tr>
<tr>
<td>Anorexia or cachexia</td>
<td>Treatment of contributing factors, if indicated: chronic nausea (antiemetics), constipation (laxatives), and depression (antidepressants)</td>
</tr>
<tr>
<td>Pharmacologic: megestrol acetate</td>
<td>Others: dietary counseling and artificial nutrition</td>
</tr>
<tr>
<td>Ascites</td>
<td>Pharmacologic diuretics (potassium-sparing and loop)</td>
</tr>
<tr>
<td>Procedural: paracentesis</td>
<td>For cholestatic pruritus: cholestyramine and self-care measures (emollients and perfume-free soaps)</td>
</tr>
<tr>
<td>Jaundice secondary to biliary obstruction</td>
<td>Percutaneous drainage and biliary stent</td>
</tr>
</tbody>
</table>

*Note. Based on information from Del Fabbro et al., 2006; Greenway et al., 1982; Jones & Bergasa, 2000; National Comprehensive Cancer Network, 2007a, 2007b.*

Pain can occur during and after transarterial chemoembolization, and patients who did not experience distressing pain levels during the procedure are vulnerable to postprocedural pain (Lee, Hahn, & Park, 2001).

Pain treatment in patients with HCC begins with a comprehensive assessment of the clinical characteristic of visceral pain. Referred visceral pain in HCC often is found in the right shoulder (Mercadante, 2002). Opioid analgesics remain the standard treatment for severe pain. Several options exist for the delivery of opioids (oral, parenteral, transdermal, transmucosal or sublingual, rectal, and spinal). The route of administration must be determined based on the patient’s ability to use the specific route, efficacy of the route in delivering adequate analgesia, ease of use for the patient and family, associated complications, and cost (Mercadante). In visceral pain, nonsteroidal anti-inflammatory drugs produce an analgesic effect similar to opioids and are particularly useful when pain is mild (Mercadante et al., 1999). Nurses should refer to the Oncology Nursing Society’s (ONS’s), 2008b) Putting Evidence Into Practice® card for pain, which provides detailed evidence-based information on the assessment and management of pain.

### Fatigue

Fatigue, a common and distressing symptom in patients with cancer, is caused by advanced disease and treatment. Fatigue is part of the postembolization syndrome associated with transarterial chemoembolization. Patients usually experience mild to moderate levels of fatigue that peak on the second day after transarterial chemoembolization (Shun et al., 2005). Although fatigue level gradually decreases two days after treatment, the level is still higher than pretreatment at six days after treatment (Shun et al.). The pattern of fatigue in patients undergoing transarterial chemoembolization with doxorubicin is similar to the pattern following systemic administration of the same agent (Lai et al., 2007).

Fatigue management in patients with HCC should begin with an in-depth assessment of contributing factors, including pain, emotional distress, sleep disturbance, anemia, nutritional deficiencies, deconditioning, and comorbidities (Mock, 2004). Treating the factors as an initial approach may increase the tolerability of fatigue. Pharmacologic interventions targeted toward the contributing factors associated with fatigue include erythropoietin for chemotherapy-induced anemia, antidepressants for depression-related fatigue, and psychostimulants for increasing energy level. Evidence in the literature also supports the use of methylphenidate for reducing fatigue in advanced cancer (Bruera et al., 2006). In addition, considerable evidence shows the efficacy of nonpharmacologic interventions (e.g., aerobic exercise) on fatigue reduction (Courneya et al., 2003; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; Mock et al., 1997; Schwartz, Mori, Gao, Nal, & King, 2001; Segal et al., 2003). Proper sleep hygiene and energy conservation are helpful self-care strategies that patients can use at home. A careful review of patients’ medications also may identify adverse effects that aggravate fatigue. In addition, ONS’s (2008a) Putting Evidence Into Practice® card for fatigue is a comprehensive resource for accessing evidence-based information on the assessment and management of fatigue.
Mr. S, an insurance agent, lived with his wife and had two grown children. Mr. S was a member of the local Greek Orthodox Church, and he reported no history of tobacco, alcohol, or drug use. He was an otherwise healthy 67-year-old man who presented with diarrhea and abdominal bloating following a course of antibiotics for treatment of a tooth abscess. He complained of persistent abdominal pain and swelling after completion of antibiotics; computed tomography scan and ultrasound confirmed a liver mass. A subsequent biopsy revealed well-differentiated hepatocellular carcinoma (HCC). The tumor was about 6 cm in size and located in the center of the left lobe. At the time of diagnosis, Mr. S also had moderate ascites. He did not have a history of viral hepatitis, although his antibody titers were positive on screening. Comorbidities included diabetes, which was well controlled with insulin. Mr. S had moderate bilateral peripheral edema of the lower extremities. On further evaluation, Mr. S had a Child-Pugh C (elevated prothrombin time, elevated total bilirubin, lowered albumin, and moderate ascites) classification. Based on its size and location, the tumor was surgically resectable, but Mr. S’s Child-Pugh classification made surgery unsafe. Mr. S was referred for chemoembolization. Spironolactone and furosemide were prescribed for his ascites. He also needed frequent paracentesis. No family history of hepatitis or HCC was present.

Mr. S was scheduled for chemoembolization using doxorubicin, mitomycin C, and cisplatin. However, the procedure was considered unsuccessful because of significant intratumoral arteriovenous shunting. He tolerated the procedure well with no severe postembolization syndrome except for mild transient abdominal pain and mild fatigue. After chemoembolization, his ascites gradually returned, and Mr. S began to experience mild abdominal distention and pain. Liver function tests also were increasing two days after the procedure. After discharge, the patient had increasing abdominal distension refractory to medications and dyspnea, so paracentesis was performed. Because of decreasing performance status and worsening liver function, Mr. S was not a candidate for further treatment.

**Case Study**

**Anorexia-Cachexia**

Weight loss is a frequent complication in patients with HCC. The incidence of weight loss is greater than 54% in most patients with cancer and reaches 80% in the terminal stage (Strasser & Bruera, 2002). Cachexia can be separated into primary (metabolic) and secondary (starvation) stages. Anorexia, a leading symptom of the metabolic cachexia syndrome, is separate from weight loss; therefore, a common term for cancer-wasting syndrome is anorexia-cachexia syndrome (Strasser & Bruera). The diagnosis of anorexia-cachexia syndrome is based on simple assessment of weight loss and anorexia, but no established tools or guidelines are available that distinguish primary and secondary cachexia. Other parameters (e.g., hypoalbuminemia, asthenia, chronic nausea, reduced caloric intake, clinical judgment of reduced muscle and fat mass) can serve as additional criteria for the presence of cachexia (Strasser & Bruera). The criteria can help patients with HCC with relevant fluid retention (e.g., ascites, edema) in which the accumulation of excess fluid masks the extent of weight loss (Strasser, 2000).

The management of anorexia-cachexia syndrome in patients with HCC begins with a thorough assessment of potential contributors, including chronic nausea, constipation, early satiety, taste alterations, and depression (Del Fabbro, Dalal, & Bruera, 2006). Pharmacologically, at least 15 randomized clinical trials have demonstrated that megestrol acetate (doses ranging from 160–1,600 mg per day) significantly improves appetite when compared to placebo (Pascual Lopez et al., 2004). Artificial nutrition (e.g., total parenteral nutrition) is used frequently but does not increase lean body mass (Muscaritoli, Bossola, Aversa, Bellantone, & Rossi Fanelli, 2006). Individualized dietary counseling in recent randomized clinical trials in patients with cancer has been effective in improving food intake, nutritional status, and quality of life (Ravasco, Monteiro-Grillo, Vidal, & Camilo, 2005).

**Obstructive Syndromes**

About 19%–40% of patients with HCC present with jaundice at the time of diagnosis, and the condition usually occurs in later stages (Qin & Tang, 2003). Only 1%–12% of patients with HCC present with obstructive jaundice as the initial clinical symptom (Lai & Lau, 2006). Obstructive jaundice occurs secondary to diffuse tumor invasion of the liver parenchyma or progressive liver failure. Intraductal tumor growth may occur in the common hepatic duct and common bile duct, causing obstructive jaundice (Qin & Tang). Jaundice is not necessarily a harbinger of advanced disease nor a contraindication for aggressive treatment (e.g., surgery).

Obstructive jaundice in patients with HCC can be managed with percutaneous drainage or the placement of a biliary stent. Cholestatic pruritus associated with obstructive jaundice can be treated using cholestyramine to decrease the enterohepatic circulation of bile acids (Jones & Bergasa, 2000). Other self-care measures include the use of emollients to maintain skin moisture and mild, fragrant-free soaps to prevent skin irritation that may exacerbate pruritus (Cherny, 2002).

Ascites accumulate as a result of an imbalance in the normal state of influx and efflux of fluid from the peritoneal cavity. The decreased rate of efflux may be caused by lymphatic blockage from tumor invasion (Keen & Fallon, 2002). Symptoms related to ascites include increased intra-abdominal pressure, abdominal wall discomfort, dyspnea, anorexia, early satiety, nausea and vomiting, esophageal reflux, pain, and peripheral edema (Keen & Fallon).

Diuretics remain the standard for managing ascites in patients with cancer, with response rates ranging from 38%–86% (Gough & Balderson, 1993; Greenway, Johnson, & Williams, 1982). A potassium-sparing diuretic combined with a loop diuretic helps treat ascites secondary to hepatic cirrhosis (Keen & Fallon, 2002). Abdominal paracentesis remains the most common procedure for treating ascites. The procedure affords quick symptomatic relief and is useful in patients with HCC when diuretics are either ineffective or require a significant lag period prior to efficacy.

**Managing the Side Effects of Sorafenib**

In pivotal clinical trials for HCC, common side effects from sorafenib include fatigue, diarrhea, and hand-foot skin reactions. The drug should be taken on an empty stomach one hour before meals or two hours after (Wood, 2006). For fatigue management, healthcare providers and patients should communicate
Nursing Implications

HCC is a leading cause of cancer-related mortality worldwide, primarily because of the high incidence of unresectable, metastatic disease in patients with HCC, which inevitably leads to poor prognosis. Therefore, aggressive symptom management of disease-related and treatment-related symptoms is critical in preserving functional status and quality of life in patients with unresectable, advanced HCC. Oncology nurses can impact the care of patients with HCC by using several methods. First, nurses should become familiar with the established guidelines for managing common cancer-related symptoms (e.g., pain, fatigue, weight loss). The guidelines are based largely on evidence presented in the literature and should aid in developing individualized strategies for symptom management based on patient preferences, physical status, and disease condition. In addition, nurses can provide counseling and education for patients with HCC on disease-related and treatment-related symptoms commonly seen in that population. Finally, nurses can bridge the communication of symptoms between patients and clinicians through advocacy and thorough symptom assessment. Early identification of symptom burden can facilitate the prompt referral of patients with HCC to experts in supportive care services (nutrition, rehabilitation, and pain specialist) for symptom control.

The complex interplay of physical, psychological, social, spiritual, existential, medical, financial, and social burdens experienced by patients with HCC make an integrative team approach imperative. Quality symptom management is best delivered in a collaborative environment that integrates the skills of medicine, nursing, and supportive care professionals. Nurses must foster collaborative, multidisciplinary methods of symptom management to improve the physical functioning and quality of life in patients with HCC.

Author Contact: Virginia Chih-Yi Sun, RN, MSN, ANP, can be reached at vsun@coh.org, with copy to editor at CJONEditor@ons.org.

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