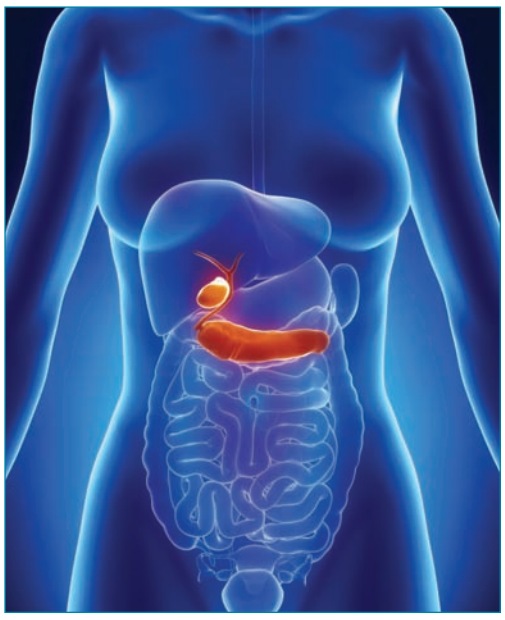
ASCO Guidelines Direct Clinical Decisions for Biliary Tract Cancer

BY CHUCK HOLT

Is adjuvant therapy, including fluoropyrimidine-based or gemcitabine-based chemotherapy and/or radiation therapy recommended for patients with resected biliary tract cancer?

That was the clinical question which guided an expert panel assembled by ASCO to develop a set of evidence-based guidelines aimed at assisting clinical practice decision-making for patients with biliary tract cancer (BTC) (*J Clin Oncol* 2019;37(12):1015-1027).

Based primarily on results from a phase III randomized controlled trial, the ASCO panel recommended patients with BTC be offered adjuvant capecitabine chemoradiation therapy for 6 months, which they concluded "may be a reasonable option to address the goal of reducing the risk of local recurrence."



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Additionally, the new guidelines recommend patients with extrahepatic cholangiocarcinoma, along with a microscopically positive surgical resection margin (R1 section), may be offered chemoradiation therapy.

Finally, a shared decision-making approach was recommended by the ASCO panel of experts, "considering the risk of harm and potential for benefit associated with radiation therapy for patients with gallbladder cancer."

The new guidelines were necessitated by a high rate of recurrence, the lack of a standard of care for adjuvant therapy, and an evidence base consisting mostly of small, retrospective studies that previously investigated treatments for BTC.

In addition to gallbladder cancer, BTC includes intrahepatic, perihilar, and distal cholangiocarcinomas, all of which involve a malignant transformation of the epithelium with biliary differentiation despite their diverse genetic makeup. Surgery and perioperative care is the typical treatment approach for these tumors. Chemoradiation therapy (CRT) is used sparingly and primarily for recurrent or metastatic disease.

BTC is found most often in the gallbladder, and depending on the stage at diagnosis, has a 5-year survival rate ranging from 2 to 70 percent. The 5-year relative survival rates for intrahepatic cholangiocarcinoma are 2-15 percent, and for extrahepatic cholangiocarcinoma they are 2-30 percent. Hilar tumors are most common and account for 60-70 percent of all cholangiocarcinomas.

And although considered relatively rare in Western countries, in 2018, there were 12,190 new diagnoses and 3,700 deaths from gallbladder cancer and extrahepatic bile duct cancer in the U.S. alone.

A Systematic Review

The primary evidence informing the new ASCO guidelines for BTC was the results of the phase III study, "Capecitabine or Observation after Surgery in Treating Patients with Biliary Tract Cancer (BILCAP)," a randomized clinical trial conducted in the U.K. (*Lancet Oncol* 2019;20(5):663-673).

The BILCAP study was the first positive phase III randomized controlled trial in resected biliary tract cancer. The study confirmed the benefit of adjuvant capecitabine, according to the ASCO panel, which "found no high-level evidence" to warrant recommending radiation therapy alone for patients with BTC.

From 2006 to 2014, the BILCAP clinical trial enrolled 447 patients, 223 of whom were randomized to a capecitabine group and the remainder to an observation group. Nearly half of the patients in each group underwent treatment involving their lymph nodes. About 38 percent of both groups had an R1 resection.

CME/CNE Article

The primary BTC sites included 84 intrahepatic (19%), 128 hilar (28%), 156 extrahepatic CCA (35%), and 79 muscle-invasive gallbladder cancers (35%). In the intention-to-treat analysis, median overall survival (OS) was 51.1 months (95% CI 34.6-59.1) in the capecitabine group and 36.4 months (29.7-44.5) in the observation group (adjusted HR 0.81, 95% CI 0.63-1.04).

In the BILCAP trial, capecitabine was dosed at 1,250 mg/m^2 twice per day during days 1-14 of a 3-week cycle for 8 cycles. The 6 months of adjuvant capecitabine chemotherapy recommended in the new guidelines for BTC should only be offered following resection, although it is fine for the dose to be determined by institutional and regional practices, the ASCO panel concluded.

In recommending patients with extrahepatic cholangiocarcinoma and R1 resection receive CRT, the ASCO panel noted how well patients tolerated radiation in the Southwest Oncology Group's phase II study, SWOG S0809 (*J Clin Oncol* 2015;33(24):2617-2622).

In that prospective, single-arm clinical trial of CRT, radiation was delivered at 45.0 Gy to regional and 54.0-59.4 Gy to the tumor beds of 79 patients with hilar cholangiocarcinoma (48%), distal cholangiocarcinoma (16%), and gallbladder cancer (32%). A similar rate of local recurrence and median OS occurred in the R0 and R1 subgroups, despite the latter being expected to have poorer outcomes.

The ASCO panel stopped short of recommending optimal dosing of CRT based on SWOG S0809, however, citing an underdeveloped evidence base. While the SWOG researchers only "cautiously attribute" the positive effect of the treatment on the R1 group of patients to the efficacy of adjuvant therapy, they noted.

Informing the Guidelines

In addition to the important phase II SWOG S0809 study, which the ASCO panel said "surpassed its predetermined threshold for efficacy and demonstrates the feasibility of conducting a national trial in this patient population," important data that informed the new guidelines was gleaned from previous phase III studies of adjuvant therapy for BTC, including the Ebata, et al, and PRODIGE 12 randomized controlled trials.

Ebata, et al, enrolled 225 patients in Japan with extrahepatic cholangiocarcinoma (45% hilar and 55% distal) (*Br J Surg* 2018;105(3):192-202). Patients with resected bile duct cancer were randomized to gemcitabine and observation groups by lymph node status, residual tumor status, and tumor location in the phase III study titled "Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer."

Patients received 1,000 mg/m^2 of gemcitabine intravenously on days 1, 8, and 15 every 4 weeks for 6 cycles. No significant differences were observed in OS (median 62.3 vs. 63.8 months, respectively; HR 1.01, 95% CI 0.70-1.45; P=0·964) or relapse-free survival (RFS) (median 36.0 vs. 39.9 months; HR 0.93, 0.66 to 1.32; P=0.693).

Because the clinical trial by Ebata, et al, failed to enroll the intended number of patients, "it may have resulted in an underpowered analysis," the ASCO panel concluded, despite the authors' position that the small size of their study was unlikely to have affected the results.

The PRODIGE 12-ACCORD 18 (UNICANCER GI) clinical trial (*Ann Oncol* 2017;28:v605-v649; suppl 5; abstr LBA29) asked if gemcitabine and oxaliplatin chemotherapy (GEMOX) would increase

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RFS and maintain health-related quality of life (HRQOL) in patients with a resection.

The French multicenter, open-label, randomized, phase III study included 196 patients with intrahepatic (46%), perihilar (8%), or distal (27%) cholangiocarcinoma, or gallbladder adenocarcinoma (20%). GEMOX was dosed as gemcitabine 1,000 mg/m^2 on day 1 and oxaliplatin 85 mg/m^2 was infused on day 2 of a 2-week cycle for 12 cycles.

At a median follow-up of 46.5 months (95% CI, 42.6-49.3 months), 126 RFS events and 82 deaths were reported, but no significant differences in RFS between the study's two arms, the time-to-definitive deterioration of global HRQOL, or OS.

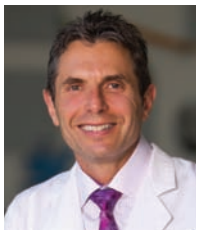
"The PRODIGE 12 trial had significant imprecision around the estimate for the primary outcome of RFS," the ASCO panel noted in the new BTC guidelines, adding, "Evidence quality (i.e., certainty) for the comparisons of gemcitabine plus oxaliplatin or gemcitabine alone versus observation was judged to be low due to these limitations."

The new ASCO guidelines for BTC also provided evidence- and consensus-based recommendation for patients with microscopically positive surgical margins. The expert panel is anticipating results from two ongoing clinical trials "will further inform clinical decision-making for this patient population."

The studies cited studies include the ACTICCA-1 randomized controlled trial comparing cisplatin and gemcitabine to capecitabine, and the Japan Clinical Oncology Group Study 1202 assessing treatment with adjuvant S-1 in patients with resected BTC, which the ASCO panel says "might shed light on the role of fluoropyrimidines."

Looking forward, future research should focus on "high-risk patient subgroups and reported results for specific biliary tract subsites and/or specific molecular alterations," say the ASCO panelists, who state collectively that they "will continue to assess the currency of these recommendations and consider the need to update this guideline on an annual basis."

Influence On Clinical Practice


ANTON BILCHIK, MD, PHD

To better understand the real-world impact on clinical practices, *Oncology Times* asked Anton Bilchik, MD, PhD, Professor of Surgery and Chief of Gastrointestinal Research at John Wayne Cancer Institute at Providence Saint John's Health Center in Santa Monica, Calif., to share his thoughts about the new ASCO guidelines to assist clinical decision-making for patients with BTC.

Bilchik is an internationally recognized surgeon and scientist who pioneered techniques to improve staging in colon cancer and minimally invasive approaches for liver and pancreas cancer. He is trained and certified in advanced laparoscopic and robotic surgery, and also serves as an investigator on international multicenter clinical trials with more than 200 publications. He is considered one of the country's leading specialists in surgical oncology.

What is your overall opinion of the new ASCO guidelines to assist clinical decision-making for patients with BTC?
"This is very important since this is the first time guidelines have been provided for the adjuvant treatment of biliary tract cancer based on level-one data. Most trials have either been negative or accrual has not been met and therefore trials have been closed prematurely."

Do you treat patients with capecitabine as adjuvant therapy as recommended by the ASCO panel? If so, what were the patient outcomes?
"Yes, we have. But most patients receive a combination of gemcitabine and cisplatin. Capecitabine is particularly appealing because it is mostly well-tolerated and can be given in pill form. The outcomes vary largely because biliary tract cancers include both bile duct cancers and gallbladder cancer."

Do you agree with the recommendation that patients with gallbladder cancer and an R1 section receive chemoradiation therapy?
"Yes, it makes sense that patients with an R1 resection should receive chemoradiation to reduce the risk of local recurrence. Most of our patients receive chemoradiation if they have a good performance status."

How important do you feel shared decision-making is in caring for this patient population?
"It is essential because these cancers mostly present late with few curative options. Furthermore, because these cancers are not that common compared with other cancers, prospective studies have been very challenging to complete, leaving decision-making often to the individual oncologist based on best judgment."

Is there anything you think the ASCO panel should have recommended but did not, or anything else you would like to add about the new guidelines?
"I think ASCO should have discussed the potential for targeted treatment such as [trastuzumab] in HER-2 positive tumors. Also, there is a wide variation in how radiation is delivered—short course (SBIRT) versus the standard long course." OT

Chuck Holt is a contributing writer.

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Learning Objectives for This Month's CME Activity:

After participating in this CME/CNE activity, readers should be better able to:
1. Analyze issues regarding biliary tract cancer (BTC) and current treatment recommendations.
2. Select evidence supporting guidelines by the American Society of Clinical Oncology (ASCO) for treating patients with BTC.

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