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EDITORIAL – HEPATOBILIARY TUMORS

Incidental Gallbladder Cancer: Permission to Operate

Suna Erdem, MD[1], and Rebekah R. White, MD[1]

University of California San Diego, La Jolla, CA

With fewer than 10,000 cases per year diagnosed in the U.S., gallbladder cancer (GBC) is uncommon but not rare. Due to lack of specific symptoms, GBC is usually not suspected preoperatively. Cholecystectomy is one of the most common surgical procedures worldwide, and the proportion of GBC cases diagnosed "incidentally" by the pathologist ranges from 0.2 to 2% of cholecystectomy specimens, depending on the country.[1–3] According to the Americas HPB Association (AHPBA) consensus meeting of international experts in 2014, re-resection is recommended in $\geq$ T1b stages, provided there is no evidence of metastatic disease, with the goal of achieving (or ensuring) an R0 resection.[4] Re-resection after initial cholecystectomy should include (at minimum) either an anatomic liver resection of segment IVb/V or a wedge resection of the gallbladder bed and portal lymph node dissection. There is ongoing debate, however, as to whether all patients, irrespective of stage, will benefit from re-resection. The recommendation for re-resection is perhaps most controversial for early stage (T1b) disease, in which the incidence of residual disease is relatively low, and for more advanced (T3) disease, in which outcomes are so poor that re-resection might be considered futile.

Several studies have demonstrated that the risk of finding residual disease at the time of re-resection increases with increasing T stage. Several studies have also demonstrated that patients who either have no residual disease or are able to undergo complete resection of residual disease have better outcomes than those who cannot. Most of these studies have been single or multi-institution retrospective database studies. Most did not include a "control" population of patients who did not undergo re-resection, since many of these patients do not ever present to the tertiary and quaternary centers that are conducting the studies. Until this issue, the only study able to capture a complete population of incidental GBC was the recent study by Lundgren et al., by cross-linking data from the Swedish Registry of Gallstone Surgery (GallRiks) with the national registry for liver surgery (SweLiv) and the Cancer Registry.[5] They observed significantly better survival in patients with T2 and T3 tumors undergoing re-resection than those who did not.

It is acknowledged that much of the perceived benefit of re-resection may be attributable to selection. Only fit patients who do not demonstrate disease progression are able to undergo complete re-resection, and patients without residual disease do much better than patients with residual disease. Perhaps these patients without identified residual disease would have done just as well without re-resection, and patients with residual disease would have done just as poorly. Despite increasing numbers of incidental GBC, it is still an uncommon disease. Thus, it would be difficult to conduct a sufficiently-sized randomized study comparing re-resection of incidental GBC to observation. Consequently, there is no high level evidence showing that re-resection actually provides a therapeutic benefit.

In this issue, de Savornin Lohman and colleagues have addressed this controversial question in another retrospective, nationwide cohort study based on patient data from the Netherlands Cancer Study Registry.[6] Patients with suspected GBC prior to operation were excluded, as well as those with T1a tumors or metastatic disease (diagnosed within 6 months of initial cholecystectomy). Re-resection was defined as any gallbladder-related operation within 6 months of initial cholecystectomy. According to the Dutch standard of care, none of these patients received adjuvant chemo- or radiotherapy. Only 24% of patients underwent re-resection, which is much lower than in the

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R. R. White, MD
e-mail: rewhite@ucsd.edu

Swedish study, and the reason(s) were not available. However, patients that underwent re-resection had significantly longer median overall survival than patients who did not (53 vs. 14 months), similar to the Swedish study. This difference persisted when analysis was limited to patients with an R0 resection margin following initial cholecystectomy (84 vs. 26 months). In subgroup analysis, the differences in survival were most apparent in patients with T2 tumors (60 vs. 18 months) but remained significant in patients with T3 tumors (23 vs. 12 months). There was not a significant difference in survival between patients with T1b tumors who underwent re-resection and those who did not, although this subgroup was small. Similar to prior studies, the most important predictor of survival following re-resection was the presence of residual disease. Although median survival in patients with residual disease was much worse than those without (23 months vs. not reached), it was still better than those who did not undergo re-resection.

The greatest strength of the current study is the relative homogeneity of the patient population and health care in the Netherlands, which is remarkably different than the health care system in the U.S. All adults living or working in the Netherlands have compulsory insurance, managed by the government, which provides the same basic health coverage across all insurers. There is variability in access to optional supplementary insurance policies that provide coverage for certain specialty services, but there is clearly less disparity than in the U.S. Furthermore, the Netherlands Cancer Registry (NCR) compiles clinical data for all patients with newly diagnosed cancer in the Netherlands. The Dutch population is not as migratory as the U.S. population, and the ability to obtain complete follow-up data on recurrence and survival is much better.

The biggest weakness of the study is that we do not know why 75% of patients did not undergo re-resection, but it suggests that Dutch surgeons were quite selective. First, patients who had metastatic disease detected on staging laparoscopy prior to planned re-resection were excluded from the study along with patients who had metastatic disease detected on imaging. The study did not report how many patients underwent staging laparoscopy prior to intended re-resection, but presumably more than 25% of patients underwent surgery with the *intent* of re-resection. Patients underoing surgery are more accurately staged than those who do not, and this type of selection may have accounted for some of the differences in survival. Second, patients who underwent re-resection were younger on average (63 vs. 72 years) than patients who did not; perhaps the decision not to offer re-resection was sometimes based on poor performance status or comorbidities. Third, certain details related to the initial surgery, such as approach, perforation, or other complications, were not reported and may have influenced the decision. However, these factors cannot completely account for such a low rate of re-resection, which suggests that there is inconsistent application of the consensus recommendations. Although not a randomized comparison, this variability in practice does create roughly comparable groups of patients that were treated differently. Overall, it seems unlikely that the large differences in survival observed in this study could be attributable to selection alone.

So, why are surgeons reluctant to reoperate on patients with incidental GBC? Even the minimal recommended procedure (wedge resection of IVB/V with portal lymph node sampling) has to be considered at least a moderate-risk procedure. We are understandably hesitant to perform a moderate-risk operation on someone whom we suspect has no residual disease. It is particularly difficult to differentiate residual disease from postoperative changes after cholecystectomy, and there are inherent unknowns to reoperative surgery, especially when we did not perform the first surgery. We are also appropriately hesitant to perform a moderate-risk operation on someone who has a high risk of already having distant metastatic disease, since we know their prognosis is dismal.

There is strong rationale for adjuvant therapy in GBC, given that the majority of patients will develop recurrent disease after surgery. Adjuvant chemoradiation has been offered to selected high-risk patients on the basis of low-level evidence.[4] For the same reasons that there have been no randomized trials addressing the role of re-resection in incidental GBC, there have been no dedicated randomized trials addressing the role of adjuvant therapy in GBC. Despite having distinct genomic profiles, they have been lumped together with cholangiocarcinoma in most studies.[7] The ABC-02 study established the combination of gemcitabine and cisplatin as the most effective regimen in patients with advanced biliary cancer, including gallbladder cancer.[8] The recent BILCAP study demonstrated a survival benefit for adjuvant capecitabine in patients with biliary cancers, including gallbladder cancers, who underwent complete radical resection of the primary tumor with liver and/or pancreas (i.e., not just cholecystectomy).[9] The findings of the BILCAP study therefore cannot necessarily be extended to patients who underwent cholecystectomy only for incidental GBC, but they should be applicable to patients who undergo radical re-resection.

None of the patients in the Dutch study received adjuvant therapy, and it is not clear whether the potential benefits of re-resection will be increased or decreased by adjuvant therapy. However, the availability of effective systemic agents raises an obvious question: should adjuvant therapy be given before re-resection to give patients a biological test-of-time? This is more appealing than adjuvant chemoradiation prior to re-resection. Yet, this

question will be even harder to answer than whether to perform re-resection at all. This is especially true since, just as gemcitabine was not the "final answer" in pancreatic cancer, capecitabine (nor gemcitabine plus cisplatin) is not going to be the "final answer" in GBC. Deeper understanding of the genomics of GBC will hopefully lead to more effective targeted and/or personalized therapies. Meanwhile, the Dutch and Swedish studies, together with the availability of moderately effective systemic agents, should help to decrease nihilism about "middle" stage GBC and increase enthusiasm for re-resection.

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