



## The Undertreatment of Gallbladder Cancer: Gaps in Seeking, Reaching, and Receiving Care

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Gallbladder cancer (GBC) is an aggressive disease that carries a poor prognosis, with a 5-year overall survival rate of 5–13%. It is a rare malignancy with an estimated annual incidence of 0.4–1.4 cases per 100,000 population.<sup>1</sup> There are a number of known risk factors associated with GBC, including chronic inflammatory states related to cholelithiasis and gallbladder polyps, as well as modifiable risk factors, such as obesity, poor diet, and chronic *Salmonella* or *Helicobacter* infections. GBC can be classified into two subgroups: incidental GBC and non-incidental, or per primum, GBC. Incidental GBC is diagnosed following routine cholecystectomy for presumed benign disease and accounts for the majority of cases, approximately 50–70%. Per primum GBC comprises the remaining 30–50% and typically presents at more advanced stages due to the lack of early clinical features.

Papageorge and colleagues conducted a retrospective review of the National Cancer Database for patients who were diagnosed with incidental GBC between 2004 and 2015 to evaluate re-resection rates and survival outcomes.<sup>2</sup> Within this study, only 7.6% of patients underwent re-resection, a trend not unique to this cohort of patients that highlights a nationwide breakdown in the management of GBC. The undertreatment of GBC is multifactorial. The authors outline two areas that represent major barriers to care: patient-specific variables, which include race and insurance status, and institutional barriers, such as institution-specific practices and type of facility. However, access

to healthcare extends beyond patient-limiting and institution-specific factors and encompasses system-wide challenges.

Indeed, GBC is a rare cancer often not encountered by many clinicians, and community general surgeons and oncologists alike may not be aware of the standard-of-care approaches to this disease, simply due to a lack of familiarity. This is particularly true for patients with incidental GBC, who undergo cholecystectomy for presumed benign disease and are subsequently referred to a medical oncologist for their newly diagnosed malignancy. This practice pattern is encountered all too frequently in the management of this rare disease, where patients are ultimately managed with only chemotherapy and/or radiation and are never referred to a surgical oncologist for re-resection.

Thus, a patient's ability to seek the appropriate care is at the mercy of their provider. Unlike the early management for more common malignancies, such as breast or colorectal cancer, which follows an algorithmic pattern of screening followed by as-needed advanced referral for an abnormal result, patients with incidental GBC rely on the expertise of their surgeon to make the appropriate referral to a hepatobiliary surgeon and/or surgical oncologist. In this setting, physicians are tasked with staying informed of practice guidelines for the management of such rare disease that most will have limited to no experience with during their career. From a surgeon's perspective, this means knowing when a simple cholecystectomy is sufficient for disease control and when patients require referral to oncology-trained specialists. Telehealth consultation and remote radiology review, particularly going forward after our experience and adaptation to the stress that coronavirus disease 2019 (COVID-19) applied to the healthcare system, may provide a new avenue to obtain a specialist's opinion. Utilizing educational platforms through large and far-reaching organizations such as the American College of

Surgeons can be very beneficial in this regard. Similarly, the American Society of Clinical Oncology (ASCO) can serve as a vital resource to disseminate this information; specifically, the value of re-resection in T-stage-appropriate incidental GBC, to medical oncologists in the community, and provide resources that will allow patients to reach the appropriate care.

Still, referral is only the first step in managing these complex diseases—reaching care has proved to be an even greater obstacle. Even as patients are referred for intervention that is T-stage appropriate, they are faced with profound physical and socioeconomic challenges that are only magnified as they attempt to navigate the healthcare system. Access to specialty-trained physicians at large academic centers is not guaranteed. The finding that a greater proportion of those who underwent re-resection were non-Black patients and patients with private insurance is not novel and underscores the continued failures of the healthcare system as a whole. How do we overcome widespread socioeconomic barriers that preclude patients from seeking care at an appropriate referral center? How do we hurdle the physical and geographic challenges that isolate patients from these large care centers?

Surgical resection offers the only potentially curative option in the management of GBC. Hepatic resection of segments IVB and V with portal lymph node dissection is recommended for T1b or greater lesions to achieve an R0 resection and remove any residual disease, whereas simple cholecystectomy with negative surgical margins is adequate for T1a tumors that are confined to the lamina propria.<sup>3</sup> As the incidence of residual disease ranges from 10 to 70% with advancing T stage,<sup>4,5</sup> re-resection is recommended for incidental GBC with T1b or greater lesions unless contraindicated due to advanced disease or poor performance status. There are other nuances related to the indication for re-resection, such as the specific location of the tumor (peritoneal vs. hepatic side) and lymph node data available at the time of cholecystectomy (e.g. Calot's node). Regardless, these decisions should be made in consort with a disease specialist and again highlights the importance of appropriate referrals. Despite some reports of residual disease in port-site specimens, routine port-site excision during re-resection for incidental GBC is not recommended due to increased morbidity in the absence of improved survival outcomes.<sup>6</sup>

Even after curative-intent resection, recurrence rates remain high, with the majority being distant recurrences.<sup>7</sup> Survival rates among patients who have disease recurrence are dismal, highlighting the role for adjuvant therapeutic options. The ASCO expert panel recommends the use of adjuvant capecitabine in all patients with GBC following resection, supported by the landmark phase III BILCAP trial, and select use of adjuvant chemoradiation in patients

with positive surgical resection margins.<sup>8</sup> However, the application of these adjuvant therapies is limited; the BILCAP trial did not meet its primary endpoint of improved survival on intention-to-treat analysis, and other studies have failed to demonstrate improved survival outcomes with the use of adjuvant radiation, highlighting the need for further prospective trials.

Another prime area for improvement and opportunity is therapies directed to the neoadjuvant setting. The Optimal Perioperative Therapy for Incidental Gallbladder Cancer (OPT-IN/EA2197) trial is an ongoing, randomized, phase II/III clinical trial through the National Clinical Trials Network (NCTN) in patients with stage II–III GBC comparing the addition of neoadjuvant chemotherapy with gemcitabine/cisplatin and the standard treatment paradigm of upfront surgical resection and adjuvant chemotherapy alone (NCT04559139). Likewise, patients are faced with the challenges of seeking and reaching care, relying on physician knowledge of these opportunities and their own ability to access them. Ongoing physician education will be vital as we continue the pursuit of better understanding these disease states and improving patient care, both in the neoadjuvant and adjuvant settings.

Nationwide, adherence to practice guidelines in the management of GBC is low. These failures stem from a lack of familiarity and resources in the community surrounding the appropriate management of this rare disease, patient-specific factors that limit a patient's ability to both reach and receive care, and system-wide barriers that further hinder patient care. Is clinician and institutional education enough to meet these challenges? Are centralized specialty care and socialized medicine necessary to overcome these ongoing challenges that plague the healthcare system? Identifying the problem is simple, finding durable solutions is a need that has not yet been met. The fact remains, we need to do better.

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