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REVIEW ARTICLE

Selecting treatment sequence for patients with incidental gallbladder cancer: a neoadjuvant approach versus upfront surgery

Leonid Cherkassky[2] · **William Jarnagin**[1]

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Abstract

At MSKCC, over 50% of the patients presenting with gallbladder cancer have been diagnosed incidentally following elective cholecystectomy for presumed benign disease. While traditional management of incidental gallbladder cancer (IGBC) dictates re-resection with the ultimate goal of achieving cure, surgical decision-making must take into account that this malignancy is characterized by poor tumor biology with frequent distant recurrence. Since early and frequent distant recurrence is the most common cause of surgical failure, the surgical oncologist's goal should be to selectively re-resect only those patients most likely to benefit from an operation. The astute surgeon recognizes the high-risk patients who likely have micrometastatic disease at the time of diagnosis and alters the treatment sequence, delivering neoadjuvant chemotherapy. This strategy acts as a selection tool, as those progressing at distant sites during therapy are spared the morbidity and mortality of surgery and furthermore has the potential to treat micrometastatic disease. However, a chemotherapy first approach must be applied selectively since a poor response risks local progression to unresectability and a decrease in functional status that comes from the toxicities of dual agent chemotherapy that can impair surgical candidacy. To balance these risks and benefits, two other criteria for a neoadjuvant approach must be met: i) reliable identification of those patients who are at high risk of distant recurrence and who are, therefore, most likely to benefit from a systemic therapy first approach and ii) availability of *effective* chemotherapy options. In this review, we will outline the data and judgement we use to select a treatment sequence at our institution.

Keywords Incidental gallbladder cancer management · Neoadjuvant chemotherapy hepatobiliary malignancies

✉ William Jarnagin
jarnagiw@mskcc.org

Leonid Cherkassky
cherkasl@mskcc.org

[1] Leslie Blumgart Chair in Surgery, Department of Surgical Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

[2] Clinical Fellow in Complex General Surgical Oncology, Department of Surgical Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

Key points

Incidental gallbladder carcinoma (IGBC) is diagnosed on pathology following cholecystectomy for presumed benign disease.

Standard management dictates re-resection to remove residual disease with the ultimate goal of cure—or at least prolonged survival.

Gallbladder cancer is characterized by an early and frequent distant recurrence pattern that is the most common cause of surgical failure.

Patients identified as high risk for early distant recurrence (node-positive, advanced T stage, residual disease, and poorly differentiated) may be best managed with neoadjuvant systemic therapy.

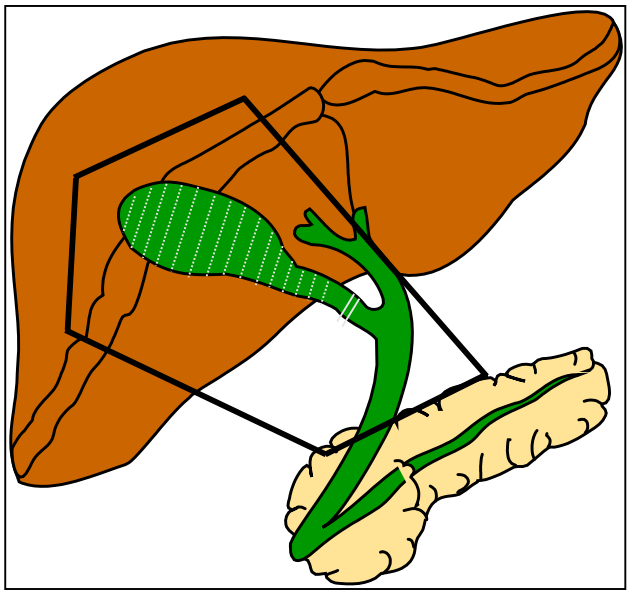

Fig. 1 The goal of re-operation and definitive resection for incidental gallbladder cancer is to clear disease from the liver and porta hepatis. The most common approach involves removal of liver tissue around the gallbladder fossa (segmentectomy 4/5) and porta hepatis lymphadenectomy

Re-resection is the standard approach to managing IGBC

The patient with IGBC presents with a histologic diagnosis of malignancy after an elective cholecystectomy for presumed benign disease. For T1b tumors (invasion into the muscle layer) and above, transection along the muscular wall-cystic plate plane is a substandard cancer operation that risks leaving residual disease within the liver and regional lymph nodes; therefore, standard management is re-resection to R0 status following adequate staging [1] to rule out measurable distant disease and selectively staging with laparoscopy to exclude peritoneal disease prior to committing to laparotomy [2]. The surgical strategy is to clear the liver and porta hepatis of residual disease, typically involving resection of liver around the gallbladder fossa (segment 4/5 partial hepatectomy) and portal lymphadenectomy (see Fig. 1). More extensive liver and extrahepatic bile duct resections are infrequently indicated or required and only performed when necessary to achieve negative margins [3].

The rational for re-resection is to remove gross and/or microscopic residual disease left behind at initial cholecystectomy, which is found in 45–60% [4–6] of re-resection specimens. When compared to nonoperative management, re-resection is associated with significantly improved oncologic outcomes. A French cohort study demonstrated 5 year OS rates of 41% for re-resection when compared to 15% for those patients treated nonoperatively [7], and in our experience a DSS of 42.8 months is achieved for all comers who proceed to re-resection [8]. Multiple other multicenter and single institution cohort studies in Japan, Europe, and the US also observed an association with a survival advantage for re-resection [9–12].

These results are achieved despite the concern that violation of the subserosal plane at the time of simple cholecystectomy would cut into invasive tumor, disseminating cells and negating the benefit of re-resection. This break in the principle of en bloc resection is of particular concern in gallbladder cancer given its predisposition to peritoneal seeding as evidenced by a propensity for port site [13, 14], biopsy tract, and peritoneal seeding in the case of bile spillage [11]. Despite this theoretical risk, the incidental diagnosis does not preclude re-resection for curative intent. Our experience is of similar outcomes for re-resected IGBC patients compared to primarily resected patients when matched for stage [8, 15]. In fact, those patients presenting with IGBC are more likely to undergo curative-intent resection (32 vs 14%) likely because of presentation at earlier stages of the disease and a lower likelihood of involvement of biliary and vascular structures. Patients who undergo re-resection reach median OS of 26 months and a 5 year OS of 35–42% for all stages [8, 15, 16] and in the case of T2 disease a 5 year OS above 60% can be achieved [8, 17, 18].

Re-resection is typically performed for AJCC (American Joint Committee on Cancer)please clarify the acronym T1b-3 tumors [19] (see Fig. 2). T1a (confined to the mucosa and not invading the muscularis layer) cancers are considered cured by cholecystectomy alone [7]. T4 tumors—staged

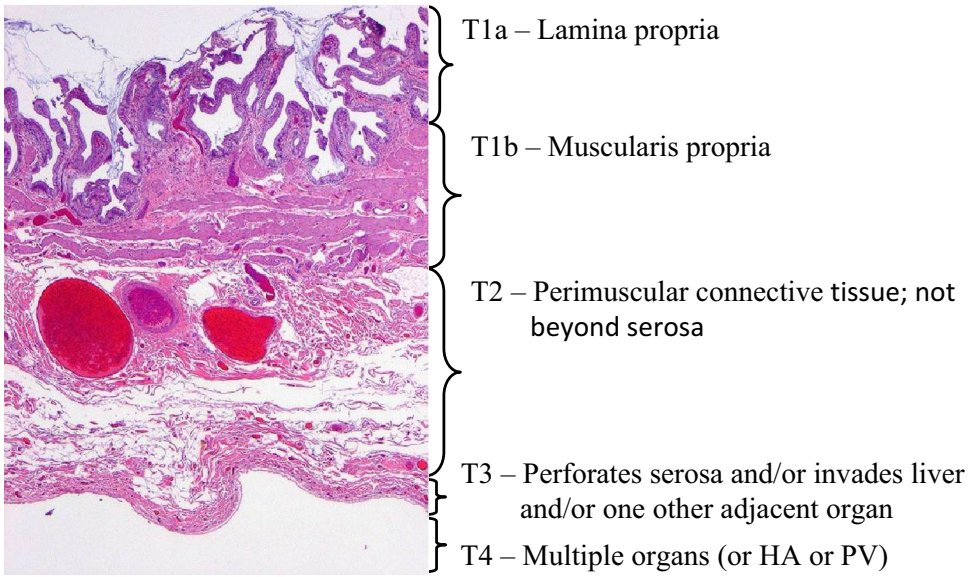

Fig. 2 T-staging system for gallbladder cancer

as such on the basis of main portal vein or hepatic artery invasion or invasion of two or more extrahepatic organs—do not benefit from resection, and are, therefore, appropriately staged in the IV category [15]. Re-resection for T1b cancers was once controversial. While some series report 95–100% 5 year overall survival rates for T1 patients who undergo simple cholecystectomy alone [11, 12], these studies are limited by a low number of T1b patients. A SEER (please specify the acronym)database (Surveillance, Epidemiology and End Results Program) study that included larger numbers found that extended cholecystectomy is associated with improved DSS and OS for extended cholecystectomy in T1b but not T1a patients [20]. Furthermore, residual disease can be present in up to 35.7% (5/14 patients in our series) of patients staged T1b following simple cholecystectomy [21], which that patients are being understaged after initial cholecystectomy (either T or N stage) and/or cells invading into the muscular layer may potentially seed the cystic plate upon violation of the subserosal plane during simple cholecystectomy. Regardless of the explanation, re-resection is indicated.

Frequent, distant recurrence is the major cause of failure of surgery

The discussion thus far has focused on data that justify re-resection for IGBC. However, when the data are analyzed more closely, there appears to be a significant fraction of patients whose outcome is characterized by poor tumor biology with early and frequent distant recurrence followed closely by death. Recurrence in gallbladder cancer occurs early: median time to recurrence is 11 months, 62% of patients who recur do so within 12 months and 88% within 24 month. And in the vast majority recurrence is distant (85%). Salvage is rare, and so the OS of 20.6 months closely mirrors the RFS curve [22, 23]. A primarily distant recurrence negates the therapeutic benefit of any local therapy such as surgery, and the earlier the recurrence the more irrelevant the surgery is in improving the patient's overall prognosis, except to lessen their quality of life. It would seem clear that such early and distant recurrence likely reflects the presence of metastatic disease that was undetectable by imaging at the time of initial diagnosis, and if that is the case, demands reconsideration of the standard approach of upfront surgery in favor of a neoadjuvant systemic therapy approach.

Rationale for neoadjuvant systemic therapy

Over the last decade, management for gastrointestinal malignancies whose tumor biology closely mirrors gallbladder cancer has steadily moved in the direction of neoadjuvant therapy (NAT). The rationale for NAT are to (a) to immediately treat micrometastatic disease, (b) optimize patient selection for surgery, (c) favor treatment compliance, (d) allow for an in vivo assessment of tumor chemosensitivity that can guide future management decisions, and (e) downstage the primary tumor. The tumor biology of each malignancy and the physiological impact of surgery dictate which of these rationales are of primary importance. For example, in the case of breast cancer, distant recurrence is typically late, outcomes are overall favorable, and surgical morbidity does not prevent treatment compliance; therefore, NAT is most useful in downstaging primary tumor to allow for breast conservation and to forego the need for complete lymph node dissection [24]. By contrast, gastric and

pancreatic cancer most closely resemble gallbladder cancer with respect to tumor biology, and the rationale for NAT is most applicable to gallbladder cancer. The arguments listed above most relevant to malignancies characterized by predisposition for micrometastatic disease and bias for early and distant recurrence of which gastric, pancreatic, and gallbladder cancer are all examples are to (1) optimize patient selection for curative-intent resection, whereby those patients who progress at distant sites during systemic treatment can be spared the morbidity and mortality of surgery, (2) to immediately treat the micrometastatic disease that will ultimately determine outcome, and (3) favor treatment compliance since postoperative patients suffer from complications and deficits in functional status that hinder delivery of chemotherapy.

For both gastric and pancreatic cancer, there is evidence supporting a neoadjuvant approach in the setting of resectable disease. It is important to make clear, however, that these data support a shifting paradigm to upfront systemic treatment for malignancies with effective chemotherapy whereas the data supporting a therapeutic benefit is limited in the case of gallbladder cancer and awaits further investigation (as we will review later). In the case of gastric cancer, there is level 1 efficacy evidence [25, 26] supporting perioperative chemotherapy. Although the intervention group for the United Kingdom MAGIC trial was surgery alone and so we do not have a direct comparison of a neoadjuvant versus upfront surgery (with adjuvant therapy), results support providing chemotherapy in the preoperative setting. In comparing delivery of pre- and post-operative chemotherapy, treatment compliance improved in the preoperative setting (86 vs 50%). And in this malignancy with a high rate of predominantly distant recurrence, perioperative ECF (epirubicin, cisplatin, and 5-FU) benefited the distant metastatic rate (as well as the overall survival) by approximately 10%. Furthermore, as witnessed in a more recent phase III trial comparing ECF with FLOT (5-FU, leucovorin, oxaliplatin, docetaxel) perioperative regimens [25], upfront therapy can select favorable tumor biology. If we accept that those patients who progress during preoperative systemic therapy would not gain any benefit from surgery, 6% for ECF and 3% in the FLOT cohort are spared unnecessary surgery.

Another example is pancreatic cancer, which follows a similar pattern of distant recurrence and historically has a similar median OS to gallbladder cancer of about 2 years and a 5 year OS rate similar to T3 gallbladder cancer [27] (approximately 20%, although recent chemotherapy regimens may extend these estimates [28]). While neoadjuvant therapy is not supported by any level 1 data, practice has evolved to treat those patients determined on cross-sectional imaging to have possible vein or arterial involvement. While in some cases this represents resectable disease, surgeons recognize that such visceral vessel involvement may represent poor tumor biology and select these patients for neoadjuvant therapy. In two single-arm phase II trials conducted by the US multicenter ALLIANCE group [29] and another at Massachusetts General Hospital [30] for borderline resectable cases, 5-18% of patients progressed at distant sites, thus sparing these patients surgical morbidity. Furthermore, patients ultimately selected for resection demonstrated a PFS of up to 48.6 months. Based on these data and the tumor biology of pancreatic cancer, some institutions now argue for this approach in all patients with pancreatic cancer [31]. Thus, experience with these two GI malignancies informs and justify a neoadjuvant approach for patients with gallbladder cancer at particularly high risk for early distant recurrence.

Time as a component of staging

As a component of the neoadjuvant strategy, the passage of time is an ally to selection strategy. A test of time allows for those patients with the most aggressive tumor biology to progress at distant sites already seeded with the disease, whereas those who remain localized are most likely to benefit from curative-intent resection and are selected for operation. Those who progress to the measurable disease within the timeframe of upfront chemotherapy likely already had metastatic spread that was simply undetectable by imaging, suggesting that the passage of time is really just a component of staging in which already metastatic disease is permitted to declare itself. In a typical neoadjuvant regimen, a gemcitabine backbone with or without a platinum may be administered for 3 months. The use of this time period as part of the selection strategy is inseparable from the actual systemic treatment.

A group from Newcastle, UK employs time as a component of staging without any concurrent systemic treatment following a diagnosis of IGBC [32]. In a published series of 49 T2 or T3 patients, these surgeons wait for 3 months without treatment or imaging. Patients are then reimaged, with 49% of patients proceeding to re-resection with curative intent, whereas the majority were inoperable at staging predominantly due to distant disease. While this series serves as a useful example to illustrate a point, a waiting period without active therapy risks local progression to unresectability and a missed window for curative-intent surgery. In addition, most patients would have difficulty waiting for such long periods without active treatment. In this series 2 patients were found locally advanced and, therefore, unresectable due to vascular involvement, and it is unknown whether they progressed to this stage during the waiting time after initial cholecystectomy. At MSKCC, a certain time component is unintentionally likely already implemented for patients referred from an outside institution even prior to

selection for NAT. The timing from initial cholecystectomy, to pathology results, and then referral to our hepatobiliary clinic with a follow-up staging CT scan is likely on the order of 1 month.

Criteria required for a successful neoadjuvant systemic therapy strategy

In addition to a tumor biology characterized by micrometastatic disease and high risk of distant recurrence, two important criteria must be met in order for the neoadjuvant approach to be successful:

1. Ability to identify those patients at high risk of distant recurrence, and therefore, most likely to benefit from NAT. In this way, chemotherapy-related toxicity is minimized in the group that should undergo upfront resection.
2. Availability of effective chemotherapy for both the local and the micrometastatic disease. While NAT makes oncologic sense, ineffective chemotherapy makes the objective impossible to achieve.

Selecting high-risk patients for neoadjuvant systemic therapy and IGBC as a unique situation

Neoadjuvant chemotherapy should be applied to selected patients most likely to progress to metastasis in the short term following curative-intent resection. This strategy optimally balances surgical morbidity with chemotherapy toxicity. Indiscriminate use subjects even low-risk patients to the impaired functional status which may delay surgery, make surgical intervention more risky, or even compromise surgical candidacy entirely. Elderly or morbid patients may be particularly predisposed to the negative effects of what may be a 70% rate of grade 3 or 4 toxicity (as seen in the ABC-02 trial for metastatic and locally advanced disease [33]). There are multiple characteristics that identify high-risk patients, including two that reflect prognostic factors readily recognized within the AJCC staging system: advanced T stage and node-positive disease. Others include residual disease—which our group at MSKCC has put forth and hepatic vs. peritoneal tumor location as identified by a multicenter group led by MD Anderson.

As we review these data it should be mentioned that IGBC provides a unique situation that provides supplemental pathology staging information prior to re-resection. This includes T staging and may include nodal staging in the case of submitted nodes in the cholecystectomy specimen. Furthermore, any positive margin at gallbladder or cystic duct likely indicates residual disease, which although a justification for re-resection, also ironically serves as a marker of poor prognosis that could potentially be used to justify neoadjuvant therapy.

Advanced T stage, node-positive disease, and other clinicopathologic factors are associated with distant recurrence

T and N stage prognosticate patient outcome (as would be expected for AJCC staging criteria [19]), and advanced T stage and node-positive disease associated with distant recurrence. A French cohort study [18] of IGBC demonstrated that 5 year OS is associated with T stage at diagnosis: 100%, 62,%, 19% and 0% of T1, T2, T3, and T4 patients were alive at 5 years. While T3 patients did benefit from re-resection, as evidenced by a tail to the overall survival curve indicating some long-term survivors, this represents only 19% of patients. This overall poor outcome especially when considering that a sizable fraction (40%) of patients died within 1 year supports a neoadjuvant approach forT3 patients. Multiple other retrospective studies including single-center studies and national database analyses have similarly identified an association between T stage and oncologic outcomes [3, 8, 34, 35].

Another high risk population are patients with node-positive disease. In a series published from our institution, 5 year DSS for node-positive patients was 17% (compared to 51% for node negative), and N stage was associated with worse DSS on multivariate analysis [3]. Consistent with the typical pattern of early distant recurrence, the time to event was less than 1 year for approximately 50% of patients. Other series similarly support an association with poor prognosis in node-positive disease [21, 34, 36]. It is important to identify node-positive disease in the discussion above as corresponding to regional nodes: those along the cystic duct, common bile duct, hepatic artery, and portal vein whereas those nodes along visceral vessels (periaortic, pericaval, superior mesenteric artery, and celiac artery) are classified as M1 [19].

Other clinicopathological factors predictive of patient survival include histologic grade of differentiation (well, moderate, or poor) [3, 21, 34, 36], lymphovascular invasion [21], achieving a total lymph node count ≥ 6 (which adequately stages patients) [34], CBD involvement [3], jaundice [8], and in keeping with predisposition to peritoneal seeding [11], a retrospective Canadian study found that bile spillage at index cholecystectomy was associated with peritoneal carcinomatosis and worse DFS [37].

Residual disease associates with poor outcomes

As a discussed above, justification for re-resection following a diagnosis of IGBC is performed with the goal of removing residual disease (RD) to achieve R0 status. Ironically, however, RD is also a marker of poor prognosis. The availability of both pathologic and imaging information may suggest the presence of RD and contribute to preoperative decision making: it may be suggested by imaging, or positive margins either at the gallbladder/liver interface or at the cystic duct. In our study of 135 patients with IGBC [21], the 61% of patients with RD demonstrated a DFS of 11 months and a DSS of 25 months as compared to 93 months and not reached for those without RD. Furthermore, RD remained an independent predictor in multivariate analysis. While an adverse impact of RD found in regional nodes or at distant sites (peritoneum, port sites, discontinuous liver lesions) on outcome is not unexpected because these findings necessarily change the stage of disease, we also observed (surprisingly) that even those patients with local RD within the gallbladder bed associated with the same poor prognosis. That local disease seems to be the clinical equivalent of regional and metastatic disease may be explained by initially inadequate staging for those patients with local disease (even when found with residual disease patients were still considered according to the original T stage), the possibility that local gallbladder fossa disease actually represented metastatic microscopic disease, and patient selection (none of these patients had grossly metastatic disease so even those patients deemed metastatic underwent curative-intent R0 resection). In any case, these results call into question the strategy of proceeding directly to re-resection in patients with known RD. And so this is a paradox: while we use the removal of RD to justify re-resection, it is for those patients with RD that we must strongly consider neoadjuvant chemotherapy.

Hepatic side tumors as a marker of poor prognosis

As part of the 8th edition AJCC staging criteria, T2 gallbladder cancers are now further stratified on the basis of the location at the hepatic or peritoneal side [19]. These staging criteria arise from a study of 437 patients conducted at four centers in the US, Chile, Italy, and Japan which found an independent association for hepatic side tumor location and worse OS following curative-intent resection specifically and only for T2 stage disease (hepatic side was 42.6% vs 64.7%) [36]. Tumors are classified as peritoneal when tumor infiltrates subserosa only at the free serosal side and as hepatic when at least part of the tumor infiltrates subserosal tissue in the part of the gallbladder wall attached to the liver. This prognostic difference may be explained by a dense network of lymphatics and larger vessels on the hepatic side of the gallbladder [38], resulting in a more direct drainage route to nodes and intrahepatic portal veins [39]. The hypothesis that this anatomical difference facilitates spread is supported by the study's finding of an association of hepatic side with distant node and intrahepatic recurrence as well as strong correlation with node-positive disease, vascular invasion, and microscopic disease in the adjacent liver. This study only stratifies patients in the T2 category. T1 tumors are associated with a good prognosis regardless of location (85–90% 5 year OS), and T3 tumors with poor prognosis (25–29% 5 year OS).

Effective chemotherapy as a necessary prerequisite for a neoadjuvant approach: extrapolating from the measurable disease setting

If we are to argue that neoadjuvant systemic therapy can be employed for immediate treatment of micrometastatic disease in this high-risk patient population, it follows that we should have effective chemotherapy to prevent or at least delay distant recurrence. In addition, effective chemotherapy is needed to ensure local control to avoid progression to unresectability and justify the potentially hazardous side effects that may impair surgical candidacy. Notably, there is no current level 1 evidence that supports a neoadjuvant systemic therapy approach to the management of IGBC. Any conclusions about the efficacy of chemotherapy in the neoadjuvant setting must, therefore, be extrapolated from adjuvant, locally advanced, and metastatic settings. The available studies unfortunately have found that systemic therapy for gallbladder cancer is not as effective when compared to therapies for other GI malignancies. Response rates are lower, and the progression of the disease more common. Typically a gem/platinum doublet therapy is used in the locally advanced and metastatic settings, as employed in the United Kingdom ABC-02 trial [33]. In this randomized controlled phase 3 trial comparing gemcitabine/cisplatin to gemcitabine alone, while doublet therapy did benefit PFS and OS, response rates were low at 26% (although disease control rate is 81%), PFS is 8 months, and OS is less than a year. Extrapolating these results to gallbladder cancer—which comprised only 36% of patients—may be limited.

Perhaps most closely resembling our described neoadjuvant setting in which patients have local measurable

disease and may be at high risk for distant recurrence, our retrospective series [40] assessed chemotherapy response in 74 patients (25 with IGBC) with either locally advanced or presumed node-positive disease. Patients were treated primarily with gemcitabine-based chemotherapy (57% treated with a gem/platinum doublet) and outcomes assessed at 2 months. Systemic therapy did demonstrate some efficacy with a 26% response rate and a 78% disease control rate with 30% proceeding to exploration and 7.4% achieving an R0 resection. But again, the risk for progression is real at 23% ($n = 17$) and 5/12 patients who proceeded to exploration were found unresectable).

Overall, although there is clearly a signal in these studies indicating treatment effect, the notably large percentage of patients with progression in these settings of measurable/macroscopic disease suggest that ability to treat disease is low and loss of local control is a real concern.

Effective chemotherapy as a necessary prerequisite for a neoadjuvant approach: extrapolating from the micrometastatic/adjuvant setting

In addition to maintaining local control of primary tumor, an additional goal and justification for neoadjuvant chemotherapy is to treat the micrometastases that are otherwise destined to cause distant recurrence and limit survival. In extrapolating to micrometastatic disease the most appropriate comparison is the adjuvant setting, addressed by two randomized controlled trials, both of which are negative. In the randomized control trial comparing adjuvant capecitabine to surgery alone (BILCAP [41]), Capecitabine demonstrated a clinically significant but not statistically significant benefit of 7 months RFS and 15 months OS for biliary tract malignancies including gallbladder cancer. The multicenter French study comparing gemcitabine and oxaliplatin with observation also did not find any benefit for RFS or OS [42]. As with the metastatic phase 3 trial, these studies contained a mix of biliary tract malignancies and gallbladder cancer represented a minority of cases. Extrapolating these data to IGBC is, therefore, further confounded since other biliary tract malignancies—notably cholangiocarcinoma—have a lower rate of distant progression.

While efficacy data are not robust and response rates for gallbladder cancer are low, we argue that the neoadjuvant approach makes oncologic sense for many patients and is a potentially valuable strategy for the surgeon who must balance the goals of achieving cure (or at least long-term survival) and limiting morbidity.

Developing a phase III randomized control trial to test the neoadjuvant approach for IGBC

Ultimately, validation of neoadjuvant chemotherapy awaits a randomized trial, one of which is in the planning stages. This will be a multicenter, international trial (not yet recruiting) and will be a direct comparison between the neoadjuvant versus upfront surgery approaches to determine the ideal treatment sequence in patients with IGBC. It will determine any therapeutic benefit of 4 cycles of preoperative gemcitabine/cisplatin to patients who then undergo re-resection followed by 6 months of postoperative capecitabine. Primary endpoint is OS at 3 years.

A few points regarding this trial are worth discussing. Inclusion criteria include T1b and T2 patients, which are not at particularly poor prognosis. However, T1b and above patients are all candidates for chemotherapy in the adjuvant setting and do still pose at least some risk for distant recurrence (especially since they may be upstaged at the time of re-resection). It will be important to determine if chemotherapy toxicities prevent any of these lower risk patients from proceeding to re-resection, which remains the only therapy capable of significantly prolonging overall survival and achieving cure.

The other debatable point is the decision to use capecitabine only in the control group (upfront surgery). The BILCAP trial measured effect size is clinically but not statistically significant and, therefore, only suggests capecitabine may be an active chemotherapy agent for biliary tract malignancy [41]; furthermore, the ABC-02 trial demonstrated that doublet therapy is more efficacious than gemcitabine monotherapy [33], perhaps not only in the measurable disease/metastatic setting as tested but also in the adjuvant setting in which the target is micrometastatic disease. While the treatment choices in this trial align with current practice (doublet therapy for metastatic disease and monotherapy in the adjuvant setting), the conclusions from this trial may be subjected to some critique since more active chemotherapy might be used in the neoadjuvant group.

Final comments

For the patient that presents with a diagnosis of incidental gallbladder cancer following cholecystectomy for presumed biliary colic, we obtain cross-sectional imaging and if negative for the distant disease, the surgeon would be completely justified in taking the traditional approach of proceeding to curative-intent resection. Taking a step back,

however, the astute surgical oncologist will examine the cholecystectomy specimen for T stage, presence of positive lymph nodes, and poor differentiation. The presence of the residual disease is suggested by positive margins either along the cystic duct margin or at the gallbladder, or by cross-sectional imaging demonstrating an infiltrating liver mass or clinically positive nodes. At MSKCC, those patients with evidence of T3, node-positive, poor differentiation or residual disease would be candidates for neoadjuvant chemotherapy. This theoretically provides immediate treatment of any micrometastatic disease in these high-risk patients and incorporates time as a selection strategy to identify those patients who will quickly progress to distant disease and, therefore, cannot benefit from surgery. Certain cases require major hepatectomy or extrahepatic bile duct resection with bilioenteric anastomosis to a nondilated bile duct, the morbidity of which should give even the most skillful surgeon pause before proceeding to the operating room.

This strategy must be balanced with risk for local progression leading to unresectability and that therapy toxicities may impair the functional status and surgical candidacy of a patient. Indeed, the weight of published evidence supports definitive re-resection as the most effective therapy in managing IGBC. This review does not change this recommendation but rather points out situations in which balancing morbidity with prolonging overall survival means altering the treatment sequence.

Compliance with ethical standards

Conflict of interest The authors have no disclosures to report.

Human and animal rights This manuscript does not involve research on human subjects or animals.

Informed consent This manuscript was a review of the literature pertaining to gallbladder cancer. Therefore, there are no issues pertaining to informed consent.

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