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Neoadjuvant therapy trials in biliary tract malignancies

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1 | INTRODUCTION

Optimal cancer care revolves around multidisciplinary care, which includes medical, radiation, and surgical oncology. In fact, particularly for solid organ malignancies, the role of the surgeon often represents the only chance for cure. Biliary tract malignancies are a prime example of this scenario in that the mainstay of curative-intent treatment is surgery. The reality is, however, that most patients are not eligible for surgery at the time of diagnosis, and even after resection, recurrence rates are high. This highlights the need for novel and effective neoadjuvant and adjuvant therapies. In this review, we will discuss the role of the surgical oncologist in perioperative therapy trials, the value and necessity of collaboration and partnership with medical and radiation oncologists, and present issues faced by clinical trial investigators. Finally, we will discuss how these concepts relate and apply to current investigations in incidental gallbladder carcinoma and intrahepatic cholangiocarcinoma (IHCC).

1.1 | The surgeon niche

The surgeon has a unique roll and fills a special niche within the doctor–patient relationship. Although trust and a deep relationship is established through providing medical care and systemic therapies, the bond forged around the physical act of surgery is distinct. The invasive nature of surgery and the fact that patients perceive that they are “putting their lives in someone else’s hands” is likely the foundation for such a connection. It is this tremendous trust and mutual respect that characterizes the surgeon niche and sets the groundwork for the important role of the surgical oncologist in novel perioperative clinical trials.

It is well known that when offered a surgery to potentially “remove their cancer,” patients will almost always choose that option. This is true even when patients are counseled that the chance of success is not 100% and that the cancer will most likely recur. In fact, a survey of 1000 patients with cholangiocarcinoma or pancreas cancer and a recent study assessing

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patient-reported outcomes in a population afflicted with cholangiocarcinoma showed exactly that (Personal Communication, Jessica Keilson, October 1, 2021). However, just because we "can" take something out, does not mean that we "should" take something out, or at least not as the first line of treatment. It is knowing this distinction where the surgical oncologist offers the greatest value.

The goal of neoadjuvant therapy is multifactorial: eradicate micrometastatic disease, decrease primary tumor size, optimize patient selection for surgery, and ultimately improve survival. This approach has been adopted for esophageal, gastric, pancreas, and rectal cancer. It is only natural that biliary tract malignancies should follow suit. When designing and implementing neoadjuvant therapy trials, it is paramount to involve the surgical oncologist, as they have their "finger on the pulse," so to say. No one better understands the realistic possibility of a technically successful upfront resection, or the level of toxicity and functional decline that a patient can sustain with preoperative therapy while remaining adequately robust with an acceptable surgical risk.

For the patient with potentially resectable disease who wishes to pursue surgery, it is the inherent bond and trust between surgeon and patient that enables a surgical oncologist to direct appropriate patients toward participation in neoadjuvant therapy clinical trials. For the patient with locally advanced unresectable disease receiving therapy on a clinical trial, it is the surgeon who must reassess for the possibility of resection during varying time points in the protocol. In the adjuvant setting, having cared for patients throughout their preoperative, intraoperative, and postoperative course, the surgeon is uniquely positioned to assess and gauge patients for their appropriateness to receive adjuvant treatment. Thus, the surgeon serves as another trusted member of the treatment team to complement the medical and radiation oncologist in designing, implementing, and advocating for clinical trials in the nonmetastatic setting. The strong and trusted bond between surgeon and patient poises the surgeon perfectly to serve within the realm of clinical trials.

1.2 | Collaborative approach

The most effective perioperative clinical trials are those designed with multidisciplinary input and involvement, namely, as partnerships of medical and radiation oncologists with surgical oncologists. It is also extraordinarily valuable and educational for surgeons to work with and learn from their medical oncology colleagues and counterparts. Their extensive experience and training in conducting clinical trials provides invaluable advice, education, mentorship, and sponsorship for the surgical oncologist. These relationships can be fostered and developed at the institutional level, through medical and surgical societies, via involvement with patient advocacy groups (Cholangiocarcinoma Foundation [CCF], PanCAN), and through participation in cooperative groups (ECOG-ACRIN, SWOG, ALLIANCE, NRG) in the National Clinical Trials Network (NCTN).

1.3 | Timing of neoadjuvant clinical trials: Pushing the envelope

The current treatment paradigm precludes therapies from entering neoadjuvant or adjuvant trials until they have proved safe and effective in the metastatic setting. This process can take up to a decade and during that time, patients with localized disease are omitted from

receiving potentially more effective therapy. We saw this in pancreas cancer with the delayed implementation of FOLFIRINOX and gemcitabine/Nab-paclitaxel to the localized disease setting until after the palliative Phase III studies were completed and reported.

We believe that we can improve patient outcomes by conducting trials of neoadjuvant and adjuvant therapy *concurrently*, rather than following palliative Phase II and III trials. The patients with localized disease may have improved outcomes by combining resection with novel medical therapies and those deemed to have unresectable tumors by their surgeon may respond to therapy and become a surgical candidate. For biliary tract malignancies, conversion to surgical resectability often represents an improvement from months to years in terms of life expectancy.

As we move toward trials in the neoadjuvant setting, however, given that resection remains the standard of care for localized early-stage biliary tract cancers, we first must establish the safety and feasibility of such an approach. Secondary outcomes can assess disease response, recurrence, survival, and novel exploratory endpoints, but again, the primary outcome must prove safety and feasibility. The goals of these preliminary Phase II trials should be to demonstrate completion of neoadjuvant therapy and surgery with an acceptable safety and toxicity profile. Interim analyses must be conducted to ensure that patients are not being harmed, which would mandate termination of the trial. These novel therapeutic trials that “push the envelope” are ideally designed and conducted in a collaborative and multidisciplinary fashion between medical, radiation, and surgical oncologists.

In addition to neoadjuvant and adjuvant trials, surgeons play a pivotal role in locally advanced, unresectable disease. The surgeon’s involvement in locoregional therapy can assist with treatment and potential conversion to resection. Intra-arterial therapy via hepatic artery infusion has been found to be safe and effective in the treatment of IHCC. This therapy involves surgical placement of a pump into the hepatic artery for direct infusion of chemotherapy while avoiding first-pass metabolism. In a 2013 multi-institutional analysis by Hyder et al., intra-arterial therapy with transarterial chemoembolization, yttrium-90, and drug-eluting beads all led to stable disease in 61.5% of patients and partial or complete response in 25.5% of patients.[1] Further investigations have included a Phase II clinical trial at Memorial Sloan Kettering Cancer Center among patients with unresectable IHCC. The authors reported a disease control rate of 84%, with 11% of patients converted to subsequent surgical resection.[2] These results have been replicated at other centers and underscore the value of surgical oncology input and involvement in clinical trials conducted in patients with localized, but unresectable disease.

2 | OUR EXPERIENCE

2.1 | Incidental gallbladder cancer

Gallbladder cancer is a rare disease worldwide, particularly in developed countries. The incidence has increased in recent decades, likely related to gallstone disease and subsequent increased rates of diagnosis after laparoscopic cholecystectomy. Today, 50%–70% of gallbladder cancer is diagnosed incidentally on pathologic review after a laparoscopic cholecystectomy performed for presumed benign biliary disease.[3–5] Current consensus

guidelines from the Americas Hepato Pancreato Biliary Association (AHPBA) for surgical treatment of incidental gallbladder cancer (IGBC) recommend upfront re-resection for all T1b, T2, and T3 lesions after appropriate staging to confirm no distant disease.[6] Re-resection typically includes a regional portal lymphadenectomy and segmental/nonanatomic hepatectomy of segments IVb/V. This recommendation is based on multiple retrospective institutional and collaborative studies showing a high incidence of residual disease after initial cholecystectomy, particularly for T2 and T3 lesions, and improved outcomes with R0 resection and lymphadenectomy.[7,8] The presence of residual disease in the re-resection specimen, however, is associated with significant reduction in disease-free and overall survival despite performing a curative-intent, R0 re-resection.[4,5] In fact, patients withT2/3 tumors but no residual disease at the time of re-resection have been shown to have improved survival compared with those with a lesser T-stage with residual disease. Furthermore, studies have shown that approximately 20% of patients are found to have sub-radiographic metastatic disease at the time of re-resection. Given these data, there is a tremendous opportunity and potential role for neoadjuvant therapy before re-resection in the treatment of IGBC.

Unfortunately, there is a dearth of level I evidence for neoadjuvant or adjuvant therapy for IGBC due to a lack of prospective randomized controlled trials for this patient population. Current treatment recommendations for adjuvant gemcitabine/cisplatin are based on retrospective data and extrapolations from prospective trials in the locally advanced or metastatic setting.[6] The ABC-02 trial found superior outcomes with combination gemcitabine/cisplatin, over gemcitabine alone, for advanced gallbladder cancer.[9] Adjuvant therapy was found to be significantly associated with improved overall survival in a retrospective meta-analysis, particularly for patients with node-positive disease or those who underwent R1 resection.[10] Two recently reported trials failed to show benefit of gemcitabine/oxaliplatin in the adjuvant setting, but did provide a signal for the benefit of 6 months of oral capecitabine.[11,12] Interestingly, disease-site subset analyses of these trials suggest a gemcitabine/platinum combination may be more effective in gallbladder cancer compared with capecitabine.[11,12] While the ASCO guidelines recommend oral capecitabine based on the results of the BILCAP study, current practice patterns worldwide still utilize gemcitabine/cisplatin in the adjuvant setting, extrapolating from the positive results of the ABC-02 trial.[13] Given the high incidence of residual disease, high recurrence rates, and the existing evidence in support of adjuvant therapy, future prospective trials to investigate the efficacy of neoadjuvant therapy before re-resection are certainly warranted.

A common referral pattern after the diagnosis of IGBC is to send the patient to a surgical oncologist/hepatobiliary surgeon for consideration of re-resection. It is the responsibility of the surgeon to educate patients as to the reality of this disease, namely, a high incidence of residual disease and high recurrence rates after re-resection. We must help patients understand the rationale and potential benefit of neoadjuvant therapy. This discussion must be conducted in an honest and open manner, emphasizing that there is equipoise in either approach. It is the inherent trust and bond between a surgeon and patient that facilitates enrollment in neoadjuvant therapy trials. Collaboration with our medical oncology colleagues is also paramount for conducting a neoadjuvant trial where the intervention is systemic chemotherapy.

It is this paradigm and process that guided the development of ECOG-ACRIN 2197. After several years of multidisciplinary discussion, mentorship, and networking within the cooperative group NCTN, a prospective randomized Phase II/III clinical trial to assess the value of neoadjuvant gemcitabine/cisplatin chemotherapy before re-resection of IGBC was approved in February 2020. EA-2197 (OPT-IN) was officially activated nationally through the NCTN in December 2020, with a surgical oncologist serving in the role of national Principal Investigator.

2.2 | IHCC

Cholangiocarcinoma is the second most common primary liver cancer and is classified by location as intrahepatic, perihilar, or extrahepatic. IHCC has increased in incidence in recent decades. Surgery is the mainstay of treatment but is often not feasible due to the typically advanced disease found at the time of presentation. Like gallbladder cancer, IHCC carries an extremely poor prognosis among those patients who are unable to undergo curative-intent surgical resection and has a high-recurrence rate after resection with a 5-year survival estimated at 30%.[14]

Treatment for cholangiocarcinoma has seen significant developments in the past 5 years, but there remains no consensus recommendation for neoadjuvant therapy before resection. A retrospective review in France noted a 39% conversion to resectability after neoadjuvant chemotherapy for cholangiocarcinoma patients with initially unresectable disease.[15] Furthermore, they demonstrated similar outcomes among this patient population when compared with patients with resectable disease at presentation who underwent upfront resection. Another multi-institutional study showed that nodal positivity after resection was a significant predictor of poor survival after resection.[14] Both of these aforementioned studies underscore the potential importance of neoadjuvant therapy, not only to broaden and better select the scope of surgical candidates but also to eradicate micrometastatic disease to improve survival outcomes.

Recent developments in treatment of inoperable IHCC have led to exciting opportunities in the neoadjuvant setting. In a single-arm Phase II clinical trial of patients with advanced, metastatic or unresectable biliary tract cancers, Shroff et al.[16] found improved survival with the addition of nab-paclitaxel to gemcitabine/cisplatin compared with the historical control of the ABC-02 trial utilizing gemcitabine/cisplatin alone. Furthermore, 20% of study participants were converted from unresectable to resectable disease and underwent resection.[16] These provocative results led to the rapid approval and accrual to S1815, an NCTN funded Phase III clinical trial comparing the triplet regimen to the standard of care doublet of gemcitabine/cisplatin.

Given the high recurrence rates and modest survival after an upfront resection approach, this triplet regimen represented an exciting and viable option to test in the neoadjuvant setting. The CCF, a patient advocacy group, provided the framework, foundation, and support for designing and conducting such a trial. Patient advocates embraced the rationale for neoadjuvant therapy. The Foundation created a multidisciplinary collegial environment where medical and surgical oncologists could work together to design this trial. The research opportunities provided through the CCF brought together a strong multi-institutional team

to conduct the trial. With the support of industry funding, this investigator-initiated trial opened at five sites. With the primary aim to demonstrate feasibility of administering the triplet regimen of gemcitabine/cisplatin/nab-paclitaxel to patients in the neoadjuvant setting before resection of oncologically high-risk cholangiocarcinoma, this trial demonstrates the success of conducting neoadjuvant trials "concurrently" instead of waiting for S1815 to report its results years from now. Again, a surgical oncologist serves in the role as Principal Investigator. Given its preliminary success, neoadjuvant gemcitabine, cisplatin, and nab-paclitaxel are now being further investigated in a Phase II clinical trial for high-risk, resectable IHCC.[17] This study, in addition to others simultaneously occurring in other countries, represents a significant advance in our approach to IHCC.

Along these lines, we continue to try to "push the envelope." In addition to augmenting chemotherapy regimens, personalized therapy has emerged in the treatment of cholangiocarcinoma. Fusions in fibroblast growth factor receptor 2 (FGFR2) with over 150 partners have been identified in approximately 15%–20% of IHCC patients, potentially approaching 25% in those with resectable disease. In a Phase II trial, Javle et al.[18] found effective disease control and improved outcomes among patients with IHCC and FGFR2 fusions using a selective FGFR kinase inhibitor in the second-line setting after progression on standard chemotherapy. These results have been replicated multiple times and has led to the Food and Drug Administration (FDA) approval of two drugs that specifically target tumors with FGFR2 fusions.[19–22] Utilizing the same framework as outlined above, we have designed the next clinical trial that will capitalize on the results of the initial trial that aimed to demonstrate feasibility of triplet gemcitabine/cisplatin/nab-paclitaxel in the neoadjuvant setting. We will continue to "push the envelope" by incorporating next generation sequencing in the preoperative setting and administering neoadjuvant targeted therapy before resection to those patients who have a tumor that harbors an FGFR2 fusion. Novel exploratory endpoints that assess circulating tumor DNA are also incorporated into the trial design. This trial has obtained industry funding. Finally, in keeping true to the strength and importance of multi-disciplinary networking and collaboration, a medical and surgical oncologist will serve as coprincipal Investigators of this innovative neoadjuvant therapy trial in biliary tract malignancies.

3 | CONCLUSION

The current treatment paradigm for biliary tract malignancies underscores the importance of surgeon involvement in clinical trials as therapeutic advances emerge. Through multi-disciplinary collaboration and continued efforts to expand neoadjuvant therapy, there lies significant opportunity to improve the historically poor survival associated with these diseases.

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