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Title	Back in the RACE: (Re)defining the role of radiation therapy in liver and gallbladder cancers
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Introduction

In this issue of the Gastrointestinal Oncology Scan, we want to acknowledge Dr. Nina Sanford and Dr. Maria Hawkins who are rotating off the GI editorial team and thank them for their valuable contributions over the last several years. We are excited to welcome Dr. Aisling Barry from the University College Cork and Dr. Randa Tao from Mayo Clinic Arizona who have been especially insightful reviewers for the Red Journal and we are confident that they will be outstanding associate editors for the GI section.

This Oncology Scan focuses on expanding the role of radiotherapy (RT) for primary liver and gallbladder (GB) cancers, which are complex and require specialized multi-disciplinary involvement. The role of RT continues to evolve for these cancers, and enthusiasm for routine use of RT has lagged behind other loco-regional therapies. Advances in technology including motion management, image guidance, and treatment conformality have improved the therapeutic ratio of RT and have achieved favorable clinical outcomes demonstrating that RT should be a standard of care for liver and GB cancers. For example, RT was recently included for the first time as a reasonable option for liver cancer in the updated 2025 European Association for the Study of the Liver (EASL) clinical practice guidelines.[1]

This progress, specifically related to hepatocellular carcinoma (HCC), is in part thanks to the two randomized trials featured in this Oncoscan. Xi et al[2] compared radiofrequency ablation (RFA) to stereotactic body radiotherapy (SBRT) in the treatment of small HCC, while Dawson et al[3] compared SBRT with sorafenib to sorafenib alone in locally advanced HCC.

Globally, the incidence of GB cancer is rare[4], and therefore obtaining level 1 evidence to support a change in practice is difficult. It is in this context that Ostwal et al[5] and Agrawal et al[6] should be commended for presenting randomized data on the integration of RT in the definitive and adjuvant settings, respectively.

Xi M, Yang Z, Hu L et al. Radiofrequency Ablation Versus Stereotactic Body Radiotherapy for Recurrent Small Hepatocellular Carcinoma: A Randomized, Open-Label, Controlled Trial. J Clin Oncol 2024 Dec 18:JCO2401532. doi: 10.1200/JCO-24-01532

Summary: Xi et al.[2] randomized patients 1:1 with small HCC measuring ≤5 cm that recurred after prior resection or thermal ablation to RFA versus SBRT. Key eligibility criteria were at least 3 months after resection/ablation to local recurrence, the absence of extrahepatic

metastasis or vascular invasion at the time of recurrence, and Child-Pugh class A liver function.

RFA was performed in a single session for tumors ≤3 cm and in multiple session for tumors >3 cm and an ablation margin of at least 1 cm was verified. Residual tumor 1 month after RFA, according to magnetic resonance imaging (MRI) and contrast-enhanced ultrasound, was treated with repeat RFA. SBRT was prescribed to 36-54 Gy in 3 fractions every other day using cone-beam computed tomography (CT) guidance. 4-dimensional CT simulation scans were obtained from which the gross tumor volume (GTV) and internal target volume (ITV) were defined. There was no additional margin for microscopic disease coverage. The planning target volume (PTV) was created from a 5 mm isotropic expansion of the ITV.

Patients were followed every 3 months for the first 2 years and every 6 months thereafter. Local progression was defined as occurring within 1 cm of the ablation region after RFA or within 1 cm of the PTV after SBRT. Local progression was defined only in the RFA arm if there was local failure after 2 consecutive RFA sessions. The primary endpoint was local progression-free survival (LPFS), defined as the time from randomization to local progression or death. The sample size was determined assuming 2-year LPFS of 75% (RFA) versus 90% (SBRT). The required total sample size was 166 assuming a 15% dropout rate.

The study completed accrual of the intended 166 patients in April 2022 and baseline characteristics were well balanced between the two arms. Prior local therapy included surgery (55%) or thermal ablation (45%). The median tumor size was 1.7 cm in the SBRT arm and 1.6 cm in the RFA arm. Only 3 of the 83 patients who were randomized to RFA had residual disease after the initial procedure, and all 3 achieved complete response after a second RFA procedure. The median prescribed SBRT dose was 45 Gy in 3 fractions.

With median follow up of 42.8 months in the SBRT arm and 42.9 months in the RFA arm, SBRT achieved significantly higher LPFS than RFA, (HR, 0.45 [95% CI,0.24 to 0.87]; P =.014). 3-year LPFS was 96.4% (95% CI, 76.5-93.0) versus 67.3% (95% CI, 56.6-78.6). 3-year local control (LC) rate also favored the SBRT arm (92.8% vs. 75.9%; P=.005). There was no overall survival (OS) difference. Subgroup analysis showed that the LPFS benefit of SBRT was greater for tumors ≤2 cm (HR 0.30 [95% CI, 0.17=0.89]; P=.020) while LC rate was superior for SBRT regardless of tumor size. There was no OS difference based on tumor size. No significant difference was found in acute or late adverse events.

Commentary: A plethora of literature is emerging supporting the role of RT as a curative intent treatment modality for patients with a localized HCC. The role of RT spans the spectrum of Barcelona Clinic Liver Cancer (BCLC) stage groupings.[7] For patients with BCLC 0-A disease,

and/or localized recurrence after prior local therapy, both thermal ablation or SBRT have been utilized with curative intent, particularly in patients who are inoperable and/or are not liver transplantation candidates. Historically, thermal ablation has been most heavily utilized and is most strongly endorsed in the current BCLC guidelines. When percutaneous thermal ablation is not suitable, the 2022 BCLC guidelines suggest that transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) are preferred alternative options. The guidelines further suggest that "stereotactic body radiation bears antitumoral activity but further prospective studies are needed to define its role." Multiple trials have recently reported and further support the role of SBRT as a curative intent treatment modality in this cohort of patients. For example, at least 4 randomized trials and associated meta-analysis have demonstrated that SBRT is associated with superior LC and comparable progression-free and OS when compared with TACE.[8-11]

While there are limited prospective randomized trials directly comparing percutaneous thermal ablation to SBRT as initial treatment for HCC, we now have at least 2 studies comparing them in the recurrent setting. Similar to the study by Xi et al., Kim et al. performed a prospective phase 3 randomized trial of 144 patients with recurrent HCC measuring <3 cm in size and ≤2 lesions, and compared proton beam therapy (66 GyE in 10 fractions) versus RFA[12]. The study was designed as a non-inferiority trial, and proton beam therapy demonstrated non-inferior, yet numerically improved, 2-year LPFS of 93% versus 83% (P<0.001).

Some may critique the studies by both Xi et al. and Kim et al. for the use of RFA as opposed to alternative forms of thermal ablation, such as microwave ablation (MWA), as MWA has suggested improved LC, particularly for lesions measuring 3-5 cm in size and/or adjacent to vasculature.[13-15] Despite this limitation, it is notable that the study by Xi et al. showed a statistically significant improvement in LC with the use of SBRT for tumors measuring ≤ 2 cm, a size in which anticipated LC would be comparable with RFA vs. MWA, and the study by Kim et al demonstrated improved LC with SBRT when restricted to tumors < 3 cm. Taken together, these studies have defined a role of RT as a curative intent treatment modality for patients with BCLC-0-A, and/or local recurrence with potential superiority over alternative forms of local treatment including TACE and percutaneous thermal ablation, with LC rates generally exceeding 90% and a favorable toxicity profile. While it is unlikely that these studies will supplant the use of trans-arterial or percutaneous thermal ablation strategies in the treatment of patients with HCC, they do support the selective use of RT for appropriate candidates including those with local recurrence and or in situations where thermal ablation is limited by lesion size, proximity to adjacent to vasculature or central biliary structures, or in a subcapsular location.[2,12,16]

Dawson LAD, Winter KA, Knox J et al. Stereotactic Body Radiotherapy vs Sorafenib Alone in Hepatocellular Carcinoma. The NRG Oncology/RTOG 1112 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2025;11(2):136-144

Summary: RTOG 1112[3] is a phase 3 randomized, multicenter trial evaluating SBRT followed by sorafenib vs sorafenib alone in patients with locally advanced HCC. Key eligibility criteria included patients with tumors unsuitable and/or refractory to surgery, ablation, or TACE, BCLC stage B or C, Child-Pugh A liver function, 5 or fewer liver tumors, sum of tumor diameter(s) ≤20 cm, metastases ≤3 cm, and no prior RT or TARE. The trial accrued participants from 23 sites across the United States, Canada, Australia, and Hong Kong between 2013-2021.

Patients were randomized 1:1 to receive sorafenib (400 mg orally twice daily) or SBRT and sorafenib (200 mg orally twice daily at 1 to 5 days after SBRT with escalation to 400 mg twice daily after 1 month). The primary endpoint was OS and secondary endpoints were progression-free survival (PFS), tumor macrovascular invasion (MVI) response rate, and improvement in patient reported outcomes measured by the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) score at 6 months. The trial was prematurely closed because of the change in the systemic therapy standard of care from sorafenib to atezolizumab/bevacizumab and the statistical analysis plan was revised to a time-driven analysis.

A total of 177 eligible patients (out of 193 screened) were randomized with 92 patients in the sorafenib arm and 85 in the SBRT followed by sorafenib arm. Most patients had HCC with MVI (74%), more than 1 tumor (59%), 4% of patients had N1 disease, 4% of patients had M1 disease, and the median tumor size (sum of the HCC diameter) was 7.8 cm (5.0-10.3 cm IQR). The median follow-up was 13.2 months for all patients and 33.7 months for surviving patients.

The SBRT prescription dose range was 27.5-50 Gy in 5 fractions with a median dose of 35 Gy (30-40 Gy IQR). Only 1 patient did not receive SBRT. The median received dose was also 35 Gy (30-40 Gy IQR, 20-50 Gy range) with 3 patients (4%) treated with 50 Gy and 12 patients (14%) treated with 45 Gy while 27 (32%) patients were treated with 30 Gy and 8 patients (10%) with 27.5 Gy all in 5 fractions. The first 3 patients per institution had central review of the SBRT plan before treatment. The overall SBRT plan review score was per protocol for 82% of patients with acceptable variation in 13%, deviation unacceptable in 1% and 4% of patients had incomplete RT due to adverse events. The majority of patients (91%) were planned with IMRT-based SBRT and no patients were treated with proton therapy. Importantly, 19 of the 92 patients (21%) in the sorafenib arm ended up receiving SBRT or hepatic RT as non-protocol treatment.

The median OS was 12.3 months in the sorafenib arm and 15.8 months in the SBRT followed by sorafenib arm (HR=0.77, 90% CI=0.59-1.01, P=.06). The 6-month OS was 71% in the sorafenib arm vs 88% in the SBRT and sorafenib arm with the 12-month OS of 53% vs 59% and 24-month OS of 23% vs 33%, respectively. When adjusting for performance status, degree of MVI, M stage, and liver function on multivariable analysis, SBRT was associated with significantly improved OS (HR=0.72, 95% CI=0.41-0.90, P=.04). The median PFS was significantly higher in the SBRT followed by sorafenib arm with 9.2 months vs 5.5 months in the sorafenib arm (*P*<.001). The 6-month PFS in the sorafenib arm vs SBRT and sorafenib arm was 41% vs 71%, at 12-months it was 20% vs 37%, and at 24-months it was 7% vs 17%, respectively.

A benefit of SBRT was seen in the OS and PFS subgroup analysis for T3/T4 tumors, BCLC class C, patients with Hepatitis B or B and C, more extensive MVI (involving the right or left main portal vein/main portal trunk/inferior vena cava), and HCC/liver volume ratio ≥10%. The response rate of MVI was much higher in the SBRT arm with 38% response vs 9% in the sorafenib arm (P<.001). Grade 3 or higher adverse events, both all-cause and treatment-related, were similar between the two arms. All-cause grade 3 GI bleeding was 5% in both arms. There was low completion of the FACT-Hep questionnaire at both baseline and 6 months; hence, statistical analysis was not done for this secondary outcome. Among the patients who completed both sets, 2 of 20 patients (10%) in the sorafenib group and 6 of 17 patients (37%) in the SBRT and sorafenib group had an improvement in FACT-Hep scores at 6 months.

Commentary: The management of locally advanced HCC is challenging, due to patient and tumor factors, with the presence of MVI known to be a poor prognostic factor.[17] Treatment options such as surgery and catheter-based therapies (CBT) are available for very select patients, but for the majority systemic therapy remains standard of care[18]. The integration of CBT, TACE/TARE[19,20], in the setting of locally advanced unresectable HCC with MVI have failed to yield equivalent outcomes to those as found in RTOG 1112[3], where combining SBRT with sorafenib demonstrated a significant OS advantage (HR 0.72; 95% CI 0.52-0.99, P=0.04), with no difference in all cause grade 3 toxicities between arms (56% vs 61% SBRT). In addition, improved response rates in patients with MVI was specifically found in the SBRT arm (38% vs 9%, P<0.001) where nearly 2/3 of patients in both arms had Vp3 (presence of tumour thrombus in first order branch of the portal vein), Vp4 (presence of tumour thrombus in the main trunk of the portal vein) or inferior vena cava involvement.[21] Conversely, both the SARAH[19] trial and SIRveNIB[20] trial compared TARE to sorafenib in a similar (but not directly comparable group, as SIRveNIB excluded patients with main portal vein thrombosis) patient population to RTOG 1112, finding no difference in median OS between groups (8 vs 9.9

months, respectively; 10 vs 8.8 months, respectively), nor any benefit, on subgroup analysis, in patients with portal vein extension. Furthermore, the YES-P study designed to answer the same question of survival benefit of TARE in HCC patients with MVI versus sorafenib was closed prematurely due to poor accrual, underlining further the challenges in recruiting to interventional studies in this group of patients.[22]

Unfortunately RTOG 1112 was slow to accrue and early closure was advised, and the statistical plan revised, due to the standard of care change in first line systemic therapy from sorafenib[23] (tyrosine kinase inhibitor [TKI]) to atezolizumab plus bevacizumab based on the publication of the IMbrave-150 trial. [17] IMbrave-150 compared an immunotherapy and VEGF combination (atezolizumab plus bevacizumab) to sorafenib in unresectable HCC (38% with MVI) demonstrating a survival advantage in the combined arm (HR 0.58; 95%CI 0.42-0.79; P<0.001). However, serious adverse events were more frequent in the combination group (38% vs 30.8% sorafenib) with more patients discontinuing treatment due to adverse events (15.5% vs 10.3%). Not all patients are eligible for (e.g. due to portal hypertension and increased bleeding risk) or tolerate or have access to immunotherapy due to the resources and cost required. Therefore, TKIs remain a (first-line) systemic option for many patients worldwide and thus SBRT is very much a relevant treatment option. RTOG 1112 highlights potential future approaches involving combination immune checkpoint inhibitors with RT to elicit an immune mediated anti-tumor response.[24]

RTOG 1112 is the only non-surgical study to include and adequately treat HCC conglomerate disease of up to 20 cm. Median size of tumor was 7.8 (range 1 – 19.1) cm and a statistically significant PFS and time to progression was found in favor of the SBRT arm (9.2 vs 5.5 months). Furthermore, disease control was seen in 75% of patients compared to 45% in the sorafenib alone arm. When SBRT was combined with TACE in patients with HCC and MVI and a median tumor size of 9.7 cm, Yoon et al demonstrated superior disease control when compared to sorafenib alone (33.3% vs 2.2%, P<0.001).[25]

Understanding the patient's experience when introducing a new treatment option is important[26], however patient reported outcome measure numbers were small in RTOG 1112, with approximately one-fifth of patients completing baseline and 6-month measures, preventing robust statistical analysis. An improvement in quality of life scores was seen in a higher proportion of patients in the SBRT arm (35% vs 10%) at 6 months.

Personalized medicine has come to the forefront in the management of HCC, paving the way for future studies to integrate radiation therapy with systemic options, including immunotherapy. The upcoming phase 3 NRG GI012 trial will randomize patients with advanced HCC to immunotherapy with or without SBRT or proton therapy. RTOG 1112 has

illuminated the importance of multi-disciplinary care in HCC and supports the role of radiotherapy as a standard of care option in the setting of unresectable locally advanced HCC.

Ostwal V, Patkar S, Engineer R et al. Adjuvant Gemcitabine Plus Cisplatin and Chemoradiation in Patients With Gallbladder Cancer A Randomized Clinical Trial. JAMA Oncol. doi:10.1001/jamaoncol.2024.1944

Summary: The GECCOR-GB study published by Ostwal et al is an open-label, randomized, non-comparator, phase 2 study investigating either a combination of gemcitabine and cisplatin (GC) or capecitabine plus capecitabine chemoradiation (CRT) as adjuvant therapy regimens after surgical resection of GB cancers.[5] The multi-institutional trial was conducted at 3 hospitals in India, where GB cancers are prevalent.

Eligibility included adult patients 18 years and older; pathologically confirmed adenocarcinoma or adenosquamous carcinoma; stage pT2-T3/N0 or pT1-T3/N1; no distant metastatic disease based on either contrast-enhanced CT or 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT scan. Surgery to remove all gross disease was required, but patients with either microscopically negative (R0) or positive (R1) margins were eligible for enrollment.

Between May 2019 and February 2022, patients were randomized 1:1 to either gemcitabine (1000 mg/m2) and cisplatin (25 mg/m2) on days 1 and 8 every 3 weeks for up to 6 cycles over 18 weeks (GC arm) or to capecitabine (2000 mg/m2) 14 days on/1 week off over 3 weeks for 2-4 cycles followed by concurrent capecitabine (1650 mg/m2) plus external beam RT over 5 weeks followed by an additional 2-4 cycles of capecitabine to complete a total of 6 cycles (CRT arm).

The initial CTV included the postoperative tumor bed, tissues adjacent to the GB fossa, and draining lymph nodes in the hilar, periportal, portocaval, and retropancreatic regions. After R1 resection, a boost CTV covered the area of positive margin at the liver or common bile duct. The CTV was expanded 5-7 mm to create the PTV. The initial CTV was treated to 45 Gy in 25 fractions. For patients with a positive margin, the boost CTV was either treated with an additional 5-9 Gy delivered sequentially using 3D-conformal radiotherapy (3DCRT) or with a simultaneous integrated boost to 52-55 Gy in 25 fractions using intensity modulated radiotherapy (IMRT). Daily cone beam CT was used for image guidance.

The primary endpoint was 1-year disease free survival (DFS), and each arm was evaluated independently. A 1-year DFS of 77% or greater was determined to represent sufficient activity of the regimen to warrant inclusion in future trials.

A total of 90 patients were randomized with 45 patients in each arm. Median follow-up was 23 months. Compared to the GC arm, the CRT arm had more stage II patients (60 vs 51%), more

patients undergoing radical cholecystectomy (56 vs. 44%), and more patients with R1 resection (9 vs. 0%). The 1-year DFS was 88.9% for the patients treated with GC and 77.8% for patients treated with CRT; both meeting the prespecified primary endpoint. The 2-year DFS was 74.8% for both regimens. There were no local recurrences in the CRT arm and 3 (7%) in the GC arm. Overall survival at 2 years was 88% for patients in the GC arm and 80.6% for patients in the CRT arm. Only 62% of CRT patients could complete CRT and all 6 cycles of capecitabine, and 82% of patients completed all 6 cycles of GC chemotherapy. Notably, 5 patients (11%) on the CRT experienced early disease progression while on capecitabine and did not receive CRT.

Commentary: Gallbladder (GB) cancer is the most prevalent biliary tract cancer (BTC) globally with the highest incidence in central and eastern Asia and South America.[27,28] However, it remains a relatively rare cancer representing approximately 1% of all cancer cases and 2% of deaths.[4] GB cancer is the most lethal of the BTCs with only 10% of patients presenting with early stage disease amenable for curative resection and a preponderance for spread to regional lymph nodes and distant metastatic sites.[29] However, due to its rarity, clinical trials focused on patients with GB cancer exclusively remain exceedingly difficult to perform and this molecularly distinct malignancy is often lumped in with other BTCs in prospective studies.

The current standard for adjuvant therapy for resected BTC, inclusive of GB cancer, remains adjuvant capecitabine based on the results of the BILCAP trial.[30,31] This study randomized 447 patients with resected cholangiocarcinoma or muscle-invasive GB cancer (18% of patients) to 8 cycles of capecitabine vs observation. The addition of adjuvant capecitabine failed to show an improvement in OS in intention-to-treat analysis, but did show a statistically significant improvement in OS in planned sensitivity analyses and per-protocol analysis (53 vs 36 months, HR=0.75, 95% CI 0.58-0.97, P=0.028).

Overall, data on the benefit of adjuvant therapy for patients with resected GB cancer, specifically, is mixed. Takada et al. performed a phase 3 randomized trial in patients with resected pancreaticobiliary cancer which included 112 patients with GB cancer.[32] Patients were randomized to surgery alone vs adjuvant mitomycin C and 5-fluorouracil. Amongst the treated patients with GB cancer, an improvement in 5-year OS was observed with administration of adjuvant chemotherapy, 26.0% vs 14.4% (P=0.037). However, in subgroup analysis, the OS benefit was only observed in patients with GB cancer who underwent a noncurative resection. Further, no benefit in OS was observed in intent-to-treat analysis of patients with GB cancer, potentially due to the larger number of stage I patients in the surgery only arm. PRODIGE 12-ACCORD 18-UNICANCER GI was a randomized phase 3 trial

investigating the addition of 12 cycles of adjuvant gemcitabine/oxaliplatin vs surveillance in 196 patients with resected BTC (20% GB).[33] No benefit in recurrence-free survival or OS was observed with adjuvant therapy neither in the overall study cohort nor in the subgroup of patients with GB cancer. In the single-center randomized trial by Saluja et al, 100 patients with R0 resected GB cancer were randomized to either surveillance or 6 cycles of adjuvant gemcitabine/cisplatin (gem/cis).[34] Adjuvant therapy did not result in an improvement in DFS or OS over surgery alone.

Regarding the role of adjuvant RT, SWOG 0809 was a single arm phase 2 trial for patients with resected pT2-4 or N+ or positive resection margin extrahepatic cholangiocarcinoma or GB cancer treated with 4 cycles of adjuvant gemcitabine/capecitabine followed by concurrent capecitabine-based CRT.[35] Patients with GB cancer represented 32% of those in the study and 32% of patients had an R1 resection. The outcomes including 2-year OS (65%) and DFS (52%), which were similar in R0 and R1 resected patients, compared favorably to historical controls. Thus, given the data to date, the role of adjuvant therapy following resection for patients with GB cancer remains murky at best.

It is in this landscape with established hurdles that GECCOR-GB was performed, and Ostwal et al. should be commended for completion of this trial.[5] As reviewed, patients treated on both arms exceeded the pre-specified trial criteria of 1-year DFS exceeding 77%. The liver was the most common site of relapse in both arms. Of note, there were no loco-regional recurrences in the CRT arm vs 3 (7%) in the gem/cis arm. While the follow-up plan for patients enrolled in GECCOR-GB is not clear, a careful review of the DFS curves of the two groups suggest that perhaps CRT may provide more durable control at later time points, but additional follow-up is needed. Regarding toxicity, rates of grade 3+ adverse events were relatively low in both arms with hematologic toxicity and fatigue the most common toxicities observed in the gem/cis group and palmar-plantar erythrodysesthesia syndrome and fatigue the most common in the CRT group. These results suggest that both regimens are worth considering as adjuvant therapy for patients with resected stage II and III GB cancer, and this initial study serves as solid bedrock for larger randomized trials.

However, in the interim, questions remain about which adjuvant therapy might be best suited for a particular patient with resected GB cancer based on the results of this trial. Tolerability could be a consideration when deciding which regimen might be most appropriate for a patient. For patients in the gem/cis arm, 82% were able to complete the planned 6 cycles of systemic therapy. In contrast, only 62% of patients were able to complete 6 cycles of capecitabine and CRT. Fifteen patients discontinued treatment including 3 patients who completed 6 cycles of capecitabine and refused CRT, 5 patients who had early progression

with capecitabine so CRT was aborted, and 7 patients who did not complete capecitabine due to adverse events. The low rates of completion in the CRT arm appear to be more of a reflection of poor tolerance of systemic therapy or ineffective systemic therapy as opposed to RT intolerance.

One could also investigate the baseline tumor characteristics in each arm to decide if one regimen might be preferred in certain clinical situations. In GECCOR-GB, there were numerically more patients with N1 disease in the gem/cis group (38% vs 29%). In addition, a higher percentage of patients in the gem/cis group underwent simple cholecystectomy followed by a revision surgery rather than upfront radical cholecystectomy (56% vs 44%) which could lead to more advanced disease if there are delays between surgical procedures. In those clinical scenarios, a more active systemic therapy may be desirable. In contrast, there were more patients with R1 resection status in the CRT group (9% vs 0%). Based on the available data from S0809, a regimen that includes RT might be considered for patients with a microscopically positive surgical resection margin as supported by the American Society of Clinical Oncology (ASCO) clinical practice guidelines.[31]

While the results of GECCOR-GB can be dissected, a larger phase 3 randomized trial is ultimately needed to determine which is the optimal therapy for this patient group with a number of recently accrued and ongoing trials that will help to provide clarity. ACTICCA-1 is a randomized phase 3 trial for patients with resected BTC, including GB cancer, randomizing patients to either 8 cycles of adjuvant gem/cis vs capecitabine, with a second randomization arm for patients with R1 resection to gem/cis vs capecitabine vs chemotherapy (gem/cis or capecitabine) followed by chemoradiation.[36] The trial is closed to accrual with results pending. Similar to other GI malignancies, multiple studies are investigating the potential for neoadjuvant therapy for GB cancer including the POLCAGB (NCT02867865) and NEOGB (NCT06712420) trials.

Ultimately, perhaps the optimal treatment is not deciding between chemotherapy or RT, but combining the most effective systemic therapy for control of distant disease and RT to help reduce the risk of local recurrence. To that end, results of the ACCELERATE trial were recently presented at ASCO GI which investigated chemotherapy alone (gemcitabine/oxaliplatin or gem/cis) to chemotherapy plus capecitabine-based CRT in patients with resected GB cancer.[37] The trial was designed to enroll a total of 200 patients, but was closed early with half of the planned sample size due to poor accrual. Initial results demonstrated no improvement in recurrence-free survival with the addition of RT.

Finally, given that this trial was conducted in a high prevalence region, how generalizable are these results? GB cancer is known to be a molecularly heterogeneous malignancy seemingly

impacted both by geographical location as well as etiology.[38,39] Therefore, as we continue to make advancements in the treatment of this malignancy, it is imperative that a “one-size-fits-all” approach is not adopted, but rather, a comprehensive approach including both genomic and clinicopathologic profiling to formulate the optimal treatment for both high and low-prevalence regions. Given the poor prognosis of GB cancer and the challenge of both local and distant control, this truly is an opportunity for multidisciplinary collaboration to design and conduct future trials to find the optimal balance between local and systemic therapy.

Agrawal S, Kapoor V, Rahul R et al. A Randomized Study of Consolidation Chemoradiation (CTRT) versus Observation after first line chemotherapy (CT) in Advanced Gall bladder Cancers (GBC):RACE-GB study. International Journal of Radiation Oncology, Biology, Physics (2024), doi: https://doi.org/10.1016/j.ijrobp.2024.11.099

Summary: The RACE-GB study[6] is a single institution, randomized, phase 3 trial[40] evaluating CRT after chemotherapy for advanced GB cancer in a low middle income country. Patients with T3-4, N1-2, retroperitoneal lymph nodes and limited metastatic disease (segments IV and V, less than 3 extrahepatic metastases) were included. Patients received 4 cycles of gemcitabine/cisplatin and were then evaluated for treatment response. Those with resectable disease underwent surgical resection. Those with stable or partial response were randomized to observation vs concurrent capecitabine plus 45 Gy plus sequential 9 Gy boost over 30 fractions total. Radiation technique was 3DCRT, targeted to the gallbladder and high-risk elective regions (liver extension, periportal, celiac, superior mesenteric artery and retroperitoneal lymph nodes until L2). Patients were reassessed for resectablity 6 weeks after completing CRT. The primary endpoint of the study was OS from randomization.

Of 200 registered patients, 65 progressed on initial chemotherapy thus 135 patients were enrolled and randomized to CRT (n=68) and observation (n=67). Patients predominantly had T3-T4 (95%) and node positive (80%) disease. Chemoradiation was not completed in 7 patients. After a median follow-up of 12 months, the median OS was 4 and 10 months in the observation and CRT groups, respectively (HR, 0.43; 95% CI, 0.32 to 0.62; P<0.001). The 1-year OS was 7.5% and 39.7%, respectively (P=0.000). The median PFS was 1 and 7 months, respectively. Patients in the CRT arm with LC had improved OS (13 vs 8 months, P=0.001). Quality of life as per FACT Hep Score showed a significant decline from baseline to 3 months in the observation group but no change in the CRT group. After upfront chemotherapy, 4 patients were eligible for resection, with an additional 3 patients deemed resectable after CRT.

Median OS for patients undergoing surgery vs observation was 21 months and 9 months, respectively (P<0.002).

Commentary: The RACE-GB trial underscores the potential benefit of CRT as a consolidation strategy for patients with locally advanced GB cancer. The study demonstrated a significant improvement in median OS in patients who received CRT compared to those who were observed after induction chemotherapy. LC was also improved in the CRT arm, and thus this trial provides valuable data supporting the routine use of CRT for select patients with advanced GB cancer. The study investigators should be commended for completing this randomized trial, which very likely could not have been done at most other centers around the world. Although the global incidence of GB cancer is low, there is a relatively high incidence in certain parts of India.

The generalizability of the trial outcomes may be limited by several factors including patient selection criteria and radiation technique. As a low-middle-income country, many centers in India have limited resources to conduct prospective clinical trials. Advanced technologies such as IMRT are not readily available or feasible due to resource constraints. It is notable that a significant improvement in LC and OS was demonstrated in the CRT arm despite the use of 3DCRT (instead of IMRT), generous margins, and the lack of motion management. If more sophisticated radiation techniques had been used it is reasonable to assume that these outcomes could have been improved and perhaps the incidence of grade 3-5 adverse events, especially related to GI bleeding (5.8%) and hepatotoxicity (13%), may have been reduced. With respect to patient selection, initial staging was done using CT scans alone and not PET scans, which may have detected distant metastatic disease especially knowing that the median PFS after randomization was short in the observation (1 month) and CRT (7 months) arms. In addition, only 4 cycles of induction chemotherapy were required and no additional chemotherapy was required after randomization except to treat disease progression. A longer induction chemotherapy duration (for example 6 or more cycles) may have enhanced patient selection for CRT by selecting out patients who were more likely to develop rapid distant progression. Lastly, the trial included a small number of patients with limited metastatic disease (all were in the CRT arm), and it is uncertain whether the addition of CRT to initial systemic therapy should be routine for these patients.

These trial results must also be taken in the context of recent advances in systemic therapy, such as those seen in the TOPAZ-1 and KEYNOTE-966 trials, which demonstrated the efficacy of immune checkpoint inhibitors (durvalumab and pembrolizumab) in combination with SOC cisplatin and gemcitabine for BTCs.[41,42] Consolidative CRT represents a different yet

complementary approach. While the addition of immunotherapy appears to provide an OS benefit (12.8 mo vs 11.5 mo in TOPAZ-1), there is unquestionably a need for further improvement. Chemoradiation provides a precise, well-tolerated treatment that may further improve the therapeutic window. Although both TOPAZ-1 and KEYNOTE-966 enrolled patients with GB cancer, all patients with biliary cancers were eligible. Unfortunately, neither were powered for robust subgroup analysis with respect to disease site and there is subsequent controversy whether all patients benefit equally from immunotherapy. Gallbladder cancer patients on TOPAZ-1 did not seem to benefit as strongly as those with extrahepatic and especially intrahepatic cholangiocarcinoma. Whether this represents a true difference in outcomes is debatable, however the RACE-GB findings suggest that for patients with locally advanced GB cancer, CRT could serve as a consolidative treatment that may prolong OS by preventing tumor regrowth in the primary site and regional lymph nodes and should be considered strongly.

Looking ahead, integrating CRT while further refining systemic therapies, including immunotherapy and molecularly targeted agents, may further improve outcomes in both GB cancer as well as other biliary cancers. Future research should focus on refining patient selection criteria using biomarkers and advanced imaging techniques to identify those most likely to benefit from aggressive local therapy. The RACE-GB trial paves the way for a multimodal treatment paradigm in GB cancer, with adjuvant chemoimmunotherapy and subsequent local therapy combined strategically to maximize survival while preserving quality of life.

Conclusion

Mounting evidence, as described above, resulting in improved rates of LC and OS, supports the use of RT as a complementary and/or alternative loco-regional therapy in many stages of liver and BTCs. Improving outcomes for patients with liver and BTCs is heavily dependent on optimising multi-disciplinary care through the inclusion of *all* evidence based interventions in personalising cancer care.

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