Gallbladder Cancer Therapy

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Gallbladder cancer (GBC) is the most common form of biliary tract cancer. It is characterized by unique pathogenetic and molecular features that differ from other biliary tract cancer forms (e.g., inflammation-based carcinogenesis and distinctive molecular alterations, strong association with female sex, and geographical clustering). Therefore, differentiated therapy is mandatory to improve patients' outcome and survival, especially regarding characteristic molecular alterations that bare the opportunity for the use of new targeted therapeutics.

Keywords: gallbladder cancer ; targeted therapy ; multidisciplinary cancer therapy

1. Neoadjuvant Therapy

In accordance with other forms of biliary tract cancer (BTC), surgical resection is the only potentially curative therapy. Since gallbladder cancer (GBC) is often characterized by an aggressive tumor biology [1], neoadjuvant therapy is not recommended for patients with the possibility of primary R0-resction [2]. Unfortunately, literature estimated that only 10% of all patients diagnosed with GBC present at an early stage with the opportunity for primary curative resection [3][4] with a higher rate for incidental GBC after cholecystectomy [5].

In contrast with these findings, a large retrospective analysis of 6437 patients with GBC from the SEER (Surveillance, Epidemiology, and End Results) registry between 1988 to 2003 identified 2835 patients (44%) that underwent resection in a curative intention [6]. However, it must be admitted that most of these patients had a locally advanced tumor stage with nodal invasion or unknown nodal status, leading to a bad prognosis.

According to GLOBOCAN 2018 data from the US, 43% of GBC are found after cancer had spread to regional organs or lymph nodes, while 42% were found after spreading to distant organs or lymph nodes [7].

Therefore, neoadjuvant concepts to archive secondary resectability after tumor downstaging are a focus of current research.

At present, a chemotherapy regimen based on gemcitabine and cisplatin in accordance with the ABC-02 phase III trial (*n* = 410) is recommended for the treatment of primary unresectable GBC [3]. This recommendation is based on an objective response rate (ORR) of 37.7% and a disease control rate (DCR) of 85.2% in the subgroup of GBC patients with doublet therapy (*n* = 61) compared to a ORR of 21.4% and a DCR of 76.8% with gemcitabine alone (*n* = 56).

In a systematic review of neoadjuvant chemotherapy or radio chemotherapy for advanced-stage gallbladder cancer, Hakeem and colleagues could identify eight studies that have investigated this issue with different therapeutic concepts (*n* = 474) [8]. Despite the poor quality of the included studies, their analysis showed that 50.4% of all pretreated GBC patients (*n* = 239) were eligible for curative-intended surgery after neoadjuvant therapy. In total, 191 patients (40.3%) received a curative resection after neoadjuvant therapy with a R0-rate of 92.5% (*n* = 160). These results demonstrate that up to one-third of all advanced-stage GBC patients could benefit from a neoadjuvant treatment in case of overall survival (OS) and disease-free survival (DFS). The OS significantly differed between patients who received surgery after neoadjuvant treatment (18.5–50.1 months) compared to those who were not eligible for surgery after neoadjuvant treatment (5.0–10.5 months). At the moment, the phase III GAIN-trial aims to prospectively recruit 333 patients with locally advanced BTC or incidental GBC, which will be randomized in a study arm with perioperative chemotherapy with gemcitabine and cisplatin and another study arm with immediately surgery and the option for adjuvant chemotherapy (NCT03673072) [9]. Other trials that are currently recruiting participants for the evaluation of neoadjuvant treatment in GBC or BTC including GBC are summarized in **Table 1**.

Table 1. Ongoing clinical trials for the evaluation of neoadjuvant therapy in locally advanced gallbladder cancer. BTC: biliary tract cancer. GBC: gallbladder cancer. OS: overall survival. ORR: overall response rate. RCT: radiochemotherapy.

RT: radiotherapy.

NCT Number	Study Phase	Condition	Study Size	Treatment Agent	Primary End Point	Institution	Completition
NCT03673072	III	Incidental GBC and BTC	300	Gemcitabine + cisplatin perioperative vs. adjuvant	OS	Krankenhaus Nordwest, Germany	November 2024
NCT02867865	II/III	GBC	314	Gemcitabine + cisplatin alone vs. RT + gemcitabine + cisplatin	OS	Tata Memorial Hospital, India	August 2022
NCT04308174	II	BTC	45	Gemcitabine + cisplatin vs. gemcitabine + cisplatin + durvalumab	R0 resection rate	Asan Medical Center, Korea	December 2023
NCT04559139	II/III	GBC	186	Gemcitabine + cisplatin perioperative vs. adjuvant	OS	Emory University, Winship Cancer Institute, United States	September 2023
NCT04480190	I	BTC	12	Gemcitabine + cisplatin followed by RCT (5FU + RT)	Therapy completion	University of Cincinnati Medical Center, United States	February 2029

A potential regimen for neoadjuvant radiochemotherapy was investigated by Engineer et al. in 28 patients with locally advanced BTC [10]. Patients received 57 Gy over twenty-five fractions in the gross tumor and 45 Gy over twenty-five fractions in the surrounding nodes in combination with gemcitabine (300 mg/m^2/week for 5 weeks). Twenty patients (71%) achieved partial or complete radiological response, and fourteen patients (56%) achieved R0 resection after pretreatment. In accordance with previous studies, R0-resected patients had a 5-year OS of 47% compared to a 5-year OS of 24% in the whole group.

2. Surgery

GBC is most discovered incidentally during elective or emergency cholecystectomy. In contrast to non-incidental GBC, these cases usually present in an earlier stage and are thus amenable to secondary resection with curative intent, if metastatic disease is ruled out. In general, simple cholecystectomy is adequate for T1a GBC and results in excellent 5-year survival rates [11], but extended oncologic resection is recommended for tumors of stage T1b or higher [3]. While the index cholecystectomy with incidental finding of GBC is often performed at smaller hospitals, patients should be referred to a center with sufficient expertise in hepatobiliary surgery for the secondary oncologic resection [12]. The optimal extent of resection is still debated, but in general, three aspects should always be considered (1) the resection of the adjacent liver parenchyma (i.e., the gallbladder fossa/segments IVb and V), (2) locoregional lymphadenectomy, and (3) the re-resection of the cystic duct, conceivably with the resection of the common bile duct.

Regarding the extent of liver resection, there is no consensus yet, in particular for T2 tumors, whether an atypical resection of a 2–3 cm wedge of segments IVb/V is sufficient or whether an anatomical resection of these segments should be performed. The location of the tumor on the peritoneal side (T2a) or hepatic side (T2b) may influence the decision to perform an atypical or an anatomical hepatectomy of segments IVb/V, but most studies have failed to demonstrate a survival difference between both strategies, and high-quality evidence in support of either approach is lacking [13]. On the other hand, patients with non-incidental GBC usually present with more advanced tumors (i.e., T3 or T4) and thus require more extended resections. While for small T3 tumors located in the corpus or fundus of the gallbladder, an anatomical resection of segments IVb/V en bloc with cholecystectomy might be sufficient, most T3/T4 tumors can only be resected curatively by more radical procedures. Advanced tumors located in the infundibulum of the gallbladder are particularly difficult to treat surgically, and an (extended) right hepatectomy, often including vascular resection, bile duct resection, or the resection of adjacent organs, such as the duodenum, pancreatic head, or the right transverse colon, is usually necessary to achieve clear margins. While some studies, especially from Asia, have reported favorable results for such extended resections, e.g., including right hepatectomy with simultaneous partial pancreatoduodenectomy [14], most centers are more reluctant regarding such radical approaches due to the high risk of morbidity and mortality and the questionable oncologic benefit [15][16]. Consequently, such extended resections should only be performed in selected

patients, e.g., young patients with good performance status and a low perioperative risk profile. Furthermore, these patients are candidates for multimodal treatment strategies, preferably within clinical trials (see above).

While the risk for lymph node metastases in T1a GBC is well below 5%, it is approximately 10–15% in T1b GBC and further increases with advanced stages [11]. Since, lymph node spread is one of the most crucial prognostic factors [17], a locoregional lymphadenectomy is mandatory in all resectable GBC of stages T1b or higher. While nearly all authors and guidelines agree that an adequate lymphadenectomy should include the lymph nodes at the cystic duct and in the hepatoduodenal ligament, there is more controversy whether it should extend to the common hepatic artery and celiac trunk and to the superior posterior pancreaticoduodenal lymph nodes [3][18]. The aortocaval lymph nodes may be sampled in cases with suspected lymph node involvement in this location, but if positive, the prognosis is poor, similar to distant metastatic disease, and thus extended resection should be critically reconsidered [19]. Whereas the anatomical extent of lymphadenectomy is still debated, it is nowadays widely accepted that optimally at least six lymph nodes should be resected, on one hand for adequate staging and on the other hand due to a potential survival benefit for patients with N0 disease based on the assessment of six nodules compared to N0 based on fewer lymph nodes [20].

Regarding bile duct resection, especially in cases with unclear resection status during the index cholecystectomy, the cystic duct stump should always be re-resected during secondary oncologic resection and should be sent for frozen section. In case of margin positivity, a resection of the common bile duct with subsequent biliodigestive anastomosis should be performed to achieve margin negativity. However, routine bile duct resection during secondary oncologic resection is not recommended due to the increased morbidity and lack of a survival benefit [3][16].

Traditionally, secondary oncologic resections of incidental GBC and primary resection of non-incidental, advanced GBC have been carried out by an open approach. However, advances in minimally invasive surgery enabled surgeons worldwide to perform such procedures without laparotomy [21]. In particular the increasing availability of robotic surgery allow even extended resections, e.g., including biliary or vascular resection and reconstruction, with the same approach as in open surgery [22]. Furthermore, modern techniques such as intraoperative indocyanine green fluorescence can be used to clarify vascular or biliary anatomy, particularly in secondary cases with (post)inflammatory alterations at the hepatouodenal ligament [23]. Although current studies suggest the safety and oncologic adequacy for minimally invasive procedures for GBC, these findings still need to be corroborated in prospective large-scale studies.

In summary, in the absence of high-quality evidence regarding the optimal extent of surgery for GBC, an individual approach respecting the above-mentioned principles to achieve margin-negative resection should be tailored for each patient. This approach should take radiologic findings, the primary operative and histological reports (in incidental GBC), and also conditional factors of the individual patient into account.

3. Adjuvant Therapy

After curative resection, one-third (33.3%) of GBC patients develop recurrent disease at a median follow-up of 15.1 months [24]. As risk factors for recurrence, operative jaundice, major hepatectomy, T-category 3/4, N-category 1/2, tumor size, poorly differentiated tumor, lymphovascular invasion, and R1 margin status could be identified [24][25]. Horgan et al. have demonstrated in their metanalysis of 6712 patients with BTC that underwent resection between 1960 and 2010 that patients with GBC benefit from adjuvant therapy, especially those with node-positive disease and R1-resection [25]. These results could be replicated in newer studies. Ma et al. conducted a pooled meta-analysis involving 3191 patients with GBC showing a significant improvement of OS in patients with adjuvant chemotherapy after resection, especially in patients with R1-resection, node-positive disease, and stage III/IV disease [26]. It is important to know that Mantripragada et al. have suggested that only a high-risk subset of patients harboring the above-listed risk factors might benefit from adjuvant treatment based on their retrospective analysis of locally advanced GBC patients that received adjuvant treatment after resection [27].

At the present moment, actual guidelines including the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), British Society of Gastroenterology (BSG), and the International Liver Cancer Association (ILCA) differ in their recommendations concerning the adjuvant treatment of BTC, and a differentiation between GBC and other BTC forms is lacking [28]. The most important data for adjuvant therapy in BTC derives from the phase III BILCAP trial, which investigated prospectively the effect of adjuvant capecitabin in 447 patients with BTC after resection containing 79 patients (18%) with muscle-invasive GBC [29]. Patients in the capecitabine arm showed improved median survival compared with those in the observation arm (51.1 vs. 36.4 months, $p = 0.028$) in the per-protocol analysis but not in the intent-to-treat analysis. Considering adverse events, it must be noted that, out of 213 patients who received at least one cycle of capecitabine, 94 (44%) had at least one grade 3 toxicity (43 patients with hand–foot syndrome,

sixteen patients with diarrhea, sixteen patients with fatigue, and nineteen other adverse events). Despite several limitations of this research and lacking subgroup analysis concerning GBC, adjuvant therapy with capecitabine after curative resection for GBC can be considered the current standard of care.

Besides the BILCAP trial, several other phase III trials have investigated the effect of different adjuvant approaches for the therapy of resected BTC with partly contradictory results.

The PRODIGE-12/ACCORD-18 phase III trial has compared the effect of adjuvant chemotherapy with gemcitabine and oxaliplatin (GEMOX) compared to an observational strategy after curative resection for BTC in 196 patients including 38 GBC (19%) patients. In opposition to the results of the BILCAP trial, the authors could not observe any advantage of the study arm considering the disease recurrence rate, relapse-free survival (RFS), and OS. Moreover, a subgroup analysis of patients with GBC showed a significantly worse RFS and OS in the study arm compared to the observation arm. In their discussion section, the authors suggest that the higher sample size leading to a high statistical power as well as the higher amount of high-risk BTC patients with early recurrence (R1-resection status and node-positive disease) might explain the different results compared to the BILCAP trial.

Another clinical phase III trial that has investigated the role of adjuvant chemotherapy in patients with BTC was the Japanese BCAT trial, which recruited 226 patients with BTC (without defining a GBC subgroup) for the evaluation of adjuvant gemcitabine therapy [30]. Disappointingly, the results did not show a difference in RFS, OS, or disease recurrence between the gemcitabine arm and the observation arm, even under consideration of a high-risk subgroup analysis (R1-resected patients, node-positive patients). Similar to the PRODIGE-12/ACCORD-18 trial, the study results have been limited due to an insufficient sample size and a smaller subset of high-risk BTC patients. Furthermore, the results are moreover limited by a lack of GBC patients.

Considering the strong limitations, the value of a clinical phase III trial by Takada et al. that has investigated the effect of an adjuvant chemotherapy with mitomycin c and 5-FU has been discussed [31]. In their study, a heterogenous study collective of 508 patients with pancreatic and BTC including GBC (n = 140) has been divided in a study arm that received adjuvant chemotherapy with gemcitabine and mitomycin c and a control group with an observation strategy after curative resection between 1986 and 1992. In the subgroup analysis of GBC patients, the 5-year OS was significantly higher in the study arm (26.0% vs. 14.4%; p = 0.0367) accompanied by a significantly improved disease-free survival (20.3% vs. 11.6%; p = 0.0210).

Another approach is the application of a combined adjuvant radio-chemotherapy, since GBC disease recurrence is often characterized by local disease relapse [24], and retrospective analysis have shown a benefit from radiotherapy in resected GBC [32][33]. In the single-arm SWOG S0809 phase II trial, Ben-Josef et al. investigated the effect of adjuvant gemcitabine and capecitabine, followed by radio-chemotherapy with capecitabine and radiotherapy with 45 Gy to regional lymph nodes and 54 to 59.4 Gy to preoperative tumor bed in 79 patients, including 25 GBC patients [34]. Considering the lack of a control arm, the results showed a promising OS and DFS without a significant difference between GBC and other BTC. Overall, there was a 2-year OS of 65% with a median follow-up of 35 months and a 2-year DFS of 52%. These results must be further replicated in a prospective phase III trial. The Chinese FDRT-PG001 phase III trial is therefore recruiting 140 patients with GBC and extrahepatic BTC after resection to compare the effect of a combined concurrent radio-chemotherapy (gemcitabine and capecitabine, followed by capecitabine and radiotherapy) with chemotherapy alone (gemcitabine and capecitabine) (NCT02798510). Unfortunately, since this research has not been updated since June 2016, it is unlikely that this trial will support further evidence for the use of radio-chemotherapy in GBC.

At the moment, the ongoing ACTICCA-1 is expected to supply further evidence for the adjuvant treatment of GBC. In their multicenter phase III trial, the authors aim to compare a combined adjuvant chemotherapy regimen of gemcitabine and cisplatin based on the results of the ABC-02 trial [35] with a control arm that receives adjuvant chemotherapy with capecitabin [36]. With an aspiredenrollment of 781 participants with resected BTC including GBC, results are estimated in April 2024.

Besides the ACTICCA-1 trial, other adjuvant chemotherapy regimens are investigated in current phase III trials. The Japanese ASCOT-trial has recruited 440 patients with BTC to compare the effect of adjuvant S-1 therapy with an observational strategy [37]. In their data presentation at the ASCO Gastrointestinal Cancers Symposium 2022, the authors could demonstrate that an adjuvant therapy with S-1 was significantly superior to a observational strategy in terms of OS and PFS for all subgroups that were evaluated (ECOG performance status, age, cancer type, cancer stage, R factor, and serum CA19-9) with tolerable adverse events. However, it must be pointed out that the results might not be applicable to non-Asiatic patients since the tumor biology of GBC has major differences between different ethnic origins (see above).

The Chinese AdBTC-1 phase III trial is currently recruiting an aspired number of 460 patients to investigate the effect of gemcitabine and capecitabine compared to capecitabine alone in resected BTC patients (NCT03779035). Unfortunately, this trial has not been updated since 2018; therefore, further evidence is unlikely.

In conclusion, patients with GBC after curative resection should be considered for adjuvant chemotherapy with capecitabine based on the results of the BILCAP trial, especially in case of risk factors for disease recurrence (R1, N+, G3/4). Nevertheless, it must be admitted that evidence for adjuvant therapy after resection in patients with BTC and even more for patients with GBC remains poor. These limitations have been further highlighted by a systematic review of the Cochrane Database which concluded that there was a lack of evidence for the adjuvant treatment of resected BTC patients and moreover possible harm due to increased adverse events [38].

4. Palliative Therapy

Since GBC is often diagnosed in an advanced, non-curative stage and OS is poor with approximately 4.5 months under the best supportive care therapy [39][40], effective chemotherapy regimens have been established to improve prognosis. Nevertheless, current evidence is mostly established for BTC in general, and specific approaches for GBC are urgently required since it is estimated that GBC differs from other BTC forms in term of therapy response to different cytostatic agents [41].

For first-line therapy, the results of the ABC-02 study and the Japanese BT-22 study led to the establishment of a combined chemotherapy with gemcitabine (1000 mg/m^2, day 1 and 8 every three weeks) and cisplatin (25 mg/m^2, day 1 and 8 every three weeks). The ABC-02 phase III study prospectively evaluated the effect of gemcitabine and cisplatin compared to gemcitabine alone in 410 patients with BTC [35]. Overall, patients who received gemcitabine and cisplatin could significantly benefit from the combined chemotherapy regimen with an OS of 11.7 months compared to 8.1 months in the gemcitabine arm and a median PFS of 8.0 months compared to 5.0 months. Additionally, no significant difference was observed regarding the occurrence of adverse events in both groups. These results were consistent in the subgroup analysis of 149 patients with GBC (36.3%) that were part of the study collective.

In the BT-22 phase 3 trial, a similar study was performed, including 83 patients with BTC with 32 patients (39.0%) with GBC [42]. Like in the ABC-02 trial, a significant benefit was found for patients in the study arm with an OS of 11.2 months compared to 7.7 months and a PFS of 5.8 months compared to 3.7 months. In the subgroup analysis of GBC patients, a slightly poorer OS of 9.1 months compared to 6.7 months was observed.

A meta-analysis of both studies could verify these results including patients with GBC but showed no benefit in OS for patients with an ECOG performance state >2 [43]. Therefore, the authors suggest considering a monotherapy with gemcitabine for patients with poor ECOG performance state. In conclusion, the results of the ABC-02 trial and the BT-22 trial form the basis for the recommendation of a combined chemotherapy regimen with gemcitabine and cisplatin as the first-line therapy for patients with primary non-resectable BTC including GBC. For patients with a poor ECOG performance state, gemcitabine monotherapy can be considered and for patients with advanced chronic kidney failure, cisplatin should be replaced by oxaliplatin [2][26][28][44].

After the failure of gemcitabine and cisplatin, data for second-line chemotherapy in a palliative setting for BTC and moreover for GBC is strongly limited.

The ABC-06 phase III trial compared the effect of FOLFOX (5-FU and oxaliplatin) compared to active symptom control alone in 162 patients with BTC (34 = 21% GBC) after the failure of gemcitabine/cisplatin [45]. Overall, a benefit in terms of OS (6.2 months vs. 5.3 months) could be observed for the study arm and adverse events in both groups remained similar. In the subgroup analysis for GBC patients (*n* = 34), a difference in OS of 5.1 months vs. 4.6 months and a 12-month OS rate of 35.3% vs. 5.9% could be demonstrated with a disease control rate of 47% in GBC patients.

As another option, the GB-SELECT phase II trial evaluated the effect of irinotecan monotherapy compared to capecitabin and irinotecan (CAPIRI) in 98 GBC patients after disease progression with gemcitabine-based first-line treatment [46]. The authors could show that no difference in terms of OS and PFS was observed between both study arms, but adverse events and the need for dose modification was higher in the CAPIRI arm. Overall, a median OS of 6.28 months and a 6-month OS of 54.2% could be demonstrated in the irinotecan arm, which is comparable to the FOLFOX regimen despite differences in terms of study conduct. A phase II clinical trial by Choi et al. compared the effect of second-line treatment with 5-FU and irinotecan (FOLFIRI) to the established FOLFOX regimen in 118 patients with BTC including 35 GBC patients (29.7%) [47]. The authors could demonstrate a similar effect in terms of OS (6.3 months in the FOLFIRI arm vs. 5.7 months in the FOLFOX arm), PFS (2.1 months vs. 2.8 months), and ORR (4.9% vs. 5.9%) between both study arms,

with a significant higher occurrence of specific adverse events (thrombocytopenia, peripheral neuropathy, vomiting, and cholangitis) in the FOLFOX arm. Therefore, the authors suggest that FOLFIRI might be a therapeutic option for patients who suffer from adverse events under FOLFOX treatment. As a limitation, it has to be admitted that, in a pooled meta-analysis, only 43.9% of GBC patients were eligible to receive second-line therapy after the failure of first-line therapy [48]. A summary of other clinical trials that have investigated the effect of different chemotherapy regimen is provided in **Table 2**.

Table 2. Clinical trials for the palliative cytostatic chemotherapy of BTC specifically including GBC patients.

NCTN	Phase	Condition	Study Size	Substance	Results	Reference
NCT00660140	II	BTC + GBC	49	gemcitabine + carboplatin	PFS 7.8 months, OS 10.6 months	[49]
Not applicable	II	GBC	20	gemcitabine + carboplatin	ORR 36.7%, PFS 33.8 weeks	[50]
NCT00009893	II	BTC + GBC	42	gemcitabine + 5FU + leucovorin	PFS 4.6 months, OS 9.7 months	[51]
NCT00003276	II	BTC + GBC	39	irinotecan	ORR 8%	[52]
NCT00033540	II	BTC + GBC	57	gemcitabine + capecitabin	ORR 25%, OS 7 months	[53]
NCT00059865	II	BTC + GBC	63	gemcitabine + pemetrexed	No benefit of combined regimen compared to gemcitabine	[54]
NCT00075504	II	BTC + GBC	33	triapine + gemcitabine	ORR 9%; no benefit with triapine	[55]

Besides above-named chemotherapy regimen, current clinical trials have evaluated other cytostatic agents in patients with advanced-stage BTC, but data quality remains poor, and no phase III study has been conducted to compare these approaches with established therapy regimens. In a systematic review and meta-analysis, Azizi and colleagues investigated the effect of different cytostatic chemotherapy regimens specifically for patients with advanced GBC [48]. The authors could include 58 studies with 1986 GBC patients that were conducted until March 2019. Overall, an ORR of 23.2% with an OS of 4.8 months and a PFS of 8.3 months could be demonstrated. The pooled analysis suggested a benefit for chemotherapy regimens containing three or four cytostatic agents, with a pooled ORR of 35.8%, an OS of 9.9 months, and a PFS of 5.9 months. Moreover, GBC patients with platinum-based chemotherapy regimens had a benefit in OS, while gemcitabine-based therapy did not show a similar effect. In total, GBC patients showed a higher ORR than non-GBC patients (odds ratio 0.65; 95%CI 0.50–0.84), but OS and PFS could not be reliably compared based on the included study data.

Based on these results, a combined chemotherapy regimen with three or four cytostatic agents might improve prognosis for patients with GBC in a palliative setting and good ECOG state.

In a single-arm phase II clinical trial, Shroff et al. administered combined chemotherapy with nanoparticle-albumin-bound (nab-) paclitaxel, gemcitabine, and cisplatin to a study collective of 62 patients with advanced BTC including 13 GBC patients (22%) [56]. Overall, a median OS of 19.2 months and a median PFS of 11.8 months with a disease control rate of 84% could be achieved. Moreover, no differences between ORR and OS between different tumor sites could be observed. It should be noted that thirty-three patients (58%) suffered from an adverse event of grade 3 or higher, which might limit the group of patients that could tolerate this regimen. Nevertheless, these promising results are investigated in the current Southwest Oncology Group 1815 phase III trial (NCT03768414) to compare this regimen to the current standard therapy with gemcitabine and cisplatin to provide further evidence.

As another treatment option, a phase II trial has investigated the effect of a combined regimen containing 5-FU, leucovorin, oxaliplatin, and irinotecan (mFOLFIRINOX) in 29 patients with unresectable GBC [57]. Despite the high frequency of adverse events of grade 3 or higher in twenty-three patients (79.3%), the study showed encouraging results with an ORR of 48.3% and a disease control rate of 79% leading to an OS of 13.8 months and a PFS of 8.4 months in patients with a response to mFOLFIRINOX therapy. At the moment, the PRODIGE38-AMEBICA phase III study is randomizing 188 patients with advanced-stage BTC from a previous phase II study [58] to compare the effect of mFOLFIRINOX to gemcitabine and cisplatin [59]. In the previous phase II study, the authors recruited 191 patients that

were randomly assigned to a mFOLFIRINOX group and a gemcitabine/cisplatin group. Disappointingly, the triplet regimen with mFOLFIRINOX did improve PFS or median OS. Moreover, the doublet group had a slightly better median PFS (7.4 months vs. 6.2 months) and median OS (13.8 months vs. 11.7 months) [58].

Since GBC often occurs in elderly patients who might not be eligible for aggressive chemotherapy regimens in a non-curative setting, palliative radiation therapy might improve local disease control while causing fewer adverse events. Unfortunately, data on the effect of definitive radiation in unresectable GBC patients are lacking, despite the progress in new radiation techniques. As reported above, Verma et al. have suggested that patients with locally advanced GBC benefit from combined radio chemotherapy compared to a solitary chemotherapy regimen, based on their retrospective analysis of 1199 patients with locally advanced, non-metastatic gallbladder cancer from the National Cancer Database [32]. Additionally, Pollom et al. investigated the effect of radiation in a geriatric cohort of 2343 patients > 70 years from the SEER–Medicare database, including 50 GBC patients who received radiation therapy [60]. The authors proposed that patients who received chemotherapy benefit from additional radiation in terms of improved survival with an adjusted hazard ratio of 0.82 (95% 0.70–0.97, p = 0.02). The primary tumor site of BTC in their analysis had no effect on these results. In a retrospective single-center analysis of forty-five patients with locally advanced GBC patients receiving chemotherapy alone vs. combined radio-chemotherapy, Sinha et al. confirmed previous findings. In their analysis, a significant benefit for patients receiving radiotherapy was observed in terms of 2-year PFS (18.6% vs. 0%, p = 0.0001) and OS (37.3% vs. 5%, p = 0.0001). Importantly, adverse events related to radiation therapy were rare. With an ongoing improvement in radiation techniques and imaging technology, radiation therapy might change local disease control in unresectable GBC. As an example, Makita et al. evaluated the effect of additional proton beam therapy in unresectable BTC patients (3 GBC), leading to a 1-year OS of 49.0% and a 1-year PFS of 29.5% with a 1-year local disease control rate of 67.7%. These results were found to be independent from the chemotherapy regimen the included patients received, but patients with a tumor size < 5 cm and an ECOG > 1 were shown to significantly benefit more from a proton beam therapy. Despite these encouraging results, further prospective studies are mandatory to provide more evidence, with a special focus on elderly patients who are not eligible for an aggressive chemotherapy regimen.

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