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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Adjuvant Chemoradiation in Patients with Lymph Node-Positive Biliary Tract Cancers: Secondary Analysis of a Single-Arm Clinical Trial (SWOG 0809)

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ABSTRACT

Background. SWOG 0809 is the only prospective study of adjuvant chemotherapy followed by chemoradiation focusing on margin status in patients with extrahepatic cholangiocarcinoma (EHCC) and gallbladder cancer (GBCA); however, the effects of adjuvant therapy by nodal status have never been reported in this population.

Methods. Patients with resected EHCC and GBCA, stage pT2-4, node-positive (N+) or margin-positive (R1) who completed four cycles of chemotherapy followed by radiotherapy were included. Cox regression was used to compare overall survival (OS), disease-free survival (DFS), local recurrence, and distant metastasis by nodal status. DFS rates were compared with historical data via a one-sample t-test.

Results. Sixty-nine patients [EHCC, $n = 46$ (66%); GBCA, $n = 23$ (33%)] were evaluated, with a median age of 61.7 years and an R0 rate of 66.7% and R1 rate of 33.3%. EHCC versus GBCA was more likely to be N+ (73.9% vs. 47.8%, $p = 0.03$). Nodal status did not significantly impact OS (hazard ratio [HR] 1.98, 95% confidence interval [CI] 0.86–4.54, $p = 0.11$) or DFS (HR 1.63, 95% CI 0.77–3.44, $p = 0.20$). Two-year OS was 70.6% for node-negative (N0) disease and 60.9% for N+ disease, while 2-year DFS was 62.5% for N0 tumors and 49.8% for N+ tumors. N+ versus N0 tumors showed higher rates of distant failure (42.2% vs. 25.0%, $p = 0.04$). The 2-year DFS rate in N+ tumors was significantly higher than in historical controls (49.8% vs. 29.7%, $p = 0.004$).

Conclusions. Adjuvant therapy is associated with favorable outcome independent of nodal status and may impact local control in N+ patients. These data could serve as a benchmark for future adjuvant trials, including molecular-targeted agents.

Biliary tract cancers (BTCs) including gallbladder cancer (GBCA) and extrahepatic and intrahepatic cholangiocarcinoma (CCA), are a rare and heterogeneous group of tumors with poor prognosis.[1–3] The majority of patients present with locally advanced disease.[4,5] Only a minority of patients (< 10% for GBCAs and 25% for CCAs) are candidates for radical resection, the only potential curative treatment.[6,7] Without further treatment, local recurrence (LR) rates remained high (60–75%) at a median 2-year follow up[8,9] following curative

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resection. This has led to the emerging role of adjuvant systemic therapy and chemoradiation for patients with resected BTCs based on the assumption that improving locoregional and systemic disease control may improve survival.[10–15]

Given the rarity and heterogeneity of these tumors, the role of adjuvant systemic plus chemoradiation therapy for BTC has not been well established. Most data are derived from small, retrospective studies that have shown conflicting results. In a retrospective analysis with propensity matching using the National Cancer Database, Nassour et al. suggested that adjuvant chemotherapy and chemoradiotherapy were associated with improved survival in resected perihilar CCA.[16] However, others have described minimal benefit from adjuvant radiotherapy on survival for patients with extrahepatic cholangiocarcinoma (EHCC) using the Surveillance, Epidemiological, and End Results (SEER) database.[17,18] Similar conflicting findings have been reported for patients with GBCA.[8,19–25] Most of these studies show a short-term survival benefit of adjuvant radiotherapy in resected GBCA patients; however, this benefit did not persist at 5-year follow up.[24,25] These discordant results created the need for a prospective study to evaluate the effect of adjuvant chemotherapy and chemoradiotherapy in patients with resected BTC.

To date, SWOG 0809 remains the only prospective clinical trial to evaluate the efficacy of adjuvant radiation in conjunction with systemic chemotherapy in patients with resected BTC. This phase II, single-arm trial included 79 patients with T2-4 EHCC or GBCA, irrespective of margin and nodal status, who received adjuvant chemotherapy with concurrent chemoradiation after curative resection and showed improved survival compared with historical controls.[26] Median overall survival was 35 months (R0, 34 months; R1, 35 months).

Furthermore, it has been well established that lymph node status is a prognostic factor for recurrence in BTCs. Recent meta-analyses have shown improved locoregional recurrence rates in this patient population receiving adjuvant radiation following resection.[27,28] A recent meta-analysis reported improved pooled locoregional control of 52.1% versus 34.9% ($p = 0.014$) for patients with and without adjuvant radiation. In the sensitivity analysis on 14 eligible studies, the authors showed a lower margin-negative rate (36.8% vs. 63.2%, $p = 0.02$) and a trend towards higher rate of node-positive (N+) disease (47.4% vs. 34.9%, $p = 0.08$) in the group of patients receiving adjuvant radiotherapy. Similar favorable outcomes using adjuvant radiation have been described in other studies, with the greatest benefit in the N+ group.[28–30] SWOG 0809 reported on the effect of adjuvant chemotherapy followed by radiation with concurrent chemotherapy with a focus on margin status. However, the effect of adjuvant chemoradiation by lymph node status for BTC has never been reported in a prospective clinical trial. Therefore, the objective of this study was to perform a secondary analysis of SWOG 0809 and delineate the effect of adjuvant chemoradiation on disease-free survival (DFS) and overall survival (OS) according to lymph node status following resection. We hypothesized that adjuvant chemotherapy and chemoradiation provided a clinical benefit to patients with N+ disease compared with historical controls.

METHODS

Patients

SWOG 0809 included patients with a diagnosis of EHCC or GBCA (pathologic stage T2-4 irrespective of nodal or margin status) who underwent complete resection.[26] Eligibility criteria for the original trial included (1) no prior systemic therapy for EHCC or GBCA, or prior radiation to the upper abdomen; (2) favorable performance status (Karnofsky Performance Status [KPS] 0, 1); and (3) an absolute neutrophil count $\geq$1500/mcL, platelets $\geq$100,000/mcL, serum creatinine $\leq$1.5 mg/dL, total bilirubin $\leq 1.5 \times$ institutional upper limit of normal, and either aspartate transaminase (AST) or alanine aminotransferase (ALT) $\leq 2.5 \times$ institutional upper limit of normal. Patients were followed every 3 months after completion of adjuvant therapy, with surveillance imaging of the chest, abdomen, and pelvis (computed tomography [CT] or magnetic resonance imaging [MRI]) every 6 months for 2 years. The primary trial analysis of SWOG 0809 included 79 eligible and evaluable patients (Fig. 1). Ten patients from the original trial were excluded from this secondary analysis (EHCC, $n = 8$; GBCA, $n = 2$) as they did not complete radiation therapy (early progression, $n = 5$; personal reasons, $n = 3$; toxicity, $n = 1$; unknown reason, $n = 1$).

Treatment

Adjuvant treatment consisted of four cycles of chemotherapy with gemcitabine (1000 mg/m^2 intravenously on days 1 and 8) and capecitabine (1500 mg/m^2/day on days 1–14, in divided doses twice daily) every 21 days. If no progression was seen on interval imaging, patients then proceeded with capecitabine (1330 mg/m^2/day, in divided doses twice daily, 7 days per week) and concurrent radiotherapy (45 Gy to regional lymph nodes [retro-pancreaticoduodenal, celiac, and portal vein nodes] and 54–59.4 Gy to the preoperative tumor bed). Radiation therapy using three-dimensional planning was administered at 54 Gy in 30 fractions. For patients who underwent

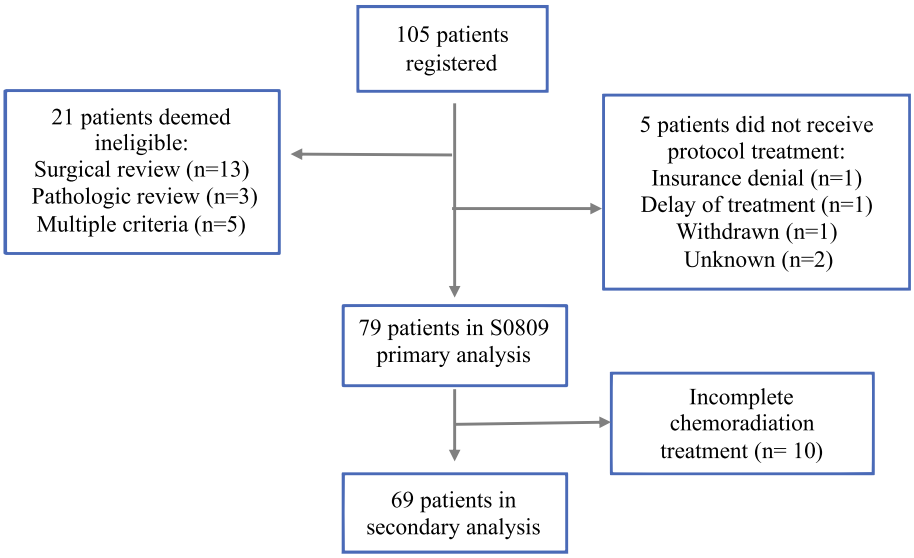


FIG. 1 Study cohort

image-guided intensity-modulated radiotherapy (IMRT), a concurrent boost was added for a total dose of 52.5 Gy in 25 fractions. Details of the radiation therapy have been summarized previously.[26]

Statistical Considerations

Statistical differences between baseline demographic and clinical characteristics according to lymph node status and disease site were assessed via Mann–Whitney and Chi-square tests. Probabilities of OS and DFS were estimated using the Kaplan–Meier method, and the probabilities of LR and distant relapse were summarized using cumulative incidence estimates; death without recurrence was treated as a competing risk for recurrence events. Data from patients last known to be alive and/or free of disease were censored at the date of last contact. Statistical differences in event rates between groups according to lymph node status were assessed via Cox regression models with stratification for disease site. The strength of associations between treatment characteristics and incidence of LR were tested via Fisher's exact test. Observed DFS rates were compared with historical data via a one-sample t-test, with historical rates calculated from previous studies[32–34] (median for N+, 13.7 months vs. N0, 39.3 months); median DFS of 13.7 months is equivalent to a 2-year DFS of 29.7%.

RESULTS

Patient Characteristics

A total of 69 patients [EHCC, $n = 46$ (66%); GBCA, $n = 23$ (33%)] with a median age of 61.7 years (range 26.1–80.6) received adjuvant therapy and were included in this secondary analysis (Table 1). The majority of node-negative (N0) patients were female (17/24, 70.8%), whereas most N+ patients were male (25/45, 55.6%; $p = 0.04$). Patients with EHCC were more likely to have N+ disease than those with GBCA (73.9% vs. 47.8%, $p = 0.03$), and patients with GBCA were more likely to have a KPS of 1 than those with EHCC (56.5% vs. 26.1%, $p = 0.02$) [Table 2]. Eighty-one percent of patients underwent IMRT, whereas only 19% received three-dimensional planning. The median dose for R0 and R1 patients was 52.5 and 54 Gy, respectively. Treatment interruptions were seen in 21 patients (while receiving radiotherapy and concurrent chemotherapy, $n = 7$; radiotherapy only, $n = 1$; chemotherapy only, $n = 13$).

Clinical Outcomes

OS and DFS were greater in patients with N0 disease compared with N+ disease, although the differences did not reach statistical significance. Two-year OS was 70.6% for N0 disease and 60.9% for N+ disease (hazard ratio [HR] 1.98, 95% confidence interval [CI] 0.86–4.54, $p = 0.11$). Two-year DFS was 62.5% for N0 disease and 49.8% for N+ disease (HR 1.63, 95% CI 0.77–3.44, $p = 0.20$) [Fig. 2a]. The observed 2-year DFS in patients

TABLE 1 Baseline characteristics by lymph node status [$n = 69$]

	N0 [$n = 24$]	N+ [$n = 45$]	p value[a]
Age, years [median (range)]	60.1 (26.1–80.6)	61.7 (26.7–80.3)	0.98
Sex			0.04
Female	17 (70.8)	20 (44.4)	
Male	7 (29.2)	25 (55.6)	
Hispanic			0.78
Yes	2 (8.3)	2 (4.4)	
No	19 (79.2)	38 (84.5)	
Unknown	3 (12.5)	5 (11.1)	
Race			0.92
Black	2 (8.3)	5 (11.1)	
Asian	1 (4.2)	3 (6.7)	
White	20 (83.3)	36 (80)	
Unknown	1 (4.2)	1 (2.2)	
Disease site			0.03
Gallbladder	12 (50)	11 (24.4)	
Bile duct	12 (50)	34 (75.6)	
Performance status			0.57
0	14 (58.3)	23 (51.1)	
1	10 (41.7)	22 (48.9)	
Resection margin			0.99
R0	16 (66.7)	30 (66.7)	
R1	8 (33.3)	15 (33.3)	
Radiation modality			0.94
IMRT	19 (79.2)	36 (80)	
3D	5 (20.8)	9 (20)	

Data are expressed as *n* (%) unless otherwise specified

[a]Mann–Whitney U-test for age and Chi-square test for categorical variables

N0 node negative, *N+* node positive, *IMRT* intensity-modulated radiation therapy, *3D* three-dimensional conformal radiation therapy

with N+ tumors was significantly higher than the historical rate of 29.7% ($p = 0.004$).

A total of 11 patients developed LR, of whom eight experienced a concurrent distant relapse; 21 patients developed distant-only relapse (Table 3). N+ versus N0 tumors showed a higher rate of 2-year distant failure (42.2% vs. 25.0%; HR 2.57, 95% CI 1.04–6.38, $p = 0.04$) [Fig. 2b] but similar LR rates (11.1% vs. 8.3%; HR 1.13, 95% CI 0.30–4.28, $p = 0.85$), suggesting improved local control for N+ patients receiving adjuvant radiation therapy.

DISCUSSION

BTCs, which include GBCA and EHCC, are a heterogeneous group of rare, biologically aggressive tumors characterized by a high frequency of regional lymph node and distant metastatic spread.[35,36] Due to the relative rarity of BTC and limited prospective clinical trials, evidence-based treatment regimens targeting these tumors are not well established. To date, SWOG 0809 has been the only phase II clinical trial that assessed the efficacy of adjuvant chemotherapy and chemoradiation for BTC patients.[26] In this study, we present a secondary analysis of the SWOG 0809 clinical trial data. Specifically, we examine the relationships between lymph node status, recurrence patterns, and survival.

Nodal involvement in both EHCC and GBCA[37,38] has been well established as playing a significant role on survival. Several retrospective studies demonstrated that lymph node status predicts survival in BTC patients.[39–44] Only a few prospective clinical trials focused on BTC report on lymph node status and survival.[32,45] However, a meta-analysis of 20 studies analyzing 6712 patients with BTC proposed lymph node positivity as an indication for adjuvant therapy.[28] In that report, adjuvant therapy was associated with a higher survival rate compared with surgery alone in patients with either N+ or margin-positive

TABLE 2 Baseline characteristics by disease site

	Bile duct [$n = 46$]	Gallbladder [$n = 23$]	p value[a]
Age, years [median (range)]	60.2 (26.1–80.3)	67.7 (41–80.6)	0.15
Sex			0.001
Female	18 (39.1)	19 (82.6)	
Male	28 (60.9)	4 (17.4)	
Hispanic			0.34
Yes	2 (4.4)	2 (8.7)	
No	37 (80.4)	20 (86.9)	
Unknown	7 (15.2)	1 (4.4)	
Race			0.12
Black	2 (4.4)	5 (21.7)	
Asian	3 (6.4)	1 (4.4)	
White	39 (84.8)	17 (73.9)	
Unknown	2 (4.4)	0	
Lymph node			0.03
N0	12 (26.1)	12 (52.2)	
N+	34 (73.9)	11 (47.8)	
Performance status			0.02
0	20 (43.5)	17 (73.9)	
1	26 (56.5)	6 (26.1%)	
Resection margin			0.37
R0	29 (63)	17 (73.9%)	
R1	17 (37)	6 (26.1%)	
Radiation modality			0.67
IMRT	36 (78.3)	19 (82.6%)	
3D	10 (21.7)	4 (17.4%)	

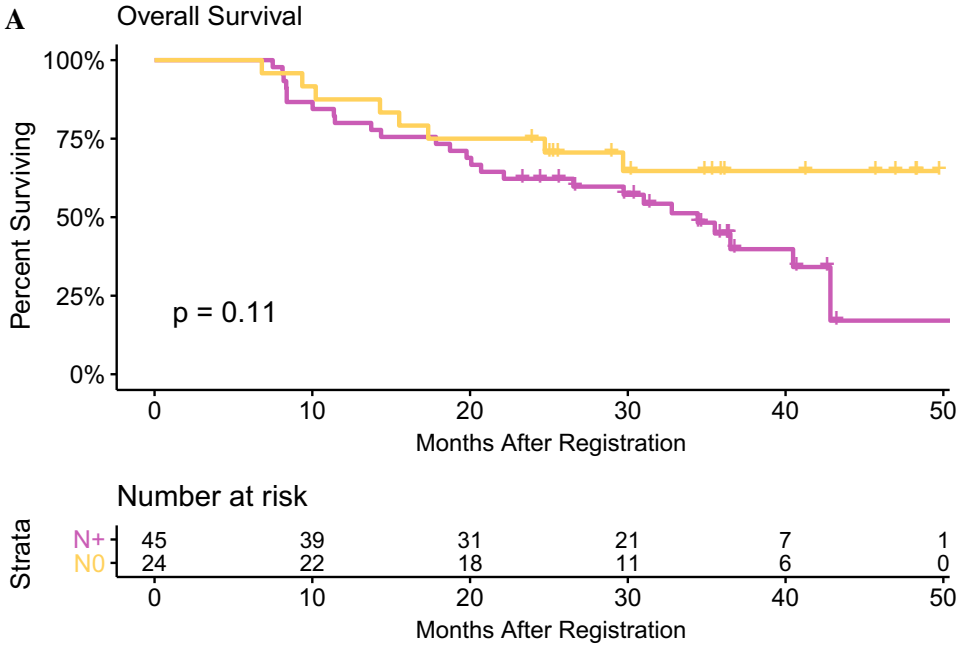
Data are expressed as n (%) unless otherwise specified

[a]Mann–Whitney U-test for age and Chi-square test for categorical variables

IMRT intensity-modulated radiation therapy, *3D* three-dimensional conformal radiation therapy

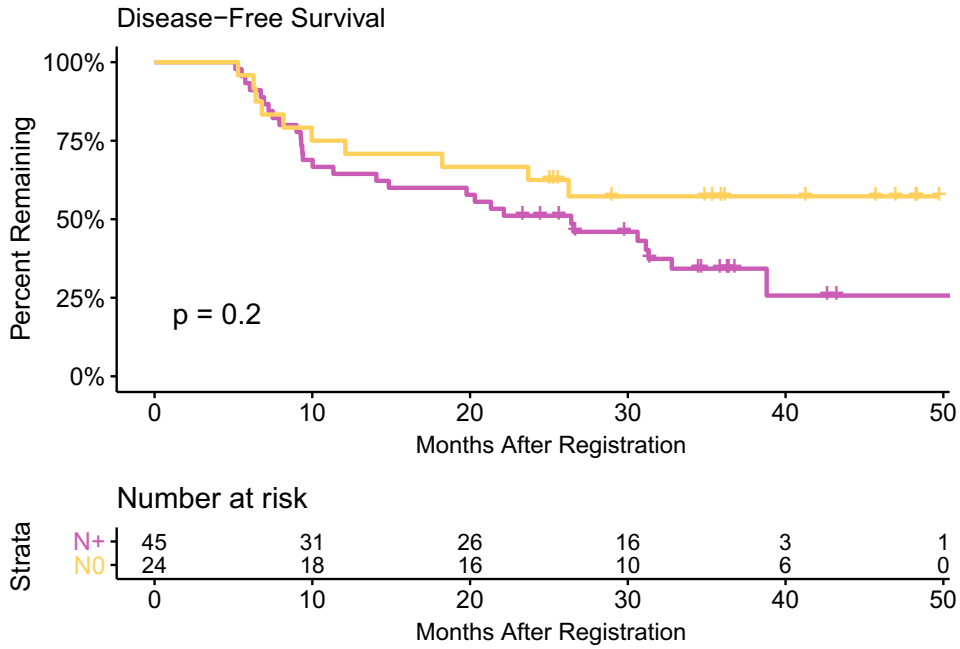
resections, but this association did not reach statistical significance (odds ratio [OR] 0.74, 95% CI 0.55–1.01, $p = 0.06$). This improvement was statistically significant with adjuvant chemotherapy or chemoradiotherapy but not with radiotherapy alone. Looking at specific subgroups, a pooled analysis of nine studies confirmed a significant survival benefit of any adjuvant therapy in patients with N+ disease (OR 0.49, 95% CI 0.30–0.80, $p = 0.004$). Of note, less than one-third of patients received combination chemoradiotherapy. Additionally, a nomogram developed for GBCA using the SEER-Medicare database suggests a survival advantage using adjuvant chemoradiation for T2 and N+ patients, and that chemoradiotherapy provides greater benefit than chemotherapy alone in all patient subsets.[46] Finally, the recent BILCAP study showed a survival benefit of adjuvant capecitabine compared with observation alone in patients with margin- and node-positive BTC in a per-protocol analysis, although the intention-to-treat analysis did not show a statistically significant difference. Although the BILCAP study did not meet its primary endpoint of improving survival in the intention-to-treat population, the prespecified per-protocol analysis suggests a potential survival benefit and has been considered standard of care. However, the benefit of adjuvant capecitabine was not seen in the hilar CCA subtype on subgroup analysis. In our secondary analysis of SWOG 0809, lymph node status did not significantly impact OS (HR 2.03, $p = 0.08$) or DFS (HR 1.75, $p = 0.13$). However, the N+ patients had higher DFS rates compared with historical controls.

It has been well described in the literature that the predominant pattern of initial treatment failure is locoregional disease for extrahepatic bile duct tumors.[47] Based on this rationale, adjuvant radiation has been offered to this patient population despite no clear evidence from randomized, phase III trials. In our clinical trial cohort, we observed a higher proportion of tumor with nodal involvement in patients with EHCA (75.6%) compared



	N0	N+
2-year OS	70.6% (47.9% - 84.8%)	60.9% (45.2% - 73.5%)

Technique	At Risk	Events
N0	24	8
N+	45	27

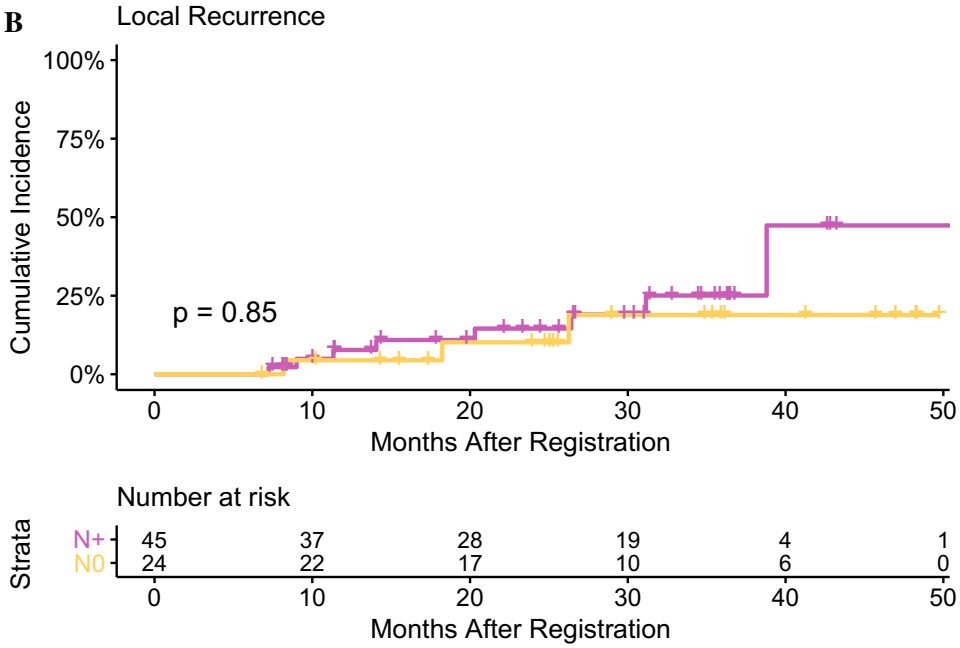


	N0	N+
2-year DFS	62.5% (40.3% - 78.4%)	49.8% (34.5% - 63.4%)

Technique	At Risk	Events
N0	24	10
N+	45	29

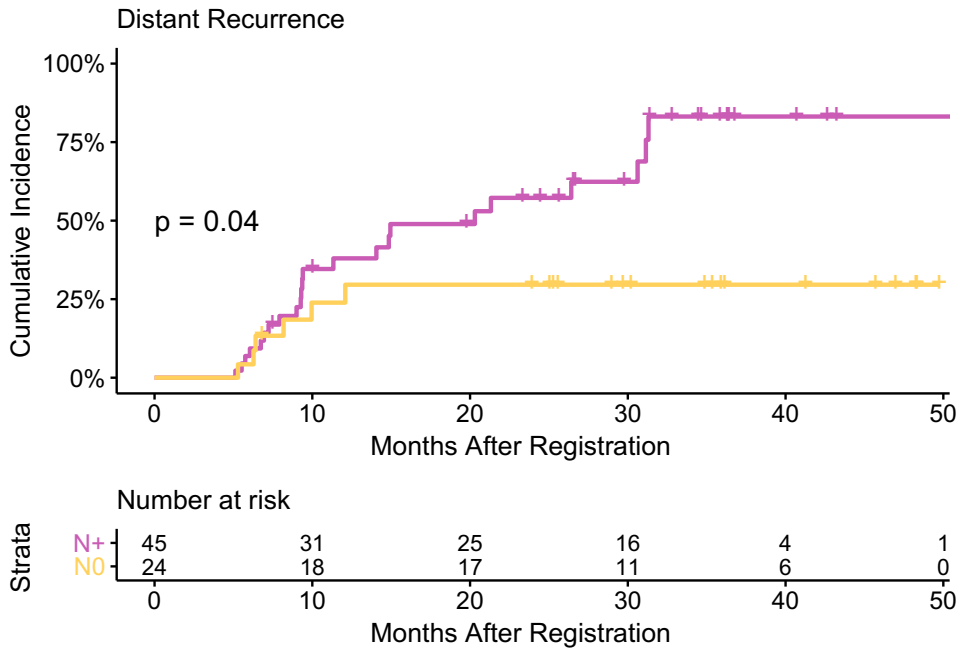
FIG. 2 **A** Overall and disease-free survival by lymph node status. **B** Local recurrence and distant recurrence by lymph node status. *OS* overall survival

FIG. 2 continued



	N0	N+
2-year Local Recurrence Rate	8.3% (1.4% - 23.8%)	11.1% (4.0% - 22.3%)

Node Status	At Risk	Events
N0	24	3
N+	45	8



	N0	N+
2-year Distant Recurrence Rate	25.0% (9.9% - 43.6%)	42.2% (27.5% - 56.2%)

Node Status	At Risk	Events
N0	24	6
N+	45	23

TABLE 3 Pattern of first relapse

Recurrence	EHCC distal [$n = 31$]	EHCC hilar [$n = 13$]	GBCA [$n = 23$]
Local only	2 (6)	1 (8)	0
Local plus distant	4 (13)	2 (15)	2 (9)
Distant only	11 (35)	1 (8)	9 (39)
Total	17 (54)	4 (31)	11 (48)

Two patients for whom complete data were not available were excluded

EHCC extrahepatic cholangiocarcinoma, *GBCA* gallbladder carcinoma

with GBCA (24.4%). With regard to patterns of recurrence, local-only recurrence was a rare event. In fact, the 2-year LR was not statistically different between N0 patients (8%) and N+ patients (11%). However, distant recurrence rates differed by disease subtype and appeared to be more dependent on nodal status, with N+ patients experiencing a 42% distant recurrence rate compared with 25% for N0 patients. For example, the distant-only failure rates were significantly higher in patients with GBCA (39%) compared with only 8% for patients with hilar CCA, despite the latter having a higher incidence of node positivity. Although limited by sample size and the single-arm design, one can speculate that these low local-only recurrence rates could be associated with treatment effects of adjuvant chemoradiation. This hypothesis remains to be formally studied in larger controlled trials. In an earlier trial of adjuvant chemotherapy for resected BTCs, mitomycin-C appeared to confer a benefit to GBCA patients but not bile duct cancer patients. However, this effect was not significant in intention-to-treat analysis. Interestingly, nodal positivity was nearly universal in both cohorts (>80%), and a significant portion of patients underwent non-curative intent surgery.[48] Given these potential biologic differences between GBCA and bile duct cancer, we would strongly advocate for disease- and site-specific trials.

Identifying relevant historical survival data from patients undergoing resection for BTC presents a challenge as results vary based on tumor type, stage, residual disease at the time of surgical exploration, and additional adjuvant therapy. For example, Butte et al. reported a median DFS of 15 versus 41 months for patients with and without nodal disease at the time of exploration for GBCA.[34] A slightly higher median DFS was reported by the same group for patients with resected GBCA (N0, 34 months; N+, 19 months). Of note, about 13–18% of patients in both studies received adjuvant chemotherapy. Similarly, worse survival data have been reported for patients with hilar CCA undergoing resection with positive lymph nodes, with a median DFS of only 7 months. The historical 2-year DFS for patients with N+ disease was 29.7%.[32–34] We show that SWOG 0809 N+ patients treated with adjuvant chemotherapy and chemoradiation experienced significantly longer DFS (49.8%, $p = 0.004$). Together, our findings suggest that a patient's lymph node status could inform treatment recommendations.

Our study is limited by several factors, including a small sample size, tumor heterogeneity (as with most BTC studies), a single-arm design, and two radiation modalities. However, to our knowledge, this is the first analysis that evaluates the impact of nodal disease on survival in patients with EHCC and GBCA who received adjuvant radiation in a prospective clinical trial setting. With the advancement of more effective systemic regimens (gemcitabine, cisplatin, and nab-paclitaxel), immune-based regimens with systemic chemotherapy, and multiple novel targeted drugs for actionable mutations for BTCs, it becomes even more critical to improve local control rates in this disease. Given the explosion of molecular profiling and FDA approval of multiple targeted agents, our findings could serve as a baseline comparison for future clinical trials.

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DISCLOSURES Sepideh Gholami, Sarah Colby, David P. Horowitz, Katherine A. Guthrie, Edgar Ben-Josef, Anthony B. El-Khoueiry, Charles D. Blanke, Philip A. Philip, Lisa A. Kachnic, Syed A. Ahmad, and Flavio G. Rocha have no conflicts of interest to declare in relation to this article.

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