ORIGINAL ARTICLE

Impact of adjuvant chemoradiation on survival in patients with resectable cholangiocarcinoma

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Abstract

Background: The ideal adjuvant therapy for resected cholangiocarcinoma remains controversial. National guidelines stratify recommendations based on margin status, though few studies are currently available for reference.

Methods: Data was abstracted on all patients with definitive resections of cholangiocarcinoma at our institution between 2000 and 2013. Adjuvant chemoradiation consisted of 45 Gy delivered to elective nodal regions and 50.4–54 Gy to the surgical bed with concurrent fluoropyrimidine-based chemotherapy. Subgroup analyses were performed delineated by margin status.

Results: Curative resection was performed on 95 patients followed by adjuvant chemoradiation in 23/95 (24%) and observation in 72/95 (76%) with a median follow-up of 21.7 months. For those receiving adjuvant chemoradiation the median overall survival was 30.2 months compared with 26.3 months for those observed ($p = 0.0695$). In a multivariable model controlling for other prognostic factors, adjuvant chemoradiation was associated with improved disease-free survival (HR 0.50, $p = 0.03$) and overall survival (HR 0.37, $p = 0.004$). In multivariable models stratified by margin status, adjuvant chemoradiation was associated with improved overall survival following both margin-negative (HR 0.34, $p = 0.035$) and margin-positive (HR 0.15, $p = 0.003$) resections.

Conclusions: Overall survival was improved with adjuvant chemoradiation following either margin-negative or margin-positive resections, which is not currently reflected in national guidelines.

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Introduction

For patients with clinically-localized cholangiocarcinoma (CC), local control remains a significant issue even following aggressive resection. Analogous to gallbladder and pancreatic adenocarcinomas, patients are often diagnosed late in the disease process with both nodal and distant metastases occurring early and often.[1–8] Among the minority of patients whose presentation is amenable to curative resection, local recurrence is the rule not the exception.[1,9–11] While the only curative treatment for CC patients remains surgical resection, post-operative outcomes have shown no significant improvements in the past several years[11] with the current five-year survival rate stagnating at a mere 5% for all CC patients.[12] Due to a historically low incidence in Western countries in addition to a low proportion of resectable disease at presentation, there are few established criteria for the treatment of CC in the post-operative setting.[13]

The high rate of local recurrence following resection suggests the need for aggressive adjuvant therapy, though few studies have addressed this issue to date. A few retrospective series have shown benefits in both local control and improved overall survival when using radiation therapy (RT) for unresectable CC,[14–18] establishing its activity in this disease. Adjuvant

chemotherapy (CT) and/or concurrent chemoradiation (CRT) for resected CC has also been associated with increased survival in pooled meta-analyses of historic international series, especially in those with involved lymph nodes or microscopic residual disease following resection.[19,20] One recent phase II trial evaluating adjuvant capecitabine and gemcitabine followed by concurrent capecitabine and RT demonstrated good tolerability and promising efficacy,[21] but there remains a need for comparative studies of adjuvant therapy for CC in Western populations.

The current lack of available data examining the benefit gained with adjuvant CRT in CC across detailed clinicopathologic features can only be rectified with prospective studies or comprehensive institutional review. The goal of this retrospective study was to specifically measure the benefit of adjuvant CRT following definitive resection of CC in the context of an in-depth examination of other potentially predictive factors.

Methods

Inclusion and exclusion criteria

Data was abstracted on all patients with a pathologic diagnosis of CC at our institution between January 2000 and December 2013. All patients with non-metastatic CC who underwent curative-intent resection surviving at least eight weeks were identified. Bile duct adenocarcinomas arising from the gallbladder or ampullary regions were excluded. Patients experiencing perioperative mortality within eight weeks of surgery were excluded, as this likely would have precluded initiation of adjuvant CRT. Only four patients received chemotherapy alone and were excluded from final analysis to avoid excess heterogeneity within the adjuvant therapy cohort. Eastern Cooperative Oncology Group (ECOG) scale was used to quantify performance statuses at time of first post-operative follow-up.[22]

Surgical and adjuvant therapy

All tumors in an intrahepatic location were resected with partial hepatectomies, perihilar tumors with common bile duct and hepatic resections with or without cholecystectomy, and distal bile duct tumors with pancreaticoduodenectomies (Whipple procedure). Margins were considered positive (R1) if tumor cells were present on, or very close (<1 mm) to, the inked specimen margin. The decision of when to employ adjuvant CRT was commonly discussed at a multidisciplinary tumor board conference. It has been our institution's practice to consider adjuvant therapy only in the setting of positive surgical margin and/or presence of other high-risk features such as nodal disease, perineural spread (PNS), lymphovascular space invasion (LVSI) or nodal extracapsular extension (ECE).

Those receiving RT were prescribed 45 Gy directed to the tumor bed and at-risk nodal stations with an additional sequential boost dose of 5.4–9 Gy to the pre-surgical tumor volume delivered in 1.8 Gy daily fractions employing intensity-modulated radiation therapy (IMRT) planning techniques (see eFig. 1 in the supplement). All patients received concurrent 5-fluorourocil or capecitabine during the course of RT. Toxicities of adjuvant CRT were characterized according to common terminology criteria for adverse events (CTCAE) version 4.03.[23]

Statistical analysis

As measured from time of diagnosis, the primary outcomes were disease-free survival (DFS) with an endpoint of recurrence, or death from any cause in the instance of no recurrence, and overall survival (OS) with an endpoint of death from any cause. If endpoints for DFS and OS were not noted, patients were censored at date of last follow-up. The independent samples t-test was used to compare means and the χ^2 test, or Fisher's exact test when the assumptions of the χ^2 test were not tenable, was used to compare proportions for categorical variables. TNM classification and group staging was recorded as described by the American Joint Committee on Cancer (AJCC) Staging Manual, 7th ed.[24]

The Kaplan–Meier method was used to estimate DFS and OS. Survival curves were compared using the log-rank test. Univariate Cox proportional hazards models were initially used to assess the relationships of study variables with OS and DFS. Variables having a univariate significance of $p < 0.2$ were included in a multivariable model. Since surgical margin status has previously been used to guide treatment recommendations,[13] we repeated the univariate and multivariate analyses within two subgroups defined by margin status. All p-values were two-sided and all statistical analyses were conducted using SAS, version 9.4.[25]

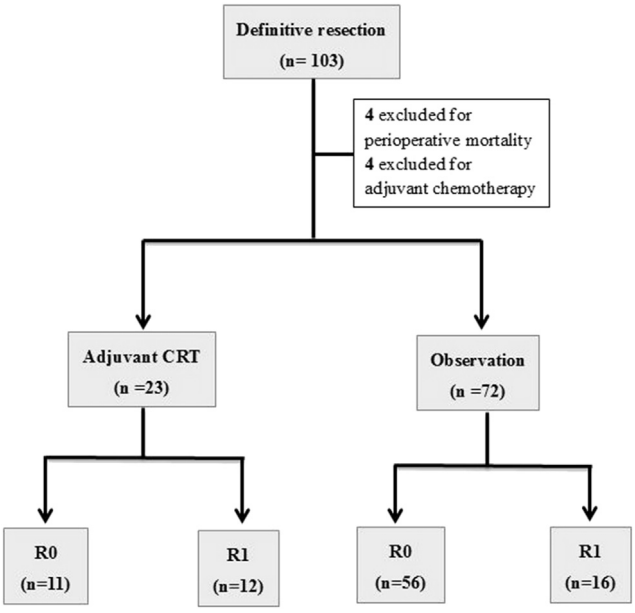

Figure 1 Study schema