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Radiotherapy for Biliary Tract Cancers

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Biliary tract cancers (BTCs), including intrahepatic, perihilar and distal cholangiocarcinomas, and gallbladder cancers, are a heterogeneous cohort of tumors that tend to present with advanced stage and with high rates of recurrence after surgical resection. While liver-directed radiotherapy was traditionally restricted to the palliative setting given concerns over hepatotoxicity, modern radiotherapy techniques have enabled safe and effective treatment of a variety of hepatic tumors, thereby expanding the role of liver-directed radiotherapy in the management of BTCs. For resected BTCs, adjuvant chemoradiotherapy is recommended for patients with involved lymph nodes and positive resection margins. For patients with hilar cholangiocarcinomas, neoadjuvant chemoradiotherapy is recommended prior to orthotopic liver transplantation. Finally, for patients with unresectable disease, definitive radiotherapy in addition to systemic therapy represents a potential opportunity to maximize both local control and overall survival. In this review, we will discuss the evidence supporting the use of liver-directed radiotherapy for BTCs, as well as ongoing clinical investigations.

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Introduction

Biliary tract cancers (BTCs) comprise a heterogeneous cohort of tumors consisting of cholangiocarcinomas, including intrahepatic, perihilar, extrahepatic, and gallbladder cancers. In the year 2018, there will be approximately 12,190 new diagnoses and 3790 deaths from gallbladder and extrahepatic biliary cancer.[1] Intrahepatic cholangiocarcinoma (ICC) accounts for approximately 15% of the 42,220 primary liver and bile duct cancers diagnosed in the US each year. While the incidence of ICC has increased in the US over the past 40 years the incidence of extrahepatic cholangiocarcinoma (ECC) has been stable.[2,3] Due to the relative rarity of cholangiocarcinomas, ICC, and ECCs have often been grouped together on randomized trials; however, there is increasing evidence that they represent distinct diseases with different molecular profiles.[4,5]

While resection is considered the optimal management for cholangiocarcinoma, many patients are not candidates for upfront resection due to local tumor extent, and those who undergo resection remain at high risk of recurrence. The development of modern and liver-directed radiotherapy has provided a promising local treatment option in both patients with resectable and unresectable disease. In this review, we will discuss the role of radiotherapy in the adjuvant, neoadjuvant, and unresectable setting for BTCs.

Adjuvant Management of Resectable Biliary Tract Cancers

ECC and Gallbladder Cancer

There are limited data to guide adjuvant treatment decisions for ECC and gallbladder cancer. Management recommendations are further complicated by inherent differences in patterns of disease recurrence between disease sites, with higher rates of distant failure in gallbladder cancer as compared to ECC.[6]

Surgical resection is the mainstay of treatment for both gallbladder cancer and ECC, and the ability to obtain a R0 resection remains a critical prognostic factor.[7,8] Many patients with gallbladder cancer are often diagnosed incidentally after simple cholecystectomy.[7] While patients with T1aN0 disease may be cured after simple cholecystectomy with widely negative resection margins,[9,10] tumors with invasion of the muscularis (T1b or higher stage) or involved lymph nodes require radical cholecystectomy with partial hepatectomy with resection of segments IVB and V as well as extensive nodal dissection due to the high risk of residual disease. Similarly, ECCs require extensive dissection and lymphadenectomy, including hilar and hepatic resection for

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proximal lesions and pancreaticoduodenectomy for distal lesions. R0 resection is associated with an improvement in survival,[8,10] and patients with R0 resection and wide negative margins have not been shown to benefit from adjuvant chemotherapy or chemoradiotherapy in a retrospective series including patients with both gallbladder cancer and cholangiocarcinoma.[11] Nonetheless, there remains a significant risk of both distant and locoregional recurrence.

Trials and retrospective series provided variable results as to the efficacy of adjuvant therapy in BTC.[12-14] Studies have been largely comprised of heterogeneous patient populations, thereby limiting the power to demonstrate an improvement in outcomes with treatment. For example, while a recent trial demonstrated an improvement in overall survival (OS) with adjuvant capecitabine, another trial of adjuvant gemcitabine and oxaliplatin failed to show an improvement in recurrence-free survival over surveillance. The BILCAP (adjuvant capecitabine for BTC) trial[15] randomized 447 patients to adjuvant capecitabine vs observation after complete resection (R0 resection rate of 62%) of cholangiocarcinoma or gallbladder cancer. The majority had involved regional lymph nodes (n = 240, 54%). There was a significant improvement in OS in the per-protocol analysis, with median OS of 53 months with capecitabine vs 36 months with observation (hazard ratio 0.75, 95% confidence interval [CI] 0.58-0.97, and P = 0.028). By contrast, the PRODIGE 12-ACCORD18 Phase III trial[16] did not show an improvement in recurrence-free survival with adjuvant gemcitabine and oxaliplatin. This trial included more patients with favorable characteristics as compared to the BILCAP trial, as the majority of patients had an R0 resection (87%) and only ~37% had involved regional lymph nodes. However, subgroup analysis of the PRODIGE12-ACCORD18 trial failed to identify a group that would benefit from adjuvant gemcitabine and oxaliplatin.

There are no randomized trials on the role of adjuvant radiotherapy or chemoradiotherapy in resected BTC. For patients with involved regional lymph nodes or positive margins, meta-analyses, retrospective data, and a Phase II trial support the role of adjuvant therapy in both gallbladder cancer and ECC.[15,17-21] A meta-analysis by Horgan et al[17] provided support for the use of adjuvant therapy in patients with nodal metastases or positive margins. This meta-analysis included 20 studies published between 1960 and 2010 involving 6712 patients. Approximately 27% of patients received adjuvant therapy, which included chemotherapy, radiotherapy, or chemoradiotherapy. Most patients with margin-positive and node-negative disease received radiation therapy alone, while patients with involved nodes and margin-negative resection typically received chemotherapy or chemoradiotherapy. There was a trend toward improvement in OS with any form of adjuvant therapy (pooled odds ratio [OR] 0.74, 95% CI 0.55-1.01, and P = 0.06), and a significant improvement in survival with the use of adjuvant therapy in margin-positive (OR 0.36 and 95% CI 0.19-0.68) or node positive (OR 0.49 and 95% CI 0.30-0.80) disease. Adjuvant radiotherapy was associated with a significant improvement in outcomes after R1, but not R0, resection. There was a larger benefit seen in patients receiving chemotherapy or chemoradiotherapy compared with radiotherapy alone.

In gallbladder cancer, a Surveillance, Epidemiology, and End Results Program (SEER) analysis[22] of 3187 patients diagnosed between 1992 and 2002 reported an improvement in survival with the use of adjuvant therapy in patients with hepatic invasion or nodal involvement. A SEER-medicare analysis[23] of 1137 patients with resected gallbladder cancer diagnosed between 1995 and 2005 reported that patients with involved lymph nodes or T2 or greater disease had improved survival with the use of chemoradiotherapy. There was a larger benefit with the use of chemoradiotherapy as compared to chemotherapy, particularly in patients with node-positive disease. A SEER analysis of 4758 patients with extrahepatic cholangiocarcinoma (EHCC) also demonstrated an improvement in survival with adjuvant radiotherapy.[24]

Until recently, there were limited prospective data demonstrating the utility of adjuvant chemoradiotherapy after radical resection for ECC or gallbladder cancer. SWOG S0809,[25] a Phase II single-arm trial of postoperative chemotherapy followed by chemoradiotherapy in patients with ECC or gallbladder cancer reported encouraging results. All patients underwent radical resection at the time of diagnosis, and were deemed to have high-risk features for recurrence as defined by pathologic stage T2-4, involved lymph nodes, or positive resection margins. A total of 105 patients were registered, and 79 were enrolled, 54 patients (68%) had ECC, and 25 patients (32%) had gallbladder cancer. Patients were stratified by resection margin, and there was a high rate (n = 54, 72%) of margin-negative resections. Treatment consisted of 4 cycles of postoperative gemcitabine and capecitabine followed by concurrent chemoradiotherapy with capecitabine. Radiotherapy dose was 45 Gy to the at-risk nodal stations and 54-59.4 Gy to the tumor bed. While most patients required dose-modifications during chemotherapy (n = 60, 76%), 85% of patients completed radiotherapy as per protocol, most of whom were treated with intensity-modulated radiotherapy (n = 56, 81%). Treatment was generally well-tolerated, with 86% of patients completing the full course of treatment as planned. OS at 2 years, which was the primary endpoint, was 65% in the overall cohort, with a median OS of 35 months. Interestingly, while the rate of local recurrence at 2 years was increased in patients with a R1 resection (16% with R1 resection vs 9% after R0 resection), there was no significant difference in 2-year OS based on extent of resection (67% in the R0 cohort vs 60% in the R1 cohort). There was a 30% rate of local failure in the 10 patients who did not receive radiotherapy, and a significant increase in the rate of local failure in patients who did not receive radiotherapy as per protocol. This trial demonstrated that adjuvant treatment was tolerable and associated with a significant improvement in OS compared with historical controls. Prospective randomized trials are under development.

ICC

The majority of patients with ICC are unable to undergo resection due to disease extent at the time of diagnosis.[26]