Adjuvant treatment in biliary tract cancer: To treat or not to treat?

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Abstract

Biliary tract cancer is a rare malignant tumor. There is limited knowledge about biology and natural history of this disease and considerable uncertainty remains regarding its optimal diagnostic and therapeutic management. The role of adjuvant therapy is object of debate and controversy. Although resection is identified as the most effective and the only potentially curative treatment, there is no consensus on the impact of adjuvant chemotherapy and/or radiotherapy on the high incidence of disease recurrence and on survival. This is mainly due to the rarity of this disease and the consequent difficulty in performing randomized trials. The only two prospectively controlled trials concluded that adjuvant chemotherapy did not improve survival. Most of the retrospective trials, which had limited sample size and included heterogeneous patients population and non-standardized therapies, suggested a marginal benefit of chemoradiotherapy in reducing locoregional recurrence and an uncertain impact on survival. Well-designed multi-institutional randomized trials are necessary to clarify the role of adjuvant therapy. Two ongoing phase III trials may provide relevant information.

Key words: Biliary tract cancer; Adjuvant therapy; Chemotherapy; Chemoradiation; Surgery

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INTRODUCTION

Biliary tract cancer (BTC) is a rare tumor accounting for approximately 4% of all malignant neoplasms of the gastrointestinal tract. Marked gender, ethnical and geographical variations exist and, in certain regions of the world, like Chile or North India, BTC is one of the most common causes of cancer mortality. The median age at presentation is the seventh decade of life with a male to female ratio of 1.5:1.

Surgical resection is the only potentially curative treatment for BTC. However, the resectability rate has been reported to range between 30% and 70%, with large variability based on tumor location (70% for ampullary cancer, 40%-50% for gallbladder, intrahepatic and distal extrahepatic cancer and 30% for hilar BTC[6-7]). The type of resection and prognosis vary with anatomical location with a 5-year overall survival (OS) rate of 20%-40% for intrahepatic adenocarcinoma, 50%-70% for ampullary cancer, 25%-50% for distal cholangiocarcinoma and for gallbladder cancer and 15%-35% for hilar BTC[8].

Due to the rarity of this disease, in which patients with curatively resected tumors are in the minority, prospective trials have been rarely performed and, sometimes, eligibility criteria allowed the enrolment of both patients with pancreatic cancer and BTC, thus hampering
the interpretation of results. Accordingly, information with a high level of evidence is lacking and wide areas of debate and controversy on optimal adjuvant therapeutic management exist.

**PROGNOSTIC FACTORS**

The 5-year OS rate with surgery alone is disappointing, ranging from 15% to 70%[10]. Complete surgical resection with histologically negative (R0) surgical margins has been reported to be the most important prognostic factor[10]. Since prognosis varies also with anatomical location, the heterogeneity of patient population of the reported studies may affect the interpretation of the data[11]. Other prognostic factors such as tumor stage, nodal status, vascular and perineural invasion, elevated baseline CA 19-9 level and histologic grade have been identified in many reports[10-13,19]. Among those, the prognostic relevance of tumor stage, nodal status, histologic grade and resection margin is almost universally accepted and should be taken into account for the stratification of the patients in prospective trials and for the interpretation of the results in non-randomized series; while the prognostic role of elevated baseline CA 19-9 level and vascular and perineural invasion is still controversial[14-48].

**THERAPEUTIC MANAGEMENT**

Most patients with BTC are not suitable for curative surgery at diagnosis, and the rate of microscopically positive resection margins (R1) has been reported to be up to 74%[14]. In addition, locoregional failure occurs in more than half of the patients, even after R0 resection[9-11,19]. Isolated locoregional disease was reported in approximately 15% of patients with gallbladder cancer, 20% with periampullary cancer and 60% with hilar cholangiocarcinoma. In contrast, systemic disease, with or without concomitant locoregional recurrence, occurred in 85% of patients with gallbladder cancer, 75% with periampullary cancer and 41% with hilar cholangiocarcinoma[10,19]. Because of poor survival after curative resection due to frequent local relapse and distant metastases[9,11,34], the role of adjuvant therapy has been widely explored[9,15,32,38,41-50].

**Chemoradiation**

Previous studies, mainly focusing on adjuvant chemoradiation therapy (CRT) with a variety of regimens, led to conflicting results and the role of this therapeutic strategy remains controversial. No large randomized trial of adjuvant CRT has ever been performed. A small phase III European Organization for Research and Treatment of Cancer trial, including 92 eligible patients with periampullary adenocarcinoma, demonstrated no statistically significant difference in survival between adjuvant CRT following resection vs observation[35]. However, since this trial included a limited number of patients and an outdated chemoradiation in terms of imaging, techniques, planning, dose and concomitant radiosensitizing chemo-

therapy, definitive conclusions on the role of modern chemoradiation are impossible to draw.

Conversely, a retrospective series of 73 patients with gallbladder cancer treated between 1985 and 2004 at Mayo Clinic[38] suggested that adjuvant CRT may obtain a statistically significant improvement in OS only for patients with lymph node involvement. Similarly, two retrospective series of fluoropyrimidine-based post-operative chemoradiation from MD Anderson Cancer Center[39] and from South Korea[40], including 96 patients affected by ampullary adenocarcinoma and 91 patients with extrahepatic bile duct cancer, respectively, suggested an improved OS only in patients with locally advanced tumor (T3/T4)[39] or with R1 resection[40]. A few other smaller retrospective series also reported a modest potential OS benefit with adjuvant CRT (Table 1)[39,40,41-50].

Apart from the controversial impact on OS, CRT may have a role in improving local control, especially in patients at higher risk of local failure, such as those with R1 margins and positive lymph nodes. In fact, 5-year local control rate raised from 40%-50% in patients with ampullary cancer treated with surgery alone to 65%-80% in those who received post-operative CRT[39,40,41-50].

Unfortunately, the retrospective nature of most of these studies, the small sample size, the lack of correction for multiple comparisons, patient selection bias; heterogeneity in terms of patients' characteristics, treatment regimens, tumor site and stage; long-lasting accrual periods, different surgical, radiotherapy and radiological techniques in different historical periods and other confounding factors do not allow to draw any firm conclusion on the role of CRT. In fact, younger and healthier patients were more likely to be offered adjuvant CRT. On the other hand, patients with high risk features were more likely to receive adjuvant therapy than those with favorable features.

**Chemotherapy**

A few studies evaluated the role of adjuvant chemotherapy in BTC. A retrospective single centre analysis on 42 patients suggested that postoperative gemcitabine-based chemotherapy may be a promising strategy to improve OS after surgical resection for hilar cholangiocarcinoma[38].

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**Table 1  Survival outcome for adjuvant chemoradiation**

| Ref. | No. of patients | Site | Therapy | OS (median) |
|------|----------------|------|---------|-------------|
| [38] | 73             | GB   | No      | 58          |
| [39] | 96             | PV   | Yes     | 35.2        |
| [41] | 49             | All  | No      | 16.4        |
| [42] | 48             | EHBD | Yes     | 44%         |
| [43] | 84             | All  | No      | 42          |
| [44] | 125            | PV   | Yes     | 67          |
| [45] | 34             | EHBD | No      | 35%         |

1Statistically significant; 5-year overall survival (OS). CRT: Chemoradiation; Obs: Observation; PV: Papilla of vater; GB: Gallbladder; EHBD: Extrahepatic bile duct; All: PV + GB + EHBD + intrahepatic bile duct; NA: Not applicable.
Consistently, the addition of fluorouracil-based chemotherapy to adjuvant CRT seemed to improve disease-free survival (3-year DFS 45% vs 27%) and OS (3-year OS 63% vs 31%) compared to CRT alone in another retrospective series of 120 patients with radically resected extrahepatic BTC.

A phase III trial addressed the role of adjuvant chemotherapy with 5-fluorouracil and mitomycin-C in a series of 508 patients with surgically treated pancreaticobiliary malignancies including 335 patients with BTC. OS was significantly increased when compared to observation arm only in the unplanned subset analysis of 61 resected patients with macroscopically positive resection margins (R2) affected by gallbladder cancer. Similarly, a more recent phase III trial exploring the role of single agent adjuvant chemotherapy with either gemcitabine or 5-fluorouracil, in 304 patients with ampullary adenocarcinoma submitted to curative resection did not demonstrate a survival benefit for any of the adjuvant therapy arms when compared to surgery alone.

GUIDELINES AND CURRENT CLINICAL PRACTICE

The National Comprehensive Cancer Network (NCCN) guidelines recommend only observation or adjuvant CRT with concomitant fluoropyrimidine for patients with R0 margins or negative lymph-nodes and adjuvant therapy with concurrent 5-fluorouracil-based CRT followed or not by additional fluoropyrimidine- or gemcitabine-based regimens in patients with R1 margins or metastatic lymph nodes. The use of chemotherapy is recommended due to the high incidence of systemic relapse and to the results observed in the therapeutic management of advanced disease. The European Clinical Practice guidelines are more vague, only suggesting CRT as a possible therapeutic option after surgery for BTC. More restrictive indications derive from a modified and implemented version of NCCN guidelines proposed by a committee of specialists of the Middle East and North Africa Region, which recommend only observation or enrolment into a clinical trial after an R0 and/or a negative regional nodes resection, because of conflicting data regarding adjuvant CRT.

Given the lack of guidelines based on high level of evidence, it is not surprising that patients submitted to curative surgery for biliary tract tumors receive heterogeneous management around the world. A survey of therapeutic strategies recommended in the clinical practice in 2001-2002, reported that adjuvant CRT was widely adopted in the majority of American centers (71%), followed by Asian/Pacific centers (55%), but only by 29% of European institutions. This scenario may have changed in more recent years with a trend towards possibly increasing use of adjuvant treatment due to the numerous positive experiences reported in the literature in the last decade. However, eighty-eight percent of the interviewed physicians recognized the unmet need for achieving higher levels of evidence from large prospective trials to support the routine use of adjuvant treatment.

FUTURE DIRECTIONS

Altogether, the available data do not allow to answer the question whether patients submitted to curative resection for BTC should receive an adjuvant therapy and which treatment strategy may provide the largest benefit.

In fact, neither adjuvant CRT nor adjuvant chemotherapy with either single agent or a 5-fluorouracil-mitomycin doublet improved OS when compared to observation alone in phase III trials, while only a modest benefit in loco-regional control rather than on OS was suggested with CRT by retrospective series that, in any case, suffer from previously mentioned methodological limitations.

The causes of this disappointing scenario and of the lack of a convincing answer are manifold. First, when compared to trials on advanced disease, trials on adjuvant therapy are more demanding, also due to the involvement of different specialists (surgeon, radiologist, oncologist and radiotherapist); more resource- and time-consuming, due to the longer patient’s life expectancy and to the inferior number of patients; and require a more selective choice of centers to be involved. Second, evidence-based information on the most active and effective chemotherapy regimen against unresectable or metastatic disease is limited as well. Accordingly, the selection of promising regimens that may have a relevant impact on disease natural history is challenging. Only recently, cisplatin and gemcitabine regimen became the new standard of treatment in advanced BTC providing a rational for investigating the role of this combination in the adjuvant setting. Additionally, two ongoing phase III trials are currently exploring the role of capcitabine (NCT00363584) and of GEMOX regimen (NCT01313377) in the adjuvant setting and may provide further information in the next future. Third, the rarity of disease limits the interest of pharmaceutical companies while investigator initiated trials are hindered by the restricted availability of agents already registered and authorized for the treatment of the disease. Fourth, the choice of the most promising therapeutic strategy is crucial in this disease that has a very high rate of both local and systemic recurrence. Systemic chemotherapy and CRT, rather than being taken as alternative therapies, should be combined taken into account in the design of post-operative management. However, the role of sequential therapy with CRT followed by systemic chemotherapy or the inverse sequence was rarely addressed in prospective trials. Fifth, the knowledge on tumor biology is limited and, at the moment, does not allow to identify new agents that may contribute to improve the outcome of the disease. Last but not least, the interpretation of trials result is often challenging due to the heterogeneity of enrolled patients population. Stratification based on tumor location, extent of resection, lymph node...
status and resection margin status will be crucial to the success of future studies.

CONCLUSION

A multi-institutional worldwide effort to conduct well designed phase III trial and to expand biological knowledge of the disease is necessary to clarify the role of adjuvant therapy in BTC.

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