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Review

The Role of Chemotherapy and Radiation in the Management of Biliary Cancer: a Review of the Literature

M. Hejna,[1] M. Pruckmayer[2] and M. Raderer[1]

[1]Department of Internal Medicine I, Division of Oncology; and [2]Department of Nuclear Medicine, University of Vienna, A-1090 Vienna, Austria

Carcinoma of the biliary tract is a rare tumour. To date, there is no therapeutic measure with curative potential apart from surgical intervention. Thus, patients with advanced, i.e. unresectable or metastatic disease, face a dismal prognosis. They present a difficult problem to clinicians as to whether to choose a strictly supportive approach or to expose patients to the side-effects of a potentially ineffective treatment. The objective of this article is to review briefly the clinical trials available in the current literature utilising non-surgical oncological treatment (radiotherapy and chemotherapy) either in patients with advanced, i.e. locally inoperable or metastatic cancer of the biliary tract or as an adjunct to surgery. From 65 studies identified, there seems to be no standard therapy for advanced biliary cancer. Despite anecdotal reports of symptomatic palliation and survival advantages, most studies involved only a small number of patients and were performed in a phase II approach. In addition, the benefit of adjuvant treatment remains largely unproven. No clear trend in favour of radiation therapy could be seen when the studies included a control group. In addition, the only randomised chemotherapeutic series seemed to suggest a benefit of treatment in advanced disease, but due to the small number of patients included, definitive evidence from large, randomised series concerning the benefit of non-surgical oncological intervention as compared with supportive care is still lacking. Patients with advanced biliary tract cancer should be offered the opportunity to participate in clinical trials.

Key words: biliary tract cancer, chemotherapy, radiation
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INTRODUCTION

CARCINOMA OF the biliary system is a rare disease [1] and remains a major challenge to surgical, medical and radiation oncologists. For cholangiocellular carcinoma, there is a slight male preponderance (60%), whereas gall-bladder cancer is somewhat more common in women (70%). Both tumour types occur preferentially in the older population, with a peak incidence in the fifth to seventh decade [1]. Numerous aetiological factors and pre-existing conditions have been linked with cancer of the biliary system. Among them are chronic inflammatory stimuli such as sclerosing cholangitis and cholecystitis, or the presence of chronic hepatobiliary parasitic infestations [2]. In addition, extrabiliary chronic inflammation, such as ulcerative colitis and Crohn's disease [1], or inflammation caused by the radiocontrast agent Thorotrast have also been documented to cause hepatic and bile duct malignancies [3, 4].

As first described by Maximilian deStoll in 1777 [5], the prognosis for patients with this disease still remains dismal. Because of the lack of characteristic early symptoms, a definitive diagnosis is often established at an advanced stage. Consequently, the late presentation of advanced biliary carcinoma usually results in a poor overall prognosis. The course of the disease is usually rapid with a median survival time of approximately 6 months [1]. Most patients die from gastrointestinal haemorrhage, progressive cachexia, or hepatic failure. Long-term control of the disease can only be obtained with potentially curative surgery, i.e. removal of all apparent tumour *in toto*. In the absence of curative forms of treatment other than surgery, many specialised centres have tended to perform aggressive surgical approaches, including caudate

Correspondence to M. Hejna.
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and hepatic lobe resection, portal vein resection, and ultimately liver transplantation [6–21].

However, due to the late presentation of the malignancy, patients who can undergo successful operation remain in the minority. As a result, a large proportion of patients are beyond the scope of curative treatment upon diagnosis, and only palliative management can be performed. In addition, also potentially curative resection is associated with a high risk of relapse [8, 11, 15].

The role of non-surgical oncological therapy remains a matter of debate, and has been thought to be largely ineffective, if not even detrimental in patients with advanced disease [22]. To date, chemotherapy for gall-bladder and bile duct carcinoma has been limited by the absence of agents and combinations with substantial antitumoral activity. Similarly, the benefit of radiotherapeutic approaches remains controversial, despite their widespread use in the adjuvant and palliative setting.

Owing to the relative rarity of the disease, generally series involving only small numbers of patients have been published, including a high percentage of case reports featuring only single individuals. This fact has prevented the possibility of meta-analyses, and the achievements of conservative management of this disease with radiation and/or chemotherapy are scattered over various reports in the literature. The objective of this article is therefore to review the current knowledge of radiation and chemotherapy for treatment of biliary cancer, extracted from the literature published between 1966 and 1997.

LITERATURE SEARCH

Using a computerised (MEDLINE) and manual search, we identified a total of 65 trials of either chemotherapy or radiation performed in patients with biliary cancer. Only papers with an English abstract were included, and no effort was made to search for unpublished trials, thus a slight amount of publication bias cannot be excluded. Information abstracted included histological verification of the diagnosis, treatment regimen (adjuvant or palliative) and dose of cytotoxic agents or radiation, pretreatment criteria including prior surgery and the presence or absence of measurable disease, number of patients, overall survival and response rates according to WHO criteria. Tumour responses were analysed as reported by the authors, but only patients achieving at least a partial remission qualified as responders, while minor response, mixed response, stable disease and progressive disease were classified as no response in our evaluation.

RADIATION THERAPY

Radiation therapy has been applied both for primary treatment of biliary tract cancer as well as adjuvant therapy after surgical resection. The techniques available to the radiation oncologist for treatment of biliary tract cancer include external beam irradiation with high energy machines, with field size reduction for boost, intra-operative irradiation using orthovoltage equipment or electrons, and intracavitary irradiation by means of ^{192}Ir-ribbon [23–26].

Adjuvant radiotherapy

The use of radiation therapy as an adjuvant is based on the likelihood of having microscopic or gross residual disease after surgical resection. Hypothetically, the small tumour load should offer the potential for effective control with radiation therapy, resulting in either improved survival or delayed onset of relapse and tumour related symptoms. Despite the rationale for adjuvant radiation therapy, the relative rarity of the tumour and the low percentage of patients who have a potentially curative resection have limited the amount of data available on the use of radiation therapy in this setting.

Vaittinen reported a median survival of 63 months for 5 patients receiving postoperative radiation therapy as compared with 29 months for 6 patients undergoing surgery alone [27]. In contrast to these data, no difference in survival could be demonstrated in the French Surgical Association survey comparing patients who underwent only surgical resection with individuals receiving additional postoperative radiation therapy. However, in patients in whom only palliative surgery could be performed, there was a trend for improved survival with radiation therapy, resulting in a median survival of 13 months versus 8 months ($P < 0.10$) in untreated subjects [28].

In a small series published by Bosset and colleagues, 5 of 7 gall-bladder cancer patients were free of disease at 5, 9, 11, 31 and 58 months after complete resection and postoperative radiation therapy with up to 54 Gy in 30 fractions [29]. Fields and Emani reported on 3 patients with gall-bladder carcinoma treated with radiation therapy for microscopic residual disease [30], two patients survived 22+ and 27 months, indicating a potential benefit of additional radiation, despite the rather limited number of subjects included.

The most recent retrospective analysis on adjuvant radiation was performed at Hospital Tenon in Paris by Houry and associates [31], including 20 patients with various stages of gall-bladder cancer. While this is one of the largest groups of patients in the literature administered radiotherapy, again patients with both curative and palliative resection were included in the study. Only limited information can be extracted concerning the use of adjuvant therapy, since only 4 patients had undergone curative resection, while 14 patients had palliative surgery and 2 laparotomy and biopsy only. The mean dose of radiation was 42 Gy in weekly doses of 10 Gy started 3 weeks after surgery, and the median survival for the whole group was 8 months. Of 4 patients with total resection, 1 was still alive at 84 months, while 3 had died at 7, 8, and 33 months, respectively. The median survival was 7 months in the cohort of patients with palliative surgery, and 5 and 7 months in the 2 patients who had undergone laparoscopy. The investigators compared their results with historical controls reported in the literature, concluding that postoperative radiotherapy may lead to increased survival after palliative surgery. With a median survival of approximately 7 months, however, these results appear to be only marginally different from survival obtained with palliative surgery alone and must be viewed with caution insofar as the series was small and treatment was not randomly assigned.

Summary. In our search, we identified five trials of adjuvant radiotherapy. These studies were performed as small trials and consequently did not include an untreated control group. In addition, many series have reported the results obtained in a mixed population, i.e. patients undergoing adjuvant as well as palliative radiation. Thus, the issue of benefit of adjuvant radiation has not yet been solved, since no clearly emerging trend could be seen with the results published so far. A prospective controlled study of adjuvant radiotherapy after resection is required in order to determine the exact clinical benefit of adjuvant radiotherapy.

Palliative radiotherapy

Despite the more widespread use of radiation as a palliative measure, most reports have included only a limited number of patients, using a straightforward phase II approach. Hence, no conclusive data about the potential benefit on survival and quality of life as compared with supportive care alone have been generated so far. Furthermore, the fact that the trials had different endpoints (objective response to treatment, survival or palliative effects) does not allow for a direct comparison of the results.

Flickinger and colleagues reported on 8 patients with gall-bladder carcinoma, considered to have unresectable recurrent disease, who were irradiated at a median dose of 47.5 Gy using an external beam with or without additional intraluminal brachytherapy [32]. The overall results were disappointing, with the median survival being only 3 months (range 2–8 months). Buskirk and associates treated 4 patients suffering from documented residual disease after gall-bladder carcinoma [33] at a tumour dose of 45 Gy. 3 patients were also given a ^{192}Ir intraluminal brachytherapy boost of 20–25 Gy, calculated at 0.5–1 cm radius. All 4 patients died of disease between 5 and 10 months after initial diagnosis. 3 of 4 patients developed diffuse peritoneal carcinomatosis, but post-mortem examination of 1 patient suggested a decreased bulk of residual disease in the irradiated volume.

In another series, 6 of 22 patients with gross residual disease after resection of biliary tract cancer were treated with external beam radiotherapy [34]. The total dose administered ranged between 12.5 and 59.4 Gy, and 4 patients received chemotherapy as well. There was no difference between treated and untreated patients, all 22 patients died within 11 months of initial diagnosis.

Series that address the subjective palliative benefit of radiotherapy as a primary endpoint are few. The results of treatment in terms of palliative effects were reported by Kopelson and colleagues [35], who analysed 5 patients with advanced gall-bladder carcinoma treated with primary radiotherapy. 4 patients achieved palliation in terms of pain, pruritus, or mass effect with a radiation dose ranging from 38 to 50 Gy. In contrast to these results, the palliative impact of radiation was much less pronounced in another study, with only 1 of 5 patients suffering from advanced biliary tract cancer achieving symptomatic palliation [36]. Tredwell and Hardin [37] published their results obtained in 41 patients with gall-bladder cancer receiving additional radiation treatment following palliative surgery. According to these data, patients given radiotherapy had a longer survival and fared significantly better in terms of palliation compared with patients not irradiated after palliative surgery, especially when tumour spread beyond the gall-bladder was present at the time of operation.

The recognition of the high incidence of local failure in biliary tract cancer after surgery has encouraged not only the exploration of external beam radiation therapy, but also of intra-operative radiation. The rationale of this approach is based on the notion that administration during surgery allows a controlled targeting of the tumour bed with the potential to exclude normal tissue from the radiation field. Todoroki and associates [38] have reported on a group of 11 patients treated with intra-operative radiation therapy for unresectable carcinoma of the biliary tract. 6 of these patients had primary gall-bladder cancer involving the extrahepatic biliary system with extension into the hepatic hilium or duodenum. 5 patients underwent gastrectomy (2 because of direct tumour involvement), and all had external biliary drainage. 5 patients did not receive intra-operative radiation therapy due to the presence of haematogenous metastases to the liver or peritoneal dissemination. Irradiation was performed at a single dose of 30 Gy before resection of the gall-bladder in order to minimise the theoretical risk of dissemination. Only 1 patient had no evidence of disease at 5 months after intra-operative radiation therapy, and 1 patient died of intercurrent disease 5 months after intra-operative radiation therapy. The remaining 4 patients died of disease with a median survival time of 13 months. All of these patients developed both local and distant recurrences.

In a small series performed at the Harvard Medical School applying an intra-operative dose of 19.2–24.5 Gy, all 4 patients with gall-bladder carcinoma included died within 14 months [39]. Iwasaki and associates [23] reported the results of a trial utilising intra-operative radiotherapy as an adjunct to surgery in 20 patients with bile duct cancer. 17 patients had proximal bile duct tumours and 3 had tumours in the mid or lower common bile duct. Of the 17 patients with proximal cancers, none underwent curative resection, but 11 had palliative resection, while 6 were treated by placement of a percutaneous transhepatic drainage only. Of the 3 patients with more distal tumours, 1 underwent curative resection and 2 non-curative surgery. Survival at 2 years for non-curative resection plus intra-operative radiotherapy was 17.1%, whereas it was 9% in 20 patients with non-curative resection, but without radiotherapy serving as a control cohort. Only 1 patient treated with intra-operative radiotherapy after drainage survived more than 2 years and he subsequently died at 34 months. In the earlier part of the study, a relatively high dose of radiation was used (mean single dose 27.5 Gy; mean field diameter 7.4 cm; mean beam energy 15 MeV), which resulted in hepatic arterial complications (stenosis and aneurysm formation) in 4 patients. Thus, the dose was consecutively reduced to a single application of 20 Gy using a smaller field (3.7 cm) and a lower beam energy (7.3 MeV), which resulted in an impressive reduction of side-effects. In an extension of their work, the authors have started a protocol including additional fractionated external irradiation (30–40 Gy over 4–5 weeks), but no definitive results are available yet.

Apart from studies testing the use of external beam radiation, brachytherapeutic measures have also been investigated, albeit in a more limited fashion. Karani and colleagues reported a median survival of 17 months with the use of intraluminal brachytherapy alone [40], while Johnson and associates found a median survival of 9 months with intraluminal brachytherapy alone as compared with 16 months with the addition of external beam radiation [41]. Meyers and Jones performed a study inserting ^{192}Ir-wires via transhepatic stents in 27 patients with bile duct cancer (23 patients with tumour involving the common hepatic duct or right or left hepatic duct, and 4 patients with distal lesions of the common bile duct) [42]. 3 patients underwent resection before the insertion of the transhepatic stent and 6 patients were not operated because pre-operative investigations disclosed an advanced tumour stage. All patients received between 30 and 50 Gy by means of internal irradiation and 22 patients also had supplementary external + beam irradiation to the liver (30–45 Gy). A mean survival of 11.5 months (range 1–58 months) could be achieved in this cohort of

patients. Patients who had internal irradiation only lived a median of 3.6 months as compared with 14.3 months in patients who received both internal and external irradiation. The 3 patients who had their tumour resected lived longer than the group as a whole (8, 15 and 53 months). However, the radiation-induced morbidity in this series was profound, with 21 of the 27 patients (80%) having episodes of severe cholangitis following irradiation, and 4 had severe haemobilia.

A different approach was chosen by Levitt and colleagues [43], who placed ^{192}Ir-wires through an endoscopically inserted nasobiliary catheter, resulting in encouraging results for the treatment of malignant bile duct obstruction. Unfortunately, the 24 patients again constituted a heterogeneous group, with 7 having cholangiocarcinoma, while the rest had pancreatic, ampullary or gall-bladder cancer. The median dose administered was 60 Gy (range 30–70). The median survival was 10 months for patients with cholangiocarcinoma; cholangitis occurred in 30%. In contrast, a rate of cholangitis of only 19% has been published after the endoscopic insertion of a stent without intraluminal irradiation [43]. Stent blockage occurred in 60%, with a median *in situ* function of the internal endoprosthesis of 4.4 months. Judging from these data, therapy with ^{192}iridium by either endoscopic or transhepatic route seems to be associated with a higher incidence of cholangitis than with an endoprosthesis alone. Therefore, a controlled series seems warranted to evaluate further the impact of this treatment on survival and quality of life as compared with placement of a stent in order to (temporarily) palliate bile duct obstruction.

Summary. Both external beam radiation and brachytherapy have been given to patients with advanced disease, but no statistically sound systematic investigations concerning the influence on survival and quality of life as compared with an untreated control group have been performed. While the results generated so far suggest a potential benefit in individual patients, data from controlled randomised trials are clearly needed before recommendations for routine clinical use can be made.

CHEMOTHERAPY

Systemic single agent therapy (Table 1)

The most extensively studied single agents for systemic application in biliary tract cancer are mitomycin C (MMC) and 5-fluorouracil (5-FU). After early reports of single agent MMC in biliary cancer with the encouraging response rate of 47% in 15 patients [46], these results could not be confirmed in later studies. The initial enthusiasm receded significantly, when only 3 of 30 patients achieved an objective response [58] in an EORTC trial of intravenous MMC for advanced gall-bladder and biliary cancer.

In a randomised phase II study of biliary malignancies, the Eastern Cooperative Oncology Group compared oral 5-FU monotherapy with oral 5-FU plus either intravenous streptozocin or intravenous lomustine (CCNU) [51]. 53 patients with gall-bladder cancer were included. The overall response was less than 10%, with no evidence that combined therapy improved response or survival as compared with 5-FU alone. UFT, a combination of the 5-FU prodrug tegafur and uracil at a 1:4 molar ratio, was given orally to 8 patients with biliary tract cancer at a daily dose of 300–600 mg in a phase II study performed in Japan. 2 of these 8 patients achieved an objective response (25%) [77].

In addition to MMC and 5-FU, monochemotherapy using cisplatin has also been tested in biliary tract cancer. A small phase II study in advanced cholangiocarcinoma found no activity in 9 patients [54]. In another trial of cisplatin administered at 80 mg/m^2 every 4 weeks, only 1 of 13 previously untreated patients with unresectable biliary tract carcinoma showed a partial response lasting for 3 months [67].

In addition to well-known and widely applied substances, newer agents have also undergone testing for treatment of biliary cancer. 15 patients with unresectable and/or metastatic carcinoma of the gall-bladder (4 patients) and bile ducts (11 patients) received intravenous paclitaxel 170 mg/m^2 over 3 h every 21 days. In total, 43 cycles of therapy were delivered during the trial. No complete or partial responses were noted [69].

1 patient with inoperable cholangiocarcinoma given three cycles of gemcitabine (1000 m/m^2 weekly$\times$3 with 1 week of rest) achieved a reduction in tumour size of almost 50%, with disappearance of virtually all infiltration of the portal vessels as documented on a computed tomography (CT) scan. Complete R0 resection of the tumour was performed, and ultrasound examination showed normal postoperative conditions without any new lesions after two adjuvant cycles [70]. In a phase II trial involving 11 patients with biliary tract cancer (3 patients with gall-bladder cancer, 4 patients with intrahepatic cholangiocarcinoma, and 4 patients with biliary duct cancer), monochemotherapy consisting of gemcitabine was given at 1000 mg/m^2 over 30 min weekly$\times$7 followed by a week of rest, and then weekly$\times$3 every 4 weeks. All patients were evaluable and received at least eight doses of gemcitabine. Despite the minimal toxicity, no objective responses could be demonstrated [73].

Summary. Taken together, the results of single agent therapy have been disappointing, with most compounds being rather ineffective in terms of inducing an objective response to treatment. While no data concerning the influence on survival or quality of life as compared with untreated patients have been published, single agent therapy as studied so far cannot be recommended for routine clinical use.

Systemic combination therapy

Because of the rather sobering results obtained with monochemotherapy, various combination regimens have been investigated in order to enhance further responses and survival. The FAM protocol, consisting of intravenous 5-FU 600 mg/m^2 on days 1 and 8, doxorubicin 30 mg/m^2 on day 1, and MMC 10 mg/m^2 on day 1, was administered to 17 consecutive patients with metastatic cholangiocarcinoma. Cycles were repeated every 4 weeks. 14 of these patients had objectively measurable disease, and a response rate of 29% (4 partial remissions/14 patients) with a median duration of 8.5 months was achieved. The median survival in this series was 6.5 months [52]. The FAB combination (intravenous ftorafur 4 g/m^2 days 1 and 22 and 2 g/m^2 days 4 and 26; intravenous doxorubicin 60 mg/m^2 day 1 and 45 mg/m^2 day 22; and intravenous carmustine (BCNU) 150 mg/m^2 day 1) was evaluated by Hall and coworkers [44]. In a mixed population of gall-bladder and bile duct cancers, a response rate of 43% was found (3 of 7), including 2 complete responses. Responders to treatment had a survival of 7, 11 and 16 months, respectively.

The clinical potential of the ECF combination was investigated in 25 patients with advanced biliary tumours. Treatment consisted of epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 on

Table 1. *Systemic chemotherapy for cancer of the biliary system*

Drug	Response (%)	Reference
Ftorafur + doxorubicin + BCNU	3/7 (43)	Hall and associates, 1974 [44]
5-FU	3/23 (13)	Davis and associates, 1974 [45]
MMC	7/15 (47)	Crooke and associates, 1976 [46]
Doxorubicin + bleomycin	1/5 (20)	Tavey and Hester, 1979 [47]
MMC	0/10 (0)	Von Eiben and associates, 1980 [48]
5-FU	4/17 (24)	Haskell, 1980 [49]
BCNU	2/4 (50)	Haskell, 1980 [49]
Doxorubicin	1/1 (100)	Adolphson and Carpenter, 1982 [50]
5-FU*	3/30 (10)	Falkson and associates, 1984 [51]
Streptozocin*	0/14 (0)	Falkson and associates, 1984 [51]
Methyl-CCNU*	1/17 (6)	Falkson and associates, 1984 [51]
5-FU + streptozocin	2/26 (8)	Falkson and associates, 1984 [51]
5-FU + methyl-CCNU	3/31 (10)	Falkson and associates, 1984 [51]
5-FU + doxorubicin + MMC	4/14 (29)	Harvey and associates, 1984 [52]
5-FU + doxorubicin + BCNU	4/10 (40)	Moertel and associates, 1986 [53]
Cisplatin	0/9 (0)	Ravry and associates, 1986 [54]
5-FU + doxorubicin + MMC	1/1 (100)	Uchiyama and associates, 1988 [55]
Etoposide + 5-FU	2/2 (100)	Shibata and associates, 1990 [56]
Ftorafur + doxorubicin	1/4 (20)	Koda and associates, 1990 [57]
Ftorafur + doxorubicin + cisplatin	1/2 (50)	Koda and associates, 1990 [57]
MMC	3/30 (10)	Taal and associates, 1991 [58]
Doxorubicin + 5-FU	9/52 (17)	Stillwagon and associates, 1991 [59]
Epirubicin + 5-FU + MMC	0/1 (0)	Novell and associates, 1991 [60]
Cyclophosphamide + IL-2 + LAK	1/1 (100)	Yamaguchi and associates, 1991 [61]
5-FU + LV + MMC + carboquone	1/1 (100)	Tsushima and associates, 1991 [62]
MMC + 5-FU + Tegafur	0/16 (0)	Kato and associates, 1993 [63]
5-FU + LV	1/7 (14)	Kato and associates, 1993 [63]
5-FU + cisplatin + epirubicin	0/4 (0)	Nio and associates, 1993 [64]
5-FU + doxorubicin + MMC	0/18 (0)	Takada and associates, 1994 [65]
5-FU	0/18 (0)	Takada and associates, 1994 [65]
Epirubicin + MTX + 5-FU + LV	0/17 (0)	Kajanti and Pyrhonen, 1994 [66]
Cisplatin	1/13 (8)	Okada and associates, 1994 [67]
Epirubicin + cisplatin + 5-FU	8/20 (40)	Ellis and associates, 1995 [68]
Paclitaxel	0/15 (0)	Jones and associates, 1996 [69]
Gemcitabine	1/1 (100)	Hehenwarter and associates, 1996 [70]
Docetaxel + irinotecan	0/1 (0)	Couteau and associates, 1996 [71]
5-FU + IFN alpha-2b	11/32 (34)	Patt and associates, 1996 [72]
Gemcitabine	0/11 (0)	Mezger and associates, 1997 [73]
5-FU + cisplatin + epirubicin	5/15 (33)	Di Lauro and associates, 1997 [74]
5-FU + cisplatin + epirubicin	7/24 (29)	Okada and associates, 1997 [75]
Paclitaxel + carboplatin	0/1 (0)	Russell and associates, 1997 [76]

*Patients failing 5-FU were randomised between streptozocin and methyl-CCNU.
5-FU, 5-fluorouracil; MMC, mitomycin C; LV, leucovorin; IFN, interferon; BCNU, carmustine; methyl-CCNU, methyl-lomustine; IL-2, interleukin-2; LAK, lymphokine activated killer.

day 1, each given every 21 days and 5-FU 200 mg/m^2/day as a continuous 24 h infusion during the whole treatment course. 8 of the 20 evaluable patients responded (40%), and a median duration of response of 10 months (range 5–22 months) was reported [68]. Tsushima and colleagues treated 1 patient with advanced cholangiocarcinoma using intra-arterial MMC (20 mg/m^2) and carboquone (4 mg/m^2), protracted continuous intravenous infusion of 5-FU (500 mg/m^2) and intravenous administration of low-dose leucovorin (30 mg/m^2). A more than 50% reduction in tumour size for a duration of more than 4 weeks could be documented [62]. In a trial initiated by Kato and coworkers, patients were divided into two groups after non-curative resection of adenocarcinoma of the gall-bladder: group A (16 patients) was given MF (MMC 6 mg/m^2, 5-FU 250 mg/m^2) by intravenous injection on the second and ninth postoperative day together with oral tegafur (600 mg/day) for a duration of 4 weeks. Group B (7 patients) was treated on a weekly basis for a duration of 6 weeks using a 48 h infusion of 5-FU (1 g/m^2/24 h) following intravenous leucovorin (30 mg/m^2). No objective responses could be documented in group A, and 1 partial remission and 6 cases of stable disease were seen in group B. The median survival was 230 days in group A and 471 days in group B ($P = 0.0008$) [63].

Combination chemotherapy including epirubicin, methotrexate (MTX) and 5-FU was applied by Kajanti and coworkers in patients with advanced cancer of the extrahepatic biliary system not amenable to surgical resection. 22 patients entered the study, and 17 were evaluable for response and toxicity (11 with extrahepatic bile duct cancer and 6 with gall-bladder cancer). The treatment schedule consisted of epirubicin 20 mg/m^2 given by intravenous bolus, MTX 150 mg/m^2 infused over 30 min and 5-FU 600 mg/m^2 as a 30 min infusion 1 h after MTX. Leucovorin rescue (15 mg by mouth every 6 h for eight doses) was started 24 h after MTX application. Treatment was administered once a

week for 3 successive weeks, followed by an interval of 2–3 weeks before the next cycle. No objective tumour regression was observed with this regimen [66].

In a phase II study of 5-FU, doxorubicin and cisplatin in measurable advanced upper gastrointestinal adenocarcinomas, Moertel and colleagues observed an objective response in 2 of 4 patients with gall-bladder carcinoma, and in 1 of 4 patients with cholangiocarcinoma [53].

35 patients (25 with cholangiocarcinoma and 10 with gall-bladder carcinoma) underwent chemotherapy with biochemically modulated 5-FU. The fluoropyrimidine was administered by continuous infusion at a dose of 750 mg/m^2/day over 5 days through a centrally placed venous catheter. According to initial findings in colorectal cancer [78], 5 MU/m^2 of r-interferon alpha-2b were injected subcutaneously on days 1, 3 and 5 to enhance further the therapeutic activity of the fluoropyrimidine. Treatment cycles were repeated every 14 days, and 11 of 32 (34%) assessable patients had a partial response. The median time to disease progression was 9.5 months, and the median survival time was 12 months [72].

Docetaxel 50 mg/m^2 by 1 h infusion followed by irinotecan infused 150 mg/m^2 over 90 min, given every 21 days, had no therapeutic activity in 1 patient with cholangiocarcinoma [71]. In another trial [74] 15 chemotherapy-naive patients with advanced biliary tract carcinoma (6 cases of gall-bladder, 5 of cholangiocarcinoma, and 4 of bile duct cancer) received intravenous cisplatin 25 mg/m^2, intravenous epirubicin 20 mg/m^2 and intravenous 5-FU 500 mg/m^2, all drugs given on days 1–3. Cycles were repeated every 4 weeks to a maximum of six courses. All patients were evaluable, and 1 complete remission and 4 partial remissions were observed, resulting in an overall response rate of 33%. The median time to progression was 4 months (range 2–11 months) and the median overall survival was 9.5 months. Okada and associates [75] treated 24 chemotherapy-naive patients with advanced gall-bladder cancer with cisplatin, epirubicin and 5-FU. Treatment consisted of cisplatin 80 mg/m^2 and epirubicin 50 mg/m^2, both intravenous on day 1, and continuous intravenous infusion 5-FU 500 mg/m^2/day on days 1–5. Among these 7 patients, 1 partial response was obtained (29%), and the median survival time was 6.4 months.

The only randomised trial published to date was performed by Glimelius and colleagues [79], who investigated the impact of chemotherapy on survival and quality of life in patients with both advanced pancreatic and biliary cancer. In this study, a total of 90 patients were randomised between chemotherapy with 5-FU, leucovorin ± etoposide or best supportive care only. Among these patients, 37 subjects suffering from biliary cancer were enrolled in the trial. Since measurable disease was not a prerequisite for study entry, no definitive conclusions in terms of objective response are possible. However, patients in the treatment arm had a significantly improved survival (median 6.5 months versus 2.5 months with best supportive care) and an improved quality of life as judged by standard questionnaires [79]. This trial is the first to investigate the palliative value of chemotherapy in advanced biliary cancer in a randomised manner. Despite the small number of patients and the poor overall survival, the authors could demonstrate the ability of chemotherapy to add to both quantity and quality of life at an acceptable level of toxicity [79].

Summary. Various combination regimens have been tested for treatment of advanced biliary cancer in a phase II approach, but response rates in excess of 30% have been difficult to achieve, irrespective of the different combinations applied. However, even in the absence of a 'standard therapy', the only randomised series published so far has disclosed the potential of (combination) chemotherapy to beneficially influence survival and quality of life in such patients.

Hepatic artery infusion chemotherapy (Table 2)

As tumours of the biliary tree progress by local extension rather than distant metastases, a regional form of chemotherapy seems a logical approach. Arterial intrahepatic infusion of chemotherapeutic agents has given promising results in the treatment of hepatic metastases from colorectal cancer [94]. The rationale for the use of the hepatic arterial route for treatment of biliary tract cancer is based upon the fact that some drugs have a high hepatic extraction upon first pass, and thus reach the bile canaliculi at high concentrations [95]. An additional advantage is the anatomical situation: while the blood supply of the lower bile duct branches predominantly from the gastroduodenal and superior mesenteric arteries, the vessels supplying the upper biliary tree and gall-bladder are derived from the hepatic artery [96]. The

Table 2. Hepatic artery infusion chemotherapy for cancer of the biliary system

Drug	Response (%)	Reference
5-FU	1/3 (33)	Massey and associates, 1971 [80]
FUdR	9/15 (60)	Warren and associates, 1972 [81]
FUdR	5/11 (45)	Watkins and associates, 1978 [82]
Doxorubicin	1/2 (50)	Garnick and associates, 1979 [83]
FUdR	2/10 (20)	Reed and associates, 1981 [84]
MMC + 5-FU	7/11 (64)	Smith and associates, 1984 [85]
MMC	3/5 (60)	Kairaluoma and associates, 1988 [86]
Cisplatin + 5-FU + MMC	1/1 (100)	Wada and associates, 1989 [87]
FUdR	7/9 (78)	Seeger and associates, 1989 [88]
Epirubicin (lipiodol suspension)	0/3 (0)	Novell and associates, 1991 [89]
MMC + 5-FU	12/29 (41)	Misra and associates, 1992 [90]
MMC	13/27 (48)	Mekela and Kairaluoma, 1993 [91]
Thiotepa	1/1 (100)	Fenn and associates, 1993 [92]
Cisplatin + 5-FU	5/8 (62)	Fukudo and associates, 1996 [93]

5-FU, 5-fluorouracil; MMC, mitomycin C; FUdR, floxuridin.

development of implantable reservoirs (Port-a-Cath) and pumps has simplified administration of chemotherapy. Because of the high hepatic extraction rate of floxuridine (FUdR) and its documented activity, this agent is the most extensively evaluated compound both in colorectal [94] and in advanced biliary tract cancer (see also Table 2).

However, only a few studies have been performed in advanced biliary cancer in spite of the compelling rationale. 15 patients with carcinoma of the biliary tract were treated by intra-arterial chemotherapy with FUdR. The overall response rate to intra-arterial chemotherapy was a promising 60% and the median survival was 12 months [81]. In a report on 5 patients treated with intra-arterial MMC, 3 objective responses were observed [86]. The median survival in these patients was 9, 14 and 16 months, respectively. The follow-up report by Mekela and Kairaluoma showed 13 responses in 27 patients with gall-bladder cancer, with a rate of major complications in 19% of patients [91]. The median survival in patients undergoing treatment was 14 months (range 8–22 months). Smith and colleagues treated 11 patients with cholangiocellular (4 patients) or gall-bladder (7 patients) carcinoma with hepatic arterial infusions of 5-FU and MMC [85]. One complete remission (gall-bladder) and 6 partial responses (4 gall-bladder cancers, 2 cholangiocarcinomas) were reported. However, the median duration of response was a disappointing 3 months. The median survival for all patients was greater than 12.5 months, demonstrating the indolent nature of biliary carcinoma in some patients. Reed and associates treated 9 patients with intra-arterial FUdR, and reported ''clinically significant regression'' in 7 patients, although CT was not used for disease measurement in this series [84]. Seeger and colleagues reported on 2 gall-bladder cancer patients treated with hepatic arterial FUdR, both of whom responded [88]. A brief response lasting 3 months in 1 of 2 patients with advanced biliary tract cancer following therapy with intra-arterial doxorubicin was reported by Garnick and coworkers [83].

8 unresectable cases of gall-bladder cancer underwent hepatic artery infusion with a combination of cisplatin and 5-FU. 5 (62.5%) patients displayed a partial response, and the median survival time was 6 months (range 3–10 months) [93].

Summary. Despite the elegant underlying biochemical rationale, only information on intrahepatic infusion of cytotoxic agents exists at the moment. While some studies have given promising results with response rates up to 78% (albeit in relatively small cohorts of patients), it is premature to judge whether there is an advantage over systemic chemotherapy.

Combined radio-chemotherapy

The rationale for combining radiation with certain cytotoxic compounds is supported by preclinical results, suggesting a radiosensitising effect of the chemotherapeutics, as well as a number of clinical trials in various tumour entities, such as rectal, head and neck or pancreatic cancer. In recent years, chemoradiation has been given to selected patients with cholangiocarcinoma at several institutions (Table 3), and the Eastern Cooperative Oncology Group [101] recently conducted a phase I study of continuous infusion 5-FU during a 6–7 week course of radiotherapy in patients with localised pancreatobiliary carcinoma.

In total, five studies involving 146 patients have been published, using various radiotherapeutic approaches along with fluoropyrimidines or MMC [97–101]. The survival time in these studies ranged between 8 and 30 months. In general, these regimens were tolerated well, but the number of patients have been small, some resected and some unresected patients have been treated, and no control patients have been included. Thus, a prospective, randomised controlled trial of chemoradiation should be undertaken in patients with biliary tract cancer.

CONCLUSION

Despite widespread use of both chemotherapy and radiation, there is no standard therapy for advanced biliary cancer, and only limited information about the use of combined modality treatment exists in the current literature. Clearly, large controlled series are warranted to judge objectively the impact this form of therapy might have on clinical management of patients with biliary cancer. In addition, the concept of adjuvant treatment after resection has not yet proved to be of definite use in clinical practice. No clear trend in favour of therapy could be seen with the studies including a control group, when radiation was applied, and chemotherapy has not extensively been tested in this setting.

Recently, the concept of improving survival and quality of life instead of judging the impact of therapy by response rates has only been given due consideration in gastrointestinal tract cancers. Unfortunately, no systematic investigations of this issue have been performed in patients receiving radiation or combined therapy. In addition, only one randomised trial with meticulous investigation of quality of life has been published in patients receiving palliative chemotherapy. In this study, Glimelius and coworkers [79] were able to demonstrate for the first time a beneficial influence of 5-FU/leucovorin-based therapy on quality of life. This finding is in contrast to the commonly expressed notion that chemotherapy should not be incorporated into routine clinical

Table 3. Chemoradiation for biliary tract cancer

Chemotherapy	Radiation	Patients	Median survival (months)	Reference
5-FU + MMC	65 Gy EBRT	12	17	Minsky and associates, 1991 [97]
MMC	^{60}Co IORT + 32–40 Gy EBRT	20	30	Koyama and associates, 1993 [98]
FUdR	35–66 Gy EBRT	9	19	Robertson and associates, 1993 [99]
Various regimens*	< 40 Gy EBRT	58	8	Krabill and associates, 1994 [100]
	> 40 Gy EBRT	38	16	
5-FU	59 Gy EBRT	9	12	Whittington and associates, 1995 [101]

5-FU, 5-fluorouracil; MMC, mitomycin C; FUdR, floxuridine; EBRT, external beam radiation therapy; IORT, intra-operative radiation therapy.
*In 31 of 96 patients.

management of biliary tract cancer [79]. While this obviously seemed to be the case, with low response rates and short survival times obtained with phase II studies, response and influence on quality of life, however, do not necessarily have to correlate. The relationship between these two issues remains unsolved at present, and larger randomised series concerning the benefit of non-surgical oncological intervention as compared with supportive care are still lacking, and are clearly warranted for all treatment modalities. Patients with advanced biliary tract cancer should be offered the opportunity to participate in clinical trials, in order to expand further our knowledge of the optimal management in terms of quality of life, survival and efficacy of treatment.

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