Journal of BUON **16:** 464-468, 2011

ORIGINAL ARTICLE

Adjuvant therapy for gallbladder and bile duct cancers: retrospective comparative study

F. Tugba Kos[1], S. Aksoy[1], H. Odabas[1], N. Ozdemir[1], B. Oksuzoglu[2], D. Uncu[1], N. Zengin[1]

[1]Ankara Numune Education and Research Hospital, Department of Medical Oncology, Ankara; [2]Dr. Abdurrahman Yurtaslan Ankara Oncology Education and Research Hospital, Department of Medical Oncology, Ankara, Turkey

Summary

Purpose: *To study the efficacy of adjuvant therapy (chemotherapy and radiotherapy) in early stages (I-III) of gallbladder and bile duct cancers.*

Methods: *The clinical and pathological characteristics, treatment details and survival data of patients operated with early stages (I-III) of gallbladder and bile duct cancers and followed up in our clinic between August 2002 - November 2009 were retrospectively evaluated.*

Results: *52 patients (median age 64 years) with early stages of gallbladder (n=36) and bile duct (n=16) cancers were analysed. Twenty-three (44.2%) patients had stage I, 23 (44.2%) stage II, and 6 (11.5%) stage III cancers. Approximately half of the patients (n=25; 48.1%) received postoperative adjuvant chemotherapy and/or radiotherapy. Patients with adjuvant treatment were younger than those without (62 vs. 71 years, p=0.06). Eighteen patients received chemotherapy alone, 2 chemotherapy followed by radiotherapy, 1 chemotherapy concurrently with radiotherapy, and 4 radiotherapy alone as adjuvant therapy. The regimen most frequently used (57.1%) was CFF (cisplatin 50 mg/m^2, day 1; folinic acid 200 mg/m^2, day 1; 5-fluorouracil [5-FU] 400 mg/m^2 bolus day 1 and 1600 mg/m^2 48h continuous infusion). Some poor prognostic factors like high tumor grade and vascular invasion were more frequent in patients who received adjuvant therapy. The median disease free survival (DFS) was 11.4 months for the patients that received adjuvant therapy vs. 8.2 months for those without adjuvant therapy (p=0.67). During follow up 11 patients (44.0%) with adjuvant therapy and 12 (44.4%) without have died (p=0.97). The estimated median survival was 29 months.*

Conclusion: *Although previous studies had shown that 5-FU-based adjuvant chemotherapy may provide a small survival advantage, this was not confirmed in the present study. Prospective adjuvant trials with a standard chemotherapy regimen and larger numbers of patients are required.*

Key words: adjuvant, bile duct, carcinoma, chemotherapy, gallbladder

Introduction

Gallbladder cancer is the 5th most common cancer of the gastrointestinal system [1]. The bile duct cancers are observed less frequently [2] and may be found at intrahepatic, hilar or distal localizations. They arise mostly (60-80%) from the perihilar region [3]. The prognosis of gallbladder and bile duct cancers is poor, the only curative therapy being surgery. However, curative surgery is rather infrequently possible since approximately 80% of the patients have advanced-stage disease at diagnosis [4,5]. Early diagnosis is difficult because of lack of specific clinical symptoms and signs. The 5-year survival is about 5% [2,6,7].

In recent years, the development of newer diagnostic methods along with radical surgical approaches contributed to improvement of survival in early-stage gallbladder cancer [1]. The potential curative treatment is complete resection, however the role of adjuvant therapy is not clear [8-10]. The rate of postoperative local recurrence in gallbladder and proximal bile duct cancers is about 50% [11]. Considering the high incidence of local recurrence, radiotherapy as adjuvant therapy has been recommended [11,12], and recent studies support the use of adjuvant radiotherapy concurrently with chemotherapy [14,15]. The adjuvant chemotherapy agents most used in gallbladder and bile duct cancers were 5-FU, adriamycin, mitomycin C and cisplatin, used as

Correspondence to: Sercan Aksoy, MD. Ankara Numune Education and Research Hospital, Department of Medical Oncology, 06100, Sihhiye, Ankara, Turkey. Tel: +90 312 508 4600, Fax: +90 312 311 2778, E-mail: saksoy07@yahoo.com

Received 06-01-2011; Accepted 02-02-2011

single-agents or in combination [3]. In addition, gemcitabine-based chemotherapy is being studied [9].

In the present study, we retrospectively analysed the data of patients with early stages of gallbladder and bile duct cancers treated and followed up in our clinic. The aim was to evaluate the patients' clinical characteristics and tumor pathological characteristics and the impact of adjuvant treatment on patient survival vs. survival of those who did not have adjuvant treatment.

Methods

The clinical and pathological characteristics, treatment details, and survival data of the patients operated with early stages (stages I-III) of gallbladder and bile duct cancers and followed up in Ankara Numune Education and Research Hospital, Department of Medical Oncology between August 2002 and November 2009 were retrieved from patient medical records and were retrospectively evaluated. Disease staging was defined according to American Joint Committee on Cancer (AJCC), 2003. Patient performance status (PS) was evaluated according to Eastern Cooperative Oncology Group (ECOG) scale.

Statistical analysis

DFS was defined as the time period from surgery to the development of metastasis-relapse or death without evidence of disease. Overall survival (OS) was the time period from surgery to the date of analysis (February 2010).

Fisher's exact test and chi-square test were used to evaluate the nominal variables and numeric data. Kaplan-Meier method and log-rank test were used to evaluate DFS and OS. A p-value<0.05 was considered statistically significant. The data were analyzed using the SPSS package, version 13.0.

Results

Patient characteristics

A total of 52 patients with early stages (I-III) of gallbladder cancer (n=36; 69.2%) and bile duct cancer (n=16; 30.7%) were analysed. Patient characteristics are listed in Table 1. Thirty-two (61.5%) of them were women and 20 (38.5%) men. ECOG PS on admission was 0-1 in approximately half of the patients (48%). Twenty-three (44.2%) patients had stage I, 23 (44.2%) stage II, and 6 (11.5%) stage III disease at diagnosis.

The median patient age was 64 years (range 42-84). The patients who had adjuvant treatment were younger compared with those who had not (62 vs. 71 years, p=0.06).

Surgical treatments

Operational methods included simple cholecystectomy (55.8%), cholecystectomy + liver wedge resection + Whipple operation (17.3%), and cholecystectomy + liver wedge resection + lymph node dissection (9.6%). Fourteen patients (26.9%) had positive surgical margins while in 2 patients this information was lacking. Surgical margin positivity was present mostly (50%) in patients who had undergone simple cholecystectomy. No patient had macroscopic residual disease (R0).

Adjuvant therapy

Twenty-five patients (48.1%) received postoperative adjuvant chemotherapy and/or radiotherapy; 18 received chemotherapy alone, 2 received chemotherapy followed by radiotherapy (200 cGy/day × 25 fractions, total dose 50 Gy), 1 patient received chemotherapy concurrently with radiotherapy (radiotherapy concomitant with 5-FU 425 mg/m^2/day for the first 4 and the last 4 days of radiotherapy), and 4 patients received radiotherapy alone. 5-FU, cisplatin, mitomycin, gemcitabine, etoposide, and adriamycin were used as single agents or in combinations (Table 2). The regimen most commonly used (57.1%) was CFF (cisplatin 50 mg/m^2, day 1; folinic acid 200 mg/m^2 day 1; and 5-FU 400 mg/m^2 day 1 bolus and 1600 mg/m^2 for 48h as continuous infusion). There were more adjacent organ invasion, perineural and vascular invasion in the adjuvant therapy group compared with the non-adjuvant therapy group. However, only the rate of vascular invasion was significant (p=0.02). The other patient characteristics were similar in both groups. Ten of 24 patients (41.7%) in the adjuvant therapy group who had surgical border information had positive surgical margins. Four of 26 patients (15.4%) without adjuvant therapy who had surgical border information had positive surgical margins (p=0.04).

Survival analysis

The median follow up period was 9.5 months (range 0.4-83.9). The median follow up period of patients treated with adjuvant therapy was 12.7 months (range 0.4-83.9) and for those without adjuvant therapy it was 5.1 months (range 0.8 - 80.7). The median DFS was 11.4 months (range 8.5-14.3) for patients that received adjuvant therapy, and 8.2 months (range 2.7-

Table 1. Patient and treatment characteristics

Characteristics	*All patients n (%)*	*Only surgery n (%)*	*Surgery+adjuvant therapy n (%)*	*p-value**
	52 (100)	27 (51.9%)	25 (48.1)	–
Gender				
Female	32 (61.5)	17 (63.0)	15 (60.0)	0.82
Male	20 (38.5)	10 (37.0)	10 (40.0)	
Age (years)				
Median	64	71	62	0.06
Range	42-84	46-79	42-84	
ECOG PS				
0-1	25 (48.0)	12 (44.4)	13 (52.0)	0.74
2	14 (26.9)	6 (22.2)	8 (32.0)	
3-4	8 (15.4)	6 (22.2)	2 (8.0)	
Unknown	5	3	2	
Primary tumor				
Gallbladder	36 (69.2)	18 (66.7)	18 (72.0)	0.47
Bile duct	16 (30.7)	9 (33.3)	7 (28.0)	
Stage				
I	23 (44.3)	15 (55.6)	8 (32.0)	0.67
II	23 (44.2)	10 (37.0)	13 (52.0)	
III	6 (11.5)	2 (7.4)	4 (16.0)	
Surgical procedure				
C	29 (55.8)	18 (66.7)	11 (44.0)	0.40
C, LWR	9 (17.3)	3 (11.1)	6 (24.0)	
C LWR, LD	5 (9.6)	2 (7.4)	3 (12.0)	
Whipple	9 (17.3)	4 (14.8)	5 (20.0)	
Histological grade				
Good	20 (38.5)	13 (48.1)	7 (28.0)	0.14
Moderate	15 (28.8)	7 (25.9)	8 (32.0)	
Poor	8 (15.4)	2 (7.4)	6 (24.0)	
Unknown	9	5	4	
Histological findings				
Perineural invasion	16 (30.8)	6 (22.2)	10 (40.0)	0.23
Vascular invasion	11 (21.2)	2 (7.4)	9 (36.0)	0.02
Liver invasion	16 (30.8)	6 (22.2)	10 (40.0)	0.23

* p-value between patients with or without adjuvant therapy.
C: cholecystectomy, LWR: liver wedge resection, LD: lymph node dissection, PS: performance status

13.7) for those without adjuvant therapy (p=0.67; Figure 1). Eleven patients (44.0%) with adjuvant therapy and 12 (44.4%) without such therapy had died (p=0.60). The estimated median OS was 29 months for adjuvant plus non adjuvant patients and was similar in both groups (Figure 2).

Table 2. Chemotherapy regimens used in this study

Chemotherapy regimens	Number of patients (%)	
CFF	12 (57.1)	Cisplatin 50 mg/m^2, day 1; Folinic acid 200 mg/m^2 day 1; and 5-FU 400 mg/m^2 day 1 bolus and 1600 mg/m^2 for 48h continuous infusion, every 15 days
FUFA	4 (19.0)	Folinic acid 200 mg/m^2 day 1; and 5-FU 400 mg/m^2 day 1 bolus and 1600 mg/m^2 for 48h continuous infusion, every 15 days
Gemcitabine	1 (4.8)	Gemcitabine 1200 mg/m^2 days 1 and 8, every 21 days
Gemcitabine+Cisplatin	1 (4.8)	Gemcitabine 1200 mg/m^2 day 1 and 8; Cisplatin 75 mg/m^2 day 1, every 21 days
Cisplatin+Etoposide	1 (4.8)	Cisplatin 80 mg/m^2 day 1; Etoposide 120 mg/m^2 days, every 21 days
5-FU+Doxorubicin+Mitomycin	1 (4.8)	5-FU 600 mg/m^2 days 1, 8, 29, 36; Doxorubicin 30 mg/m^2 day 1 and 29; Mitomycin-C 10 mg/m^2 day 1, every 56 days

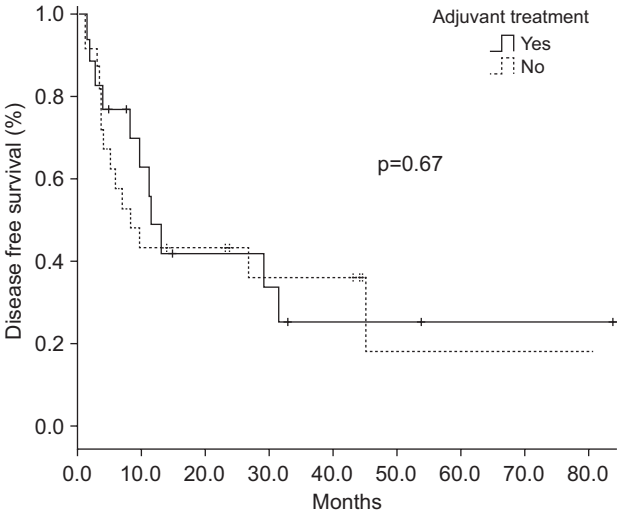

Figure 1. Disease free survival of both groups.

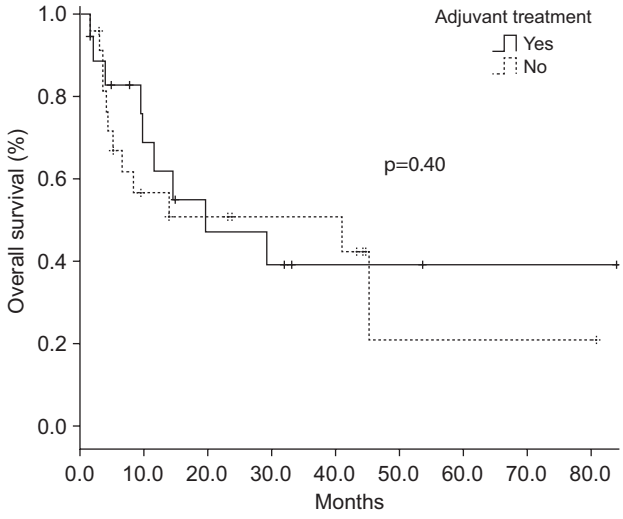

Figure 2. Overall survival of both groups.

Discussion

Gallbladder and proximal bile duct cancers are very rarely seen and their mortality is high. Generally, they are identified incidentally during screening for cholelithiasis and their rate is 1-2% among all kinds of cancer [16]. The curative treatment of both of these conditions is surgery. However, curative surgery is infrequently possible due to delayed diagnosis because of lack of specific clinical signs and symptoms. In the series published by Nakeeb et al. the rate of resectability was about 56-60% in the proximal bile duct cancers (intrahepatic and perihilar) [17]. Radical cholecystectomy that consists of hepatic wedge resection and lymph node dissection is recommended for gallbladder cancers [18]. Radical cholecystectomy may be recommended for selected patients that are diagnosed following simple cholecystectomy [19]. In our study cholecystectomy was the surgical procedure most commonly used and 25% of the patients who underwent simple cholecystectomy had positive surgical margins. None of our patients underwent second surgical procedure.

The role of adjuvant therapy in gallbladder and bile duct cancers is controversial. There is no prospective study for adjuvant chemotherapy and literature data are restricted to small retrospective studies with few patients showing that adjuvant radiotherapy reduces local recurrence; however, radiotherapy offers survival advantage in palliative cases [13]. Also, a retrospective study of adjuvant radiotherapy showed OS advantage only in node-positive patients and in those with hepatic infiltration [20].

There are numerous studies with postoperative adjuvant or palliative chemotherapy. The largest randomized study with postoperative adjuvant or palliative chemotherapy is the one performed by Takada et al. which included patients with pancreatic and ampulla of Vater tumors, as well as 112 patients with gallbladder and 118 patients with bile duct cancer [10]. The patients were randomized to postoperative adjuvant chemotherapy (mitomycin, 5-FU) and surgery alone arms. Excluding patients with stage I and IV disease, 5-year survival rate of the gallbladder cancer patients was significantly higher in the chemotherapy group (chemotherapy group 26% vs. surgery alone group 14.4%, p=0.036).

No significant differences in OS in relation to stage (p=0.67) and ECOG PS (p=0.74) were present between groups. Adjuvant therapy was given to younger patients due to better tolerability (p=0.01).

The studies performed so far can not clearly show the role and the type of the adjuvant therapy (chemotherapy, radiotherapy, chemoradiotherapy) for patients with curative resection. It is stated that 5-FU-based regimens may provide a small survival advantage for the gallbladder patients with non-curative resection according to the recommendations of ESMO guidelines. However, this does not apply for patients with bile duct cancers, and patient-based evaluation for the best care and chemotherapy and/or radiotherapy is recommended [11].

No clear guidelines exist for adjuvant therapy. Although previous studies showed that adjuvant 5-FU-based regimens may provide a small survival advantage for the gallbladder and bile duct tumors, this was not confirmed in the present study. Prospective adjuvant phase III trials with larger numbers of patients are required to clarify the present controversial situation.

References

1. Gourgiotis S, Kocher HM, Solaini L, Yarollahi A, Tsiambas E,

Salemis NS. Gallbladder cancer. Am J Surg 2008; 196: 252-264.
2. Mosconi S, Beretta GD, Labianca R, Zampino MG, Gatta G, Heinemann V. Cholangiocarcinoma. Crit Rev Oncol Hematol 2009; 69: 259-270.
3. Todoroki T. Chemotherapy for bile duct carcinoma in the light of adjuvant chemotherapy to surgery. Hepatogastroenterology 2000; 47: 644-649.
4. Ogura Y, Mizumoto R, Isaji S, Kusuda T, Matsuda S, Tabata M. Radical operations for carcinoma of the gallbladder: present status in Japan. World J Surg 1991; 15: 337-343.
5. Schauer RJ, Meyer G, Baretton G, Schildberg FW, Rau HG. Prognostic factors and long-term results after surgery for gallbladder carcinoma: a retrospective study of 127 patients. Langenbecks Arch Surg 2001; 386: 110-117.
6. Bartlett DL, Fong Y, Fortner JG, Brennan MF, Blumgart LH. Long-term results after resection for gallbladder cancer. Implications for staging and management. Ann Surg 1996; 224: 639-646.
7. Piehler JM, Crichlow RW. Primary carcinoma of the gallbladder. Surg Gynecol Obstet 1978; 147: 929-942.
8. Jarnagin WR, Ruo L, Little SA et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 2003; 98: 1689-1700.
9. Murakami Y, Uemura K, Sudo T et al. Gemcitabine-based adjuvant chemotherapy improves survival after aggressive surgery for hilar cholangiocarcinoma. J Gastrointest Surg 2009; 13: 1470-1479.
10. Takada T, Amano H, Yasuda H et al; Study Group of Surgical Adjuvant Therapy for Carcinomas of the Pancreas and Biliary Tract. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002; 95: 1685-1695.
11. Eckel F, Jelic S. ESMO Guidelines Working Group. Biliary cancer: ESMO clinical recommendation for diagnosis, treatment and follow-up. Ann Oncol 2009; 20 (Suppl 4): 46-48.
12. Mcdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002; 11: 941-954.
13. Mahe M, Stampfli C, Romestaing P, Salerno N, Gerard JP. Primary carcinoma of the gallbladder: potential for external radiation therapy. Radiother Oncol 1994; 33: 204-208.
14. Czito BG, Hurwitz HI, Clough RW et al. Adjuvant external-beam radiotherapy with concurrent chemotherapy after resection of primary gallbladder carcinoma: a 23-year experience. Int J Radiat Oncol Biol Phys 2005; 62: 1030-1034.
15. Kresl JJ, Schild SE, Henning GT et al. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys 2002; 52: 167-175.
16. Barone JE, Lincer RM. A prospective analysis of 1518 laparoscopic cholecystectomies. The Southern Surgeons Club. N Engl J Med 1991; 324: 1073-1078.
17. Nakeeb A, Pitt HA, Sohn TA et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996; 224: 463-473; discussion 473-475.
18. Donohue JH, Nagorney DM, Grant CS, Tsushima K, Ilstrup DM, Adson MA. Carcinoma of the gallbladder. Does radical resection improve outcome? Arch Surg 1990; 125: 237-241.
19. Shirai Y, Yoshida K, Tsukada K, Muto T. Inapparent carcinoma of the gallbladder. An appraisal of a radical second operation after simple cholecystectomy. Ann Surg 1992; 215: 326-331.
20. Mojica P, Smith D, Ellenhorn J. Adjuvant radiation therapy is associated with improved survival for gallbladder carcinoma with regional metastatic disease. J Surg Oncol 2007; 96: 8-13.