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Efficacy of Adjuvant Chemotherapy for Fatty Acid Synthase-Positive and Negative Distal Bile Duct Cancer and Ampullary Cancer: A Retrospective Analysis

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Abstract

Objective: Immunohistochemical fatty acid synthase expression is a prognostic marker in several cancers and is related to cancer aggressiveness. Here, we analyzed fatty acid synthase expression as an indicator of adjuvant chemotherapy for distal bile duct and ampullary cancer cases.

Methods: Forty-three cases of distal bile duct cancer and thirty-seven ampullary cancer cases resected between 2000 and 2017 were examined. We investigated immunohistochemical fatty acid synthase expression in resected specimens and the involvement of lymph nodes. We compared these findings with patient prognosis using medical history of postoperative adjuvant chemotherapy. Patient survival was expressed by the Kaplan-Meyer method and analyzed by a log-rank test.

Results: There were twenty-two fatty acid synthase-positive cases for distal bile duct cancer and seventeen for ampullary cancer. For distal bile duct cancer cases, the relapse-free survival and overall survival of fatty acid synthase-positive cases were shorter than those for fatty acid synthase-negative cases (p=0.0094 and p=0.0327, respectively). For ampullary cancer cases, the relapse-free survival and overall survival of fatty acid synthase-positive cases were also shorter than those for fatty acid synthase-negative cases (p=0.0225 and p=0.0103, respectively). Adjuvant chemotherapy occurred in twelve of the twenty-two fatty acid-positive distal bile duct cancer cases and in eight of the seventeen fatty acid-positive ampullary cancer cases. Relapse-free survival and overall survival of cases with adjuvant chemotherapy did not differ from those without adjuvant chemotherapy in both distal bile duct cancer and ampullary cancer.

Conclusion: Although fatty acid synthase expression was a prognostic factor in bile duct cancer and ampullary cancer, it was not an indicating marker for adjuvant chemotherapy.

Keywords: Distal bile duct cancer; Ampullary cancer; Fatty acid synthase; Adjuvant chemotherapy; Prognosis

Introduction

Distal bile duct cancer arises in the biliary epithelium from the liver to the duodenum and has a poor prognosis [1]. Surgical resection is the only curative treatment for bile duct cancer [2,3], but recurrence often occurs after resection [4]. In general, recurrence is commonly experienced in digestive tract malignancies. The efficacy of adjuvant therapy after surgical resection is well-known in gastric cancer [5], colon cancer [6], and pancreatic cancer [7,8]. Postoperative adjuvant chemotherapy prolongs survival time and reduces recurrence. In distal bile duct cancer [9,10] and ampullary cancer [11-13], lymph node involvement is a prognostic factor. Adjuvant therapy benefits bile duct cancer patients who have lymph node metastasis [14-17]. In ampullary cancer, a patient who has lymph node metastasis is also considered for adjuvant therapy [18]. Fatty acid synthase (FAS) is a cytoplasmic enzyme that contributes to cellular proliferation [19], and expression is related to the prognosis of cancer [20] and to the prognosis of distal bile duct cancer and ampullary cancer in particular [21,22]. However, there are no reports of the efficacy of adjuvant chemotherapy for patients with biliary tract cancer according to pathological FAS expression. In this report, we investigated the efficacy of adjuvant chemotherapy for bile duct cancer and ampullary cancer according to FAS expression.

Materials and Methods

Materials

Specimens from forty-three distal bile duct cancer patients and thirty-eight ampullary cancer patients that were resected in our department between 2000 and 2017 were examined. Bile duct cancer, ampullary cancer, and lymph node involvement were diagnosed by hematoxylin and eosin staining.

Immunohistochemical analysis

For FAS expression analysis, five-micrometer-section specimens were formalin-fixed, paraffin-embedded, and examined by immunohistochemical staining. Anti-human FAS rabbit IgG was obtained from Immuno-Biological Laboratories Co. Ltd. (Fujioka, Gunma, Japan), and FAS staining was performed using an automated slide stainer (Bench-Mark XT; Ventana Medical Systems Inc., Tucson AZ). FAS staining intensity was measured by the classification previously described [22]. A FAS-positive case was defined as over one third of tumor cells stained strongly as adipocytes, and negative was

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defined as positive staining in less than one-third of tumor cells (Figure 1). Chemotherapy histories and prognoses were obtained from patient medical records.

Statistical analysis

Statistical analysis was performed using a log-rank test. All analyses were conducted using Graph Pad Prism5® statistical software (Graph Pad Software Inc., La Jolla, CA, USA). A p-value less than 0.05 was considered significant. The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Ethical Committee of our hospital.

Results

Clinicopathological findings of bile duct cancer and ampullary cancer

The clinicopathological features of forty-three bile duct cancer patients are listed in Table 1. Forty-two patients underwent pancreatoduodenectomy, one underwent bile duct resection, and all were curative resection. In the pathological findings, fourteen cases (32.6%) had lymph node involvement. There were twenty-two FAS-positive cases (51.1%). Eighteen patients underwent adjuvant chemotherapy. Chemotherapy agents are listed on Table 1. Of the twenty-two FAS-positive cases, twelve patients were administered adjuvant chemotherapy.

The clinicopathological features of thirty-seven ampullary cancer patients are listed in Table 2. All patients underwent curative resection, which was a pancreatoduodenectomy. In the pathological findings, eleven cases (29.7%) had lymph node involvement, and there were seventeen FAS-positive cases (45.9%). Fourteen patients underwent adjuvant chemotherapy. Of the seventeen FAS-positive cases, eight patients were administered adjuvant chemotherapy.

The chemotherapy agents were gemcitabine or S-1. The duration of gemcitabine 1000 mg/m^2 (administered on day 1, 8, and 15 every 28 days) or S-1 80 mg/m^2/day (administered every two weeks with a one-week break in between) was 6 months. Gemcitabine was administered for twenty-three patients, and S-1 was administered for nine patients. In twenty FAS-positive patients who were administered adjuvant chemotherapy, seventeen were administered gemcitabine, and three were administered S-1.

Efficacy of the prognostic evaluation of FAS expression and lymph node involvement in distal bile duct cancer cases

The prognoses of distal bile duct cancer cases according to lymph node involvement are shown in Figure 2. The relapse-free survival of lymph node-positive cases was shorter than that of node-negative cases (50% relapse-free survival was 7 months and undefined, respectively, p=0.0002) in Figure 2A. However, for overall survival, there was no significant difference between node-positive cases and node-negative

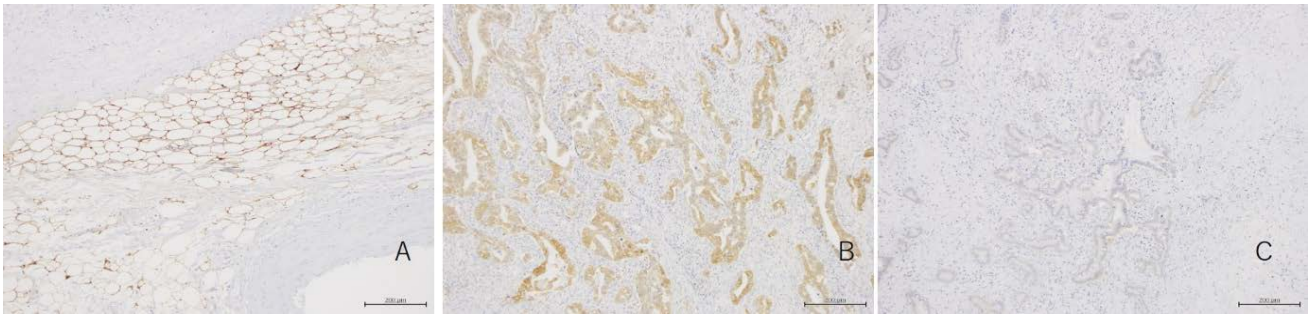

Figure 1: Immunohistochemical FAS expression **(A)** FAS staining of adipocytes, adipocytes were stained for FAS. The thin and round cytoplasm of adipocytes had a strong positive stain (100x) **(B)** a FAS-positive stained case, immunohistochemically, over one-third of the tumor cells were positive, which means it was counted as a FAS-positive case (100x distal bile duct cancer, adenocarcinoma) **(C)** a FAS-negative stained case, immunohistochemically, less than one-third of the tumor cells were positive, which means it was counted as a FAS-negative case (100x distal bile duct cancer, adenocarcinoma).

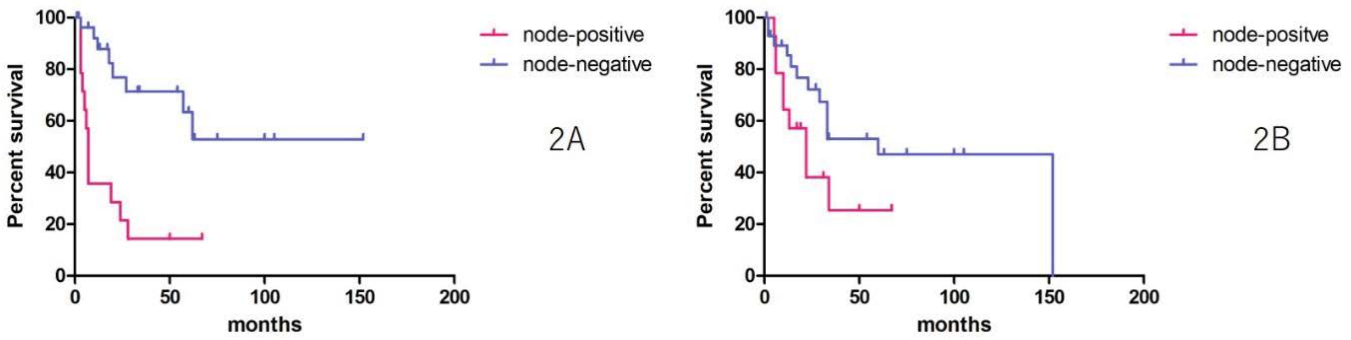

Figure 2: The prognoses of distal bile duct cancer according to node involvement **(A)** Relapse-free survival curve of node-positive and -negative cases, the relapse-free survival of node-positive cases was shorter than that of node-negative cases (50% relapse-free survival was 7 months and undefined, respectively, p=0.0002) **(B)** Overall survival curve of node-positive and -negative cases, there was no significant difference between node-positive cases and node-negative cases (mean survival time was 22 months and 60 months, respectively, p=0.0925).

cases (mean survival time was 22 months and 60 months, respectively, p=0.0925) in Figure 2B.

In Figure 3, the survival curves of distal bile duct cancer cases according to lymph node involvement are shown. The relapse-free survival of FAS-positive cases was shorter than that of FAS-negative cases (50% relapse-free survival was 12 months and undefined, respectively, p=0.0094) in Figure 3A. The overall survival of FAS-positive cases was also shorter than that of FAS-negative cases (mean survival time was 22 months and 152 months, respectively, p=0.0327) in Figure 3B.

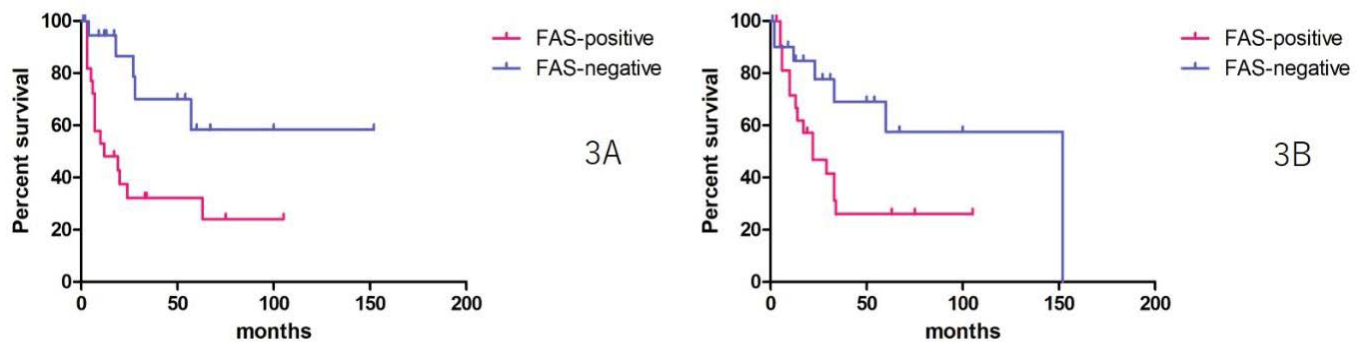

Figure 3: The prognoses of distal bile duct cancer according to FAS expression **(A)** Relapse-free survival curve of FAS-positive and FAS-negative cases the relapse-free survival of FAS-positive cases was shorter than that of FAS-negative cases (50% relapse-free survival was 12 months and undefined, respectively, p=0.0094) **(B)** Overall survival curve of FAS-positive and FAS-negative cases the overall survival of FAS-positive cases was also shorter than that of FAS-negative cases (mean survival time was 22 months and 152 months, respectively, p=0.0327).

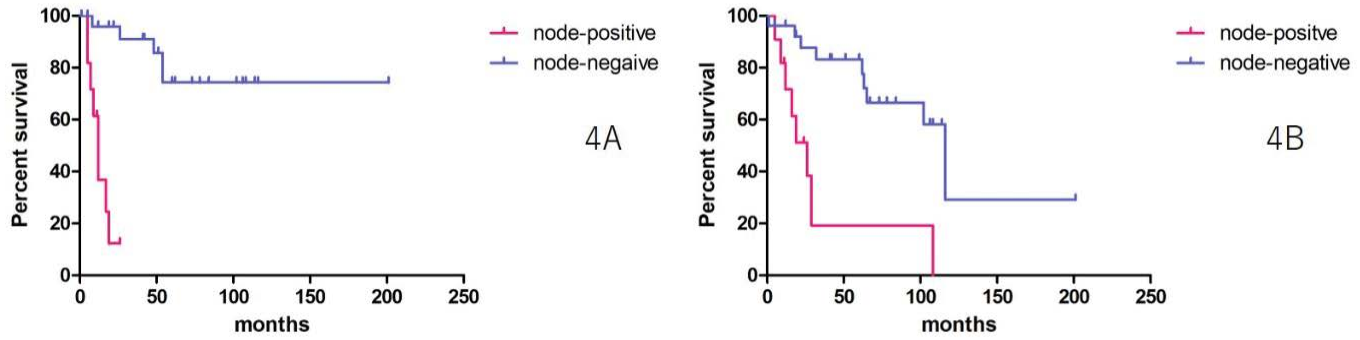

Figure 4: The prognoses of ampullary cancer according to node involvement **(A)** Relapse-free survival curve of node-positive and -negative cases the relapse-free survival of node-positive cases was shorter than that of node-negative cases (50% relapse-free survival was 12 months and undefined, respectively, p<0.0001) **(B)** Overall survival curve of node-positive and -negative cases the overall survival of node-positive cases was also shorter than that of node-negative cases (mean survival time was 26 months and 116 months, respectively, p=0.0004).

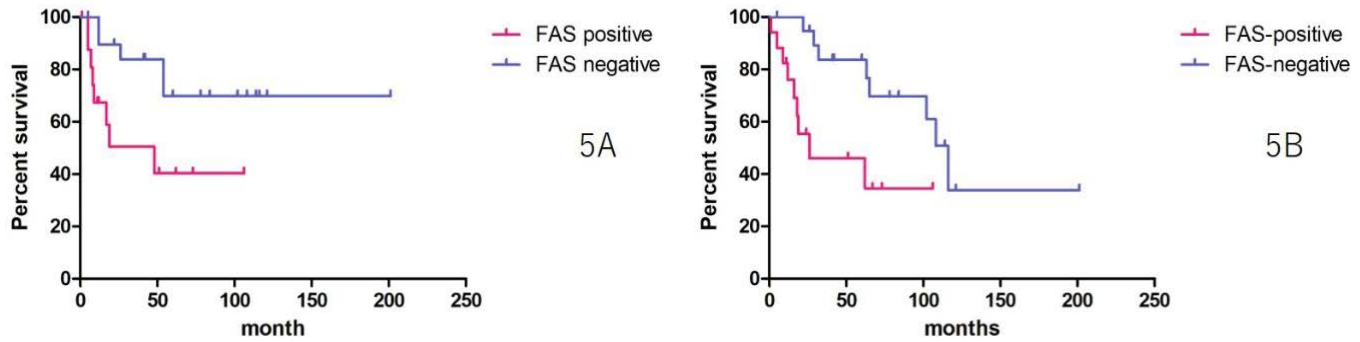

Figure 5: The prognoses of ampullary cancer according to FAS expression **(A)** Relapse-free survival curve of FAS-positive and FAS-negative cases the relapse-free survival of FAS cases was shorter than that of FAS-negative cases (50% relapse-free survival was 19 months and undefined, respectively, p=0.0225) **(B)** Overall survival curve of FAS-positive and FAS-negative cases the overall survival of FAS-positive cases was also shorter than that of FAS-negative cases (mean survival time was 26 months and 116 months, respectively, p=0.0103).

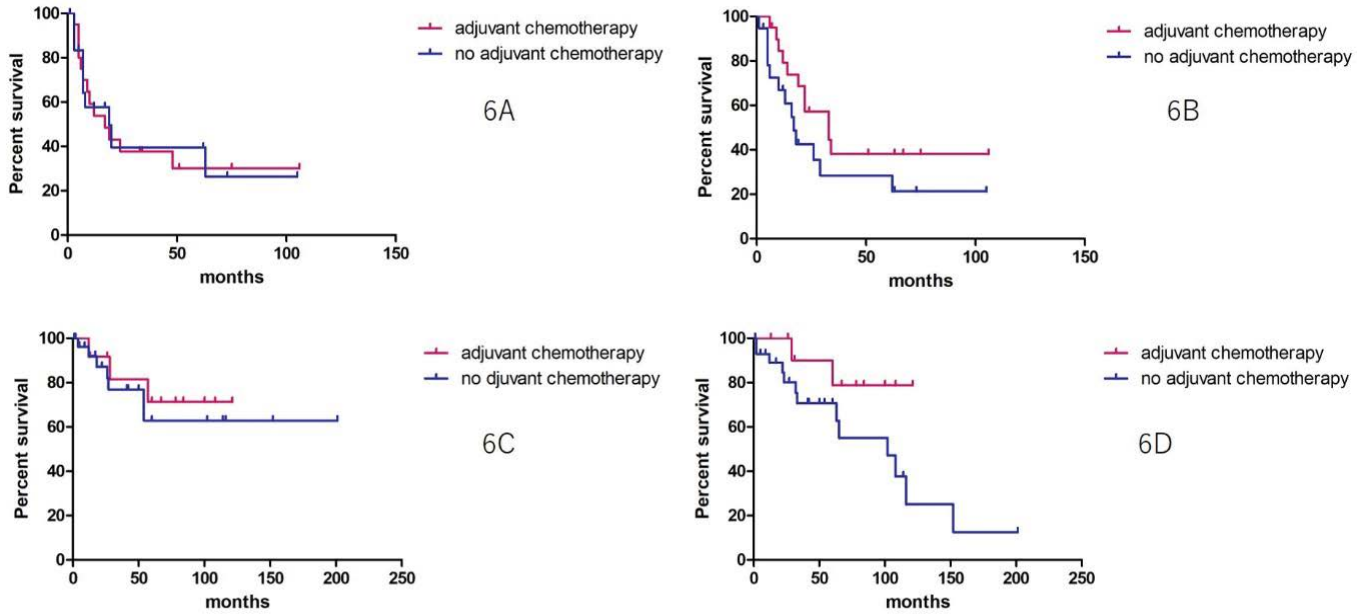

Figure 6: Efficacy of adjuvant chemotherapy for FAS-positive cases **(A)** Relapse-free survival of FAS-positive cases with or without adjuvant chemotherapy the relapse-free survival of cases with adjuvant chemotherapy did not differ from that of cases without adjuvant chemotherapy (p=0.9391) **(B)** Overall survival of FAS-positive distal bile duct cancer cases with or without adjuvant chemotherapy the overall survival of cases with adjuvant chemotherapy did not differ from that of cases without adjuvant chemotherapy (p=0.1537) **(C)** Relapse-free survival of FAS-negative distal bile duct cancer cases with or without adjuvant chemotherapy the relapse-free survival of cases with adjuvant chemotherapy did not differ from that of cases without adjuvant chemotherapy (p=0.5925) **(D)** Overall survival of FAS-negative distal bile duct cancer cases with or without adjuvant chemotherapy. The overall survival of cases with adjuvant chemotherapy did not differ from that of cases without adjuvant chemotherapy (p=0.1246).

Clinical factors	Parameters	Number of cases
Total		43
Sex	Male	27
	Female	15
Age (y.o.)		51 - 82 (median 74)
Surgical treatment	Pancreatoduodenectomy	42
	Bile duct resection	1
Node involvement		14 (32.6%)
Positive FAS expression		22 (51.1%)
Adjuvant chemotherapy	Gemcitabine	13
	S-1	5
Adjuvant chemotherapy for FAS expression	FAS-positive	12
	FAS-negative	6

Table 1: Clinicopathological features of 43 distal bile duct cancer cases.

Clinical factors	Parameters	Number of cases
Total		37
Sex	Male	20
	Female	17
Age (y.o.)		53 - 75 (median 70)
Surgical treatment	Pancreatoduodenectomy	37
Node involvement		11 (29.8%)
Positive FAS expression		17 (45.9%)
Adjuvant chemotherapy	Gemcitabine	10
	S-1	4
Adjuvant chemotherapy for FAS expression	FAS-positive	8
	FAS-negative	6

Table 2: Clinicopathological features of 37 ampullary cancer cases.

Efficacy of the prognostic evaluation of FAS expression and lymph node involvement in ampullary cancer cases

In Figure 4, survival curves of ampullary cancer cases according to lymph node involvement are shown. The relapse-free survival of node-positive cases was shorter than that of node-negative cases (50% relapse-free survival was 12 months and undefined, respectively, $p < 0.0001$) in Figure 4A. The overall survival of node-positive cases was also shorter than that of node-negative cases (mean survival time was 26 months and 116 months, respectively, p=0.0004) in Figure 4B.

The relapse-free survival of FAS-positive cases was shorter than that of FAS-negative cases (50% relapse-free survival was 19 months and undefined, respectively, p=0.0225) in Figure 5. The overall survival of FAS-positive cases was also shorter than that of FAS-negative cases (mean survival time was 26 months and 116 months, respectively, p=0.0103) in Figure 5. These results showed that FAS expression was a prognostic factor similar to lymph node involvement.

Efficacy of adjuvant chemotherapy for FAS-positive or -negative bile duct cancer and ampullary cancer cases

For both distal bile duct cancer and ampullary cancer, FAS-positive cases had poorer prognoses than negative cases. We examined the efficacy of adjuvant chemotherapy for twenty-two FAS-positive distal bile duct cases and seventeen FAS-positive ampullary cancer cases. Of these thirty-nine cases, twelve of the twenty-two distal bile duct cancer patients and eight of the seventeen ampullary cancer patients underwent chemotherapy (gemcitabine: seventeen, S-1: three). In the FAS-positive cases, the relapse-free survival and overall survival of cases with adjuvant chemotherapy did not differ from those of cases without adjuvant chemotherapy (p=0.9391 and p=0.1537, respectively)

in Figure 6. We also studied forty-one FAS-negative cases, and twelve patients underwent adjuvant chemotherapy (six distal bile duct cancer cases and six ampullary cancer cases). For the fatty acid synthase-negative cases, there were also no differences between the adjuvant chemotherapy cases and the non-adjuvant chemotherapy cases for relapse-free survival and overall survival (p=0.5925 and p=0.1246, respectively) in Figure 6.

Discussion

Although ampullary cancer is included as a biliary tract cancer, its clinical behavior is said to differ from that distal bile duct cancer [14,23]. Ampullary cancer has been treated separately from biliary tract cancer, but FAS-positive cases have poorer prognoses for both distal bile duct cancer and ampullary cancer. In this study, we examined the clinical behavior of both FAS-positive distal bile duct cancer and ampullary cancer cases. Increased FAS expression is often observed in several types of cancers and is related to cancer aggressiveness [20]. In our investigation, FAS expression was similar to lymph node metastasis as a prognostic factor in distal bile duct cancer and ampullary cancer. There are no previous reports investigating the clinical effect of adjuvant chemotherapy for FAS-positive malignancies of bile duct, and it is unknown if there is a relationship between FAS positivity and chemotherapy efficacy in cancer treatment. We analyzed both FAS-positive distal bile duct cancer and ampullary cancer cases, but there were no significant effects for FAS-positive cases. Although our investigation was retrospective, adjuvant chemotherapy of gemcitabine or S-1 may have no significant effects on FAS-positive distal bile duct cancer and ampullary cancer. Inhibition of FAS decreases FAS-positive cellular proliferation [24], and it is expected that FAS-inhibiting agents are available for FAS-positive cancers.

Adjuvant therapy after resection for distal bile duct cancer is controversial. Some retrospective reports suggest that adjuvant chemotherapy is indicated regardless lymph node involvement in distal bile duct cancer [25-27] and in periampullary cancer [23]. However, Lee et al. reported that postoperative adjuvant chemotherapy did not improve survival after surgical resection for extrahepatic bile duct cancer [28]. There were no differences in relapse-free survival and overall survival between patients who underwent adjuvant chemotherapy and those who went without adjuvant chemotherapy (data not shown). Recently, a randomized control trial reported that gemcitabine adjuvant administration did not improve outcomes [29], which suggests that there is no evidence for the efficacy of adjuvant chemotherapy for distal bile duct cancer.

Conclusion

Further clinical trials are needed to determine the efficacy of adjuvant chemotherapy for distal bile duct cancer or ampullary cancer and for adjuvant treatment for lymph node-positive or FAS-positive distal bile duct or ampullary cancer cases. Because the prognoses for distal bile duct cancer and ampullary cancer are poor, it is important to develop adjuvant treatments to improve outcomes after surgical treatment.

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