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ORIGINAL ARTICLE

Clinicopathologic features of advanced gallbladder cancer associated with adenomyomatosis

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Abstract Adenomyomatosis of the gallbladder has not been considered to have malignant potential, but gross features of adenomyomatosis are sometimes encountered in gallbladders resected under a diagnosis of gallbladder carcinoma. The purpose of this study was to determine the clinicopathologic features and survival rates in cases of gallbladder cancer with gross features of adenomyomatosis. The study subjects were 97 surgically treated gallbladder carcinoma patients. Only gallbladder showing typical gross features of adenomyomatosis was judged as adenomyomatosis-positive gallbladder cancer. In terms of gross findings, 25 cases (25.8%) were classified as adenomyomatosis-positive. The status of adenomyomatosis was significantly associated with the T stage (P=0.0004), lymph node (LN) metastasis (P<0.0001), distant metastasis (P=0.008), and stage (P=0.0005). In the adenomyomatosis-positive group, 16 of the 25 cases (64.0%) were classified as segmental type and 9 cases (36.0%) were classified as fundal type. No diffuse-type cases were present in this series. The status of adenomyomatosis correlated significantly with survival (P=0.0007). However, the multivariate analysis of significant variables identified from the univariate analysis identified only T stage (P=0.0178) and LN metastasis (P=0.0048) as independent prognostic factors. Subset analysis with T stage according to the status of adenomyomatosis showed no significant impact on survival. These results indicate that adenomyomatosis-positive gallbladder cancer is more often diagnosed clinically in the advanced stages. Since preceding adenomyomatosis may prevent the early detection of gallbladder cancer, the usefulness of preventive cholecystectomy in cases of asymptomatic adenomyomatosis should be considered.

Keywords Gallbladder carcinoma · Adenomyomatosis · Rokitansky–Aschoff sinuses

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Introduction

Adenomyomatosis of the gallbladder is defined as an epithelial proliferation and hypertrophy of the muscularis with outpouching of the mucosa into or through the thickened muscular layer, forming the so-called Rokitansky–Aschoff sinuses (RAS) [1, 2]. These histological changes are often distributed diffusely or segmentally, or are found at the fundus, and form well-known gross features categorized as diffuse-type, fundal (localized)-type, and segmental-type adenomyomatosis [1–3].

Adenomyomatosis of the gallbladder has not been considered to have malignant potential. However, several reports have suggested that gallbladder cancer may originate from adenomyomatosis [4–8] or have insisted that segmental-type adenomyomatosis shows an increased risk of progression to gallbladder cancer [3, 9]. As these previous studies were limited to investigations of excised gallbladder specimens due to gallbladder disease as well as other surgical diseases involving the gallbladder, they reported the incidence of gallbladder cancer in large numbers of cholecystectomy specimens, but the details of clinicopathologic findings that might clarify relationships between gallbladder cancer, adenomyomatosis, and

survival outcomes were not shown. The incidence of gallbladder cancer in adenomyomatosis reportedly ranged from 1% to 6.6% in all excised gallbladders with adenomyomatosis [3, 9, 10]. Despite the low incidence of incidental gallbladder cancer in adenomyomatosis, the gallbladders excised due to gallbladder cancer sometimes show gross features of adenomyomatosis.

The purpose of this study was to determine the clinicopathologic features and survival rates in cases of gallbladder cancer with gross features of adenomyomatosis.

Material and methods

Patients and staging

The study subjects were 97 consecutive gallbladder cancer patients who underwent surgical treatment between 1989 and August 2010 at Saga University Hospital under a diagnosis of gallbladder cancer or suspected gallbladder cancer as the primary lesion. Informed consent for the use of the resected tissue was obtained from all patients, and the study protocol was approved by the Ethics Committee of the Faculty of Medicine at Saga University. Clinical and histopathological staging were based on the TNM Classification of Malignant Tumors by the International Union Against Cancer [11].

Pathological evaluation of adenomyomatosis

The evaluation of adenomyomatosis was performed based on the gross features of specimens, according to a previous study [3]. The judgment of adenomyomatosis was restricted to typical gross cases of gallbladder cancer because only RAS formation is common in the gallbladder. Briefly, adenomyomatosis was classified as one of three types, as follows. The segmental type was defined as an annular stricture comprising a thickened wall dividing the gallbladder lumen into separate interconnected compartments with or without diffuse wall thickening on the fundal side. The fundal type was defined as a hemispheric elevated lesion with a central dimple located at the tip of the fundus. The diffuse type was defined as a thickened wall throughout the entire gallbladder. Even if RAS was histologically identified in the background gallbladder, cases that did not show gross features were categorized into the non-adenomyomatosis group. The predominant histological subtype of gallbladder cancer was identified based on each pathological report.

Statistical analysis

Statistical analyses were performed using the JMP version 8 software program (SAS Institute, Cary, NC, USA). The statistical analyses comparing the two groups were performed using Student's t test, the χ^2 test, and Fisher's exact test, as appropriate. All survival analyses were performed using disease-specific survival, determined from the time of surgery to the time of cancer-related death or the most recent follow-up. Postoperative survival was calculated using the Kaplan–Meier method. Differences in survival curves were compared using the log-rank test. Cox proportional hazards models were applied for the multivariate analysis. Values of $P<0.05$ were considered to be statistically significant.

Results

Clinicopathologic features of gallbladder cancer with or without adenomyomatosis

The 97 patients with surgically treated gallbladder cancer included 31 males and 66 females. Mean age at the time of surgery was 68.7 years (range, 40–87 years). According to the classification of gross findings, 25 cases (25.8%) were classified as adenomyomatosis-positive gallbladder cancer (Table 1). The absence of adenomyomatosis was significantly associated with the T stage ($P=0.0004$), lymph node (LN) metastasis ($P<0.0001$), distant metastasis ($P=0.008$), and stage ($P=0.0005$). Of the 25 patients in the adenomyomatosis-positive group with T2–T4 lesions, 21 patients showed LN metastasis (84.0%) and 11 patients displayed distant metastasis (44.0%). The presence or absence of adenomyomatosis was not associated with age and sex. Of the 97 patients with gallbladder cancer, 36 patients (37.1%) were accompanied with gallstone disease, which was not associated with adenomyomatosis.

Histologic type of adenomyomatosis in patients with gallbladder cancer

The rate of the predominant histologic type in the adenomyomatosis-positive and adenomyomatosis-negative groups is shown in Fig. 1. The details of histologic typing of adenomyomatosis-positive gallbladder cancer were as follows: well-differentiated tubular carcinoma, $n=7$ (28.0%); moderately differentiated tubular carcinoma, $n=10$ (40.0%); poorly differentiated adenocarcinoma, $n=3$ (12.0%); and other histologic type, $n=5$ (20.0%), comprising mucinous carcinoma, adenosquamous carcinoma, solid carcinoma, small cell carcinoma, and undifferentiated carcinoma spindle and giant cell type ($n=1$ each). The details of the histologic typing of adenomyomatosis-negative gallbladder cancer were as follows: papillary adenocarcinoma, $n=18$ (25.0%); well-differentiated tubular adenocarcinoma, $n=21$ (29.2%); moderately differentiated tubular carcinoma, $n=20$ (27.8%); poorly differentiated

Table 1 Clinicopathologic features of gallbladder cancer with or without adenomyomatosis

Characteristics	No. of patients (%)			*P* value
	Total	Adenomyomatosis (−)	Adenomyomatosis (+)	
No. of patients	97	72	25	
Age (mean±SD)	68.7±9.3	68.3±9.7	69.7±8.1	0.5288
Gender				0.3135
Male	31 (32.0)	25 (34.7)	6 (24.0)	
Female	66 (68.0)	47 (65.3)	19 (76.0)	
TNM classification				
T				0.0004
1a	11 (11.3)	11 (15.3)	0	
1b	8 (8.3)	8 (11.1)	0	
2	32 (33.0)	27 (37.5)	5 (20.0)	
3	39 (40.2)	21 (29.2)	18 (72.0)	
4	7 (7.2)	5 (6.9)	2 (8.0)	
N				<0.0001
0	50 (51.6)	46 (63.9)	4 (16.0)	
1	47 (48.4)	26 (36.1)	21 (84.0)	
M				0.008
0	77 (79.4)	62 (86.1)	15 (60.0)	
1	20 (20.6)	10 (13.9)	10 (40.0)	
Stage				0.0005
IA	18 (18.6)	18 (25.0)	0	
IB	22 (22.7)	20 (27.8)	2 (8.0)	
IIA	10 (10.3)	7 (9.7)	3 (12.0)	
IIB	21 (21.7)	14 (19.4)	7 (28.0)	
III	6 (6.2)	3 (4.2)	3 (12.0)	
IV	20 (20.6)	10 (13.9)	10 (40.0)	
Gallstone				0.077
Present	36 (37.1)	23 (31.9)	13 (52.0)	
Absent	61(62.9)	49 (68.1)	12 (48.0)	

adenocarcinoma, n=6 (8.3%); and other histologic type, n=7 (9.7%), comprising mucinous carcinoma (n=1), undifferentiated carcinoma (n=1), adenosquamous carcinoma (n=2), squamous cell carcinoma (n=1), signet ring cell carcinoma (n=1), and solid adenocarcinoma (n=1). A significant difference in the histologic types was seen between the adenomyomatosis-positive and adenomyomatosis-negative groups (P=0.01).

Clinicopathologic features of gallbladder cancer according to the gross type of adenomyomatosis

The clinicopathologic features of gallbladder cancer according to the gross type of adenomyomatosis are shown in Table 2. Of the 25 cases of adenomyomatosis-positive gallbladder cancer, 16 cases (64.0%) were classified as segmental-type adenomyomatosis (Fig. 2) and 9 cases (36.0%) were classified as fundal-type adenomyomatosis (Fig. 3). No diffuse-type adenomyomatosis was identified in our gallbladder cancer patient group. The segmental type includes cases showing diffuse wall thickening on the fundal side. Cancer had developed at the fundal side of segmental adenomyomatosis in 14 of the 16 cases. In the remaining two cases, the cancer had developed at the lumen of the neck side (Fig. 4). Cases suggesting gallbladder cancer that had developed from the RAS (Fig. 5) or cases of multiple cancers developing at the fundal side of segmental adenomyomatosis (Fig. 6) were included in this series. No significant differences in age, sex, or TNM classification were observed between the cases of segmental-type and fundal-type adenomyomatosis. Of the 25 cases of adenomyomatosis-positive gallbladder cancer, 13 cases (52.0%) were accompanied by gallstone disease. Although the segmental-type adenomyomatosis group showed a relatively high frequency of concomitant gallstone disease (10 out of 16 cases, 62.5%), no significant association was identified between the type of adenomyomatosis and the frequency of concomitant gallstone disease. However, a comparison between the

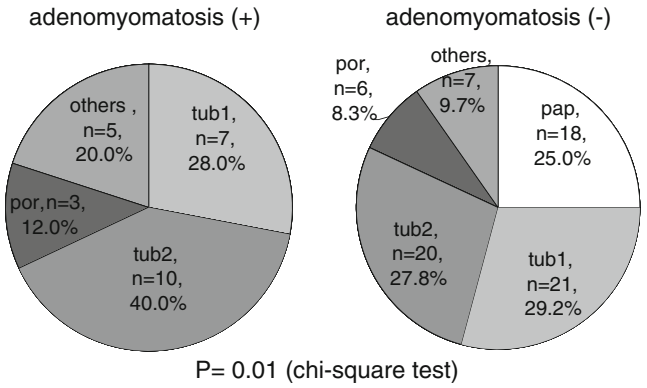

Fig. 1 The rate of predominant histologic type in adenomyomatosis-positive and adenomyomatosis-negative gallbladder cancer groups. *pap* papillary adenocarcinoma, *tub1* well-differentiated tubular carcinoma, *tub2* moderately differentiated tubular adenocarcinoma, *por* poorly differentiated adenocarcinoma. Details of others in adenomyomatosis-positive gallbladder cancer are as follows: mucinous carcinoma, $n=1$; adenosquamous carcinoma, $n=1$; solid carcinoma, $n=1$; small cell carcinoma, $n=1$; undifferentiated carcinoma spindle and giant cell type, $n=1$. Details of others in adenomyomatosis-negative gallbladder cancer are as follows: mucinous carcinoma, $n=1$; undifferentiated carcinoma, $n=1$; adenosquamous carcinoma, $n=2$; squamous cell carcinoma, $n=1$; signet ring cell carcinoma, $n=1$; solid adenocarcinoma, $n=1$

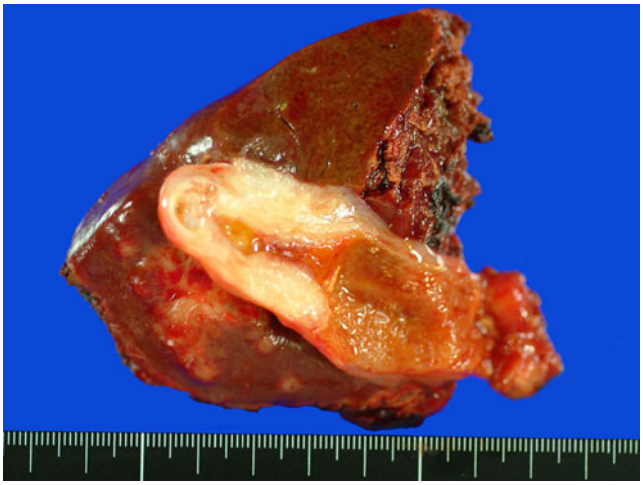

Fig. 2 A representative gross image of segmental-type adenomyomatosis-positive gallbladder cancer. Segmental type includes cases showing diffuse wall thickening on the fundal side

segmental adenomyomatosis group ($n=16$) and the other 81 gallbladder cancer cases showed a significantly higher rate of concomitant gallstones in patients with segmental adenomyomatosis ($P=0.0214$).

Table 2 Clinicopathologic features of gallbladder cancer according to the type of adenomyomatosis

Characteristics	No. of patients (%)			*P* value
	Total	Adenomyomatosis (s)	Adenomyomatosis (f)	
No. of patients	25	16 (64.0)	9 (36.0)	
Age (mean±SD)	69.7±8.1	67.5±8.9	73.6±4.3	0.0654
Gender				0.3135
Male	6 (24.0)	3 (18.8)	3 (33.3)	
Female	19 (76.0)	13 (82.3)	6 (66.7)	
TNM classification				
T				0.0929
2	5 (20.0)	4 (25.0)	1 (11.1)	
3	18 (72.0)	12 (75.0)	6 (66.7)	
4	2 (8.0)	0	2 (22.2)	
N				0.5312
0	4 (16.0)	2 (12.5)	2 (22.2)	
1	21 (84.0)	14 (87.5)	7 (77.8)	
M				0.6079
0	15 (60.0)	9 (56.3)	6 (66.7)	
1	10 (40.0)	7 (43.8)	3 (33.3)	
Stage				0.9752
IB	2 (8.0)	1 (6.3)	1 (11.1)	
IIA	3 (12.0)	2 (12.5)	1 (11.1)	
IIB	7 (28.0)	4 (25.0)	3 (33.3)	
III	3 (12.0)	2 (12.5)	1 (11.1)	
IV	10 (40.0)	7 (43.8)	3 (33.3)	
Gallstone				0.1583
Present	13 (52.0)	10 (62.5)	3 (33.3)	
Absent	12 (48.0)	6 (37.5)	6 (66.7)	

Adenomyomatosis (s) segmental type of adenomyomatosis, *Adenomyomatosis (f)* fundal type of adenomyomatosis

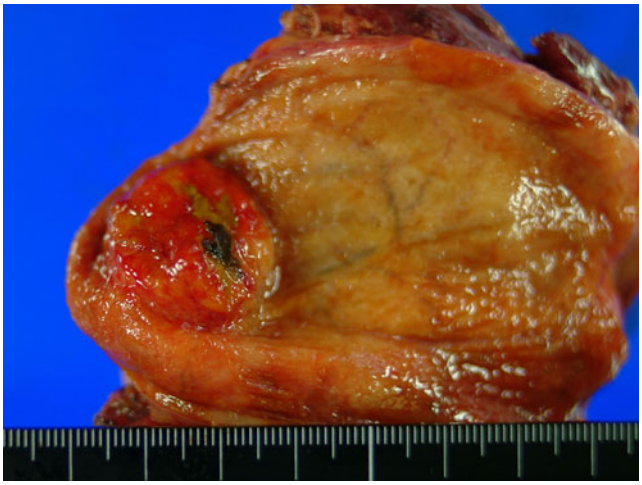

Fig. 3 A representative gross image of fundal-type adenomyomatosis-positive gallbladder cancer

Survival analysis

The median duration of follow-up was 25.3 months (range, 6–120 months). The results for disease-specific survival in the 97 gallbladder cancer patients are shown in Table 3. In the univariate analysis, the presence of adenomyomatosis correlated significantly with survival (P=0.0007). Other variables showing significant correlations with survival were sex (P=0.0426), T stage (P<0.0001), LN metastasis (P<0.0001), and distant metastasis (P<0.0001). A multivariate analysis of the significant variables identified from the univariate analysis was performed using Cox's proportional hazards model, revealing that only the T stage (P=0.0178) and LN metastasis (P=0.0048) were independent prognostic factors.

The survival curves for all 97 patients according to the status of adenomyomatosis are shown in Fig. 7. The adenomyomatosis-positive gallbladder cancer group showed a significantly worse survival (P=0.0001). This difference in survival disappeared in the subset analysis of the patients with stage T2 or T3 disease according to the status of adenomyomatosis. In the 25 gallbladder cancer patients with adenomyomatosis, no significant difference in survival was observed between those with segmental-type and fundal-type adenomyomatosis.

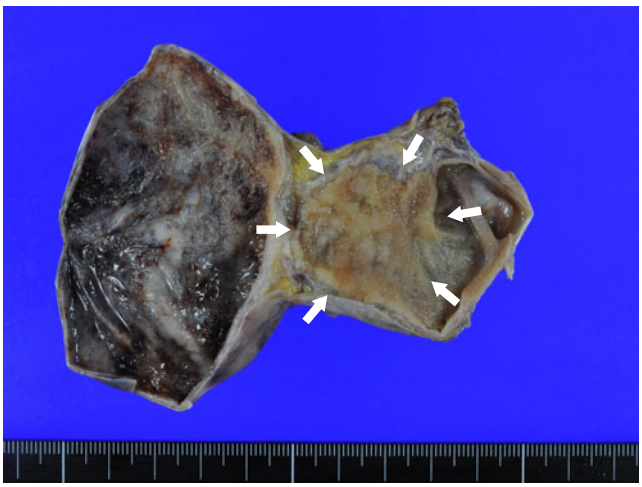

Fig. 4 A case in which the tumor (*arrows*) developed on the neck side of segmental-type adenomyomatosis

Discussion

Adenomyomatosis of the gallbladder is relatively common and usually asymptomatic, typically being discovered incidentally on abdominal imaging or on histological examination of cholecystectomy specimens taken for concomitant cholelithiasis or cholecystitis [12, 13]. Several investigators have suggested a relationship between gallbladder cancer and adenomyomatosis [3, 9]. However, carcinogenesis of the gallbladder is generally considered to correlate with the presence of gallstones rather than the presence of adenomyomatosis [10, 14]. The magnitude of risk for gallbladder cancer in patients with adenomyomatosis has not yet been clearly established.

The present study demonstrated a relatively high incidence of gross adenomyomatosis features (25.8%) in gallbladder cancer. In our university hospital, many patients with advanced gallbladder cancer have been treated, while the numbers of ordinary cholecystectomies performed have been relatively small. Therefore, there were few cases of incidentally detected gallbladder cancer during cholecystectomy in our series. Consistent with previous reports, our series contained no cases of diffuse-type adenomyomatosis [3, 9]. The survival analysis revealed a significantly worse survival of the adenomyomatosis-positive group. However, no significant differences were observed in the survival analysis of each T stage subgroup. This result indicates that adenomyomatosis-positive gallbladder cancer is often diagnosed clinically at an advanced stage.

Whether the gross appearance of adenomyomatosis really precedes carcinogenesis or if it forms as a result of cancerous invasion into the gallbladder wall still remains to be solved. We speculate that "gross appearance of adenomyomatosis precedes carcinogenesis" based on the following findings: many cases of segmental adenomyomatosis showed no sequence of cancerous tissue to the annular stricture and some cases of adenomyomatosis were identified by medical checkup before gallbladder cancer was found. If adenomyomatosis precedes carcinogenesis, the next question is whether the cancer is derived directly from the RAS or not. In our series, the RAS was consistently observed at the annular structure and/or the thickened wall of the adenomyomatosis. Although some cases suggested that carcinogenesis arose

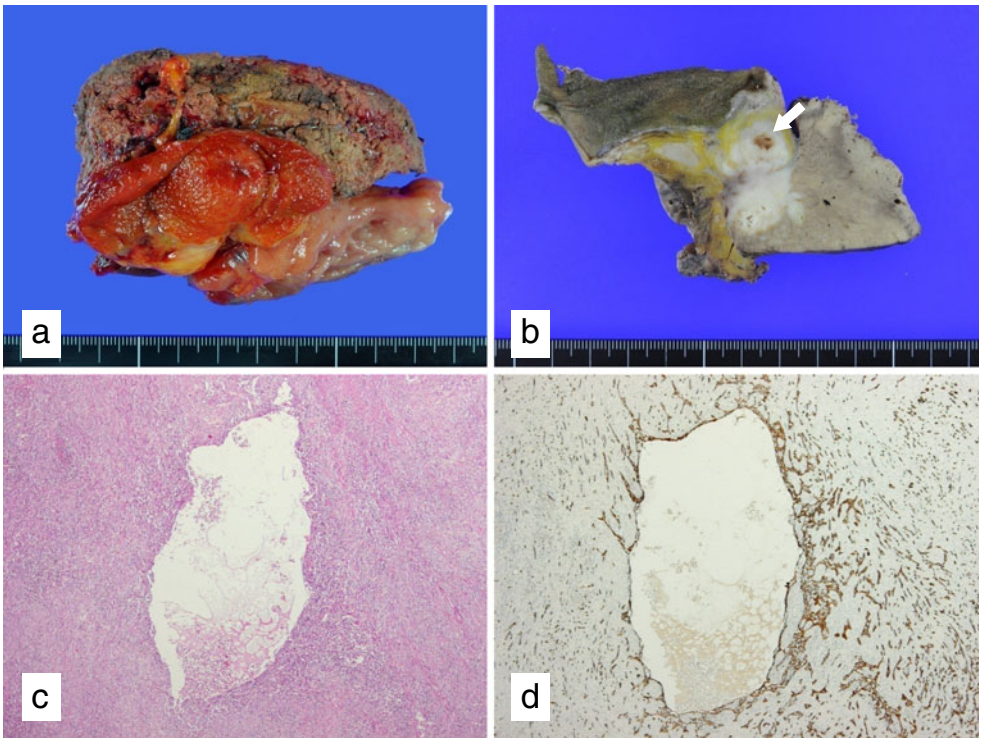

Fig. 5 Case presentation suggesting the development of gallbladder cancer from RAS. **a** Gross appearance. Fundal-type adenomyomatosis with a central dimple is defined. **b** The tumor predominantly proliferated in subserosal tissue and directly invaded into liver parenchyma, while showing no sequential connection to mucosal tissue. The dilated RAS contains bile-like material (*arrow*). **c** A RAS-like structure surrounded by spindle-shaped tumor and mesenchymal cells (original magnification, ×20). No sequential connection of mucosa and tumor was identified on histopathological examination. **d** Immunohistochemistry for cytokeratin 7. Spindle-shaped tumor cells were highlighted by cytokeratin 7. This case was finally diagnosed as undifferentiated carcinoma spindle and giant cell type (original magnification, ×20)

from the RAS, extensive cancer invasion prevented the pathological evaluation of carcinogenesis from RAS in most of the cases. To address this possibility, a study of the early stage cases specifically describing metaplasia, dysplasia, and carcinoma in the RAS would be needed. No cases of in situ or microinvasive cancer arising from RAS were found in our study population.

Gallstone disease is closely associated with carcinogenesis in gallbladder cancer [15–17] and segmental-type adenomyomatosis is frequently accompanied by gallstone disease [18]. The incidence of gallstone disease was relatively low in the present series (37.1%) compared to previous reports, but was high (62.5%) in patients with segmental-type adenomyomatosis. An elevated intraluminal pressure

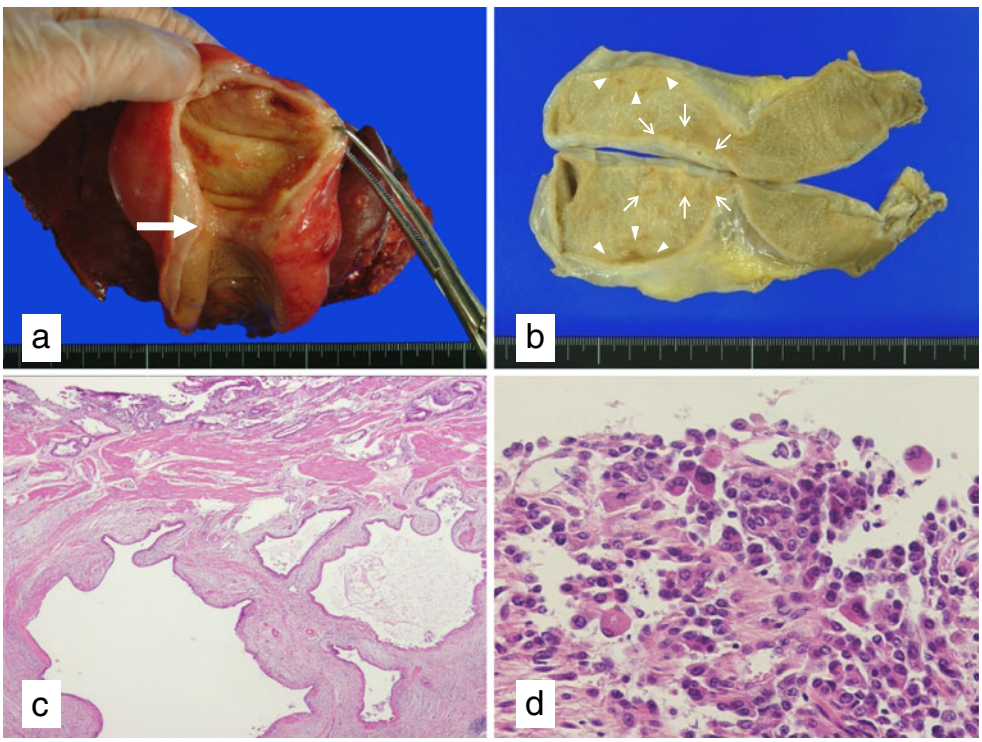

Fig. 6 Cases of multiple cancers that developed on the fundal side of segmental adenomyomatosis. **a** Gross appearance. Segmental-type adenomyomatosis with annular stricture (*arrow*) is defined. **b** Two discontinuous cancer lesions were microscopically identified in this case (*arrows* poorly differentiated carcinoma penetrating the serosa, *arrowheads* moderately differentiated tubular adenocarcinoma invading up to the muscularis propria). Although the volume of tumor was relatively small at the gallbladder, multiple metastatic nodules had already formed at the liver. **c** Many of RAS were identified at the annular structure. **d** Poorly differentiated adenocarcinoma proliferated at the mucosa and then invaded. No sequence of tumor and RAS was identified in this case (original magnification, ×200)

Table 3 Survival analysis

Characteristics		Number	Univariate analysis		Multivariate analysis	
			HR (95%CI)	*P* value	HR (95%CI)	*P* value
Adenomyomatosis	Negative	72	1	0.0007	1	0.9716
	Positive	25	3.85 (1.81–7.97)		0.98 (0.42–2.28)	
Age	<69	45	1	0.1205		
	≤69	52	0.97 (0.94–1.01)			
Gender	Male	31	1	0.0426	1	0.80
	Female	66	2.35 (1.02–6.31)		0.88 (0.33–2.60)	
T	T1, T2	51	1	<0.0001	1	0.0178
	T3, T4	46	7.56 (3.47–18.31)		3.06 (1.21–8.35)	
N	N0	50	1	<0.0001	1	0.0048
	N1	47	12.71 (5.45–34.76)		5.99 (1.72–21.80)	
M	M0	77	1	<0.0001	1	0.1335
	M1	20	7.67 (3.65–16.04)		1.87 (0.82–4.43)	

HR hazard ratio, *CI* confidence interval

and metaplasia at the fundal lumen in case of segmental adenomyomatosis is also considered to be a risk factor for gallbladder cancer [3, 9]. In fact, the present study and previous investigations have shown that gallbladder cancer arises predominantly at the fundal side of segmental-type adenomyomatosis [3, 9, 10]. No adenomyomatosis-specific molecule-based study has been reported. Mutations of the *KRAS*, *TP53*, and *CDNK2A* genes have been reported in invasive gallbladder carcinoma [14], but molecular pathways of carcinogenesis in the gallbladder have not been clearly established. Gallbladder cancer arising with fundal-type adenomyomatosis has also been reported [4, 8] and our series included nine cases of fundal-type adenomyomatosis-positive gallbladder cancer. The risk factors for fundal-type adenomyomatosis have been little investigated and remain unclear.

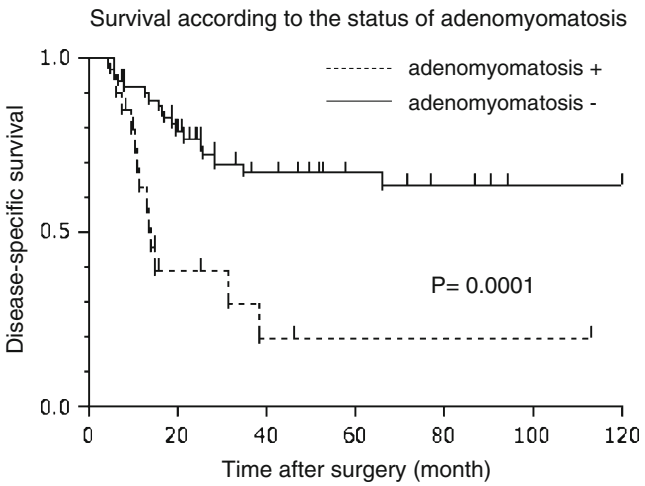

Fig. 7 Kaplan–Meier curves for all 97 patients according to the presence or absence of adenomyomatosis. The adenomyomatosis-positive gallbladder cancer group showed significantly poorer outcomes (P=0.0001)

The histological tendencies in adenomyomatosis-associated gallbladder cancer have not been investigated in previous studies. All of our present cases were stage T2 or higher, and no cases showed a predominant histologic type of papillary adenocarcinoma. Papillary-type gallbladder cancer associated with adenomyomatosis has been reported, but has been restricted to in situ or microinvasive cancer [4–8]. Adenomyomatosis-positive gallbladder cancer was also more frequently associated with the poorly differentiated histologic type compared to adenomyomatosis-negative cases. This could be explained by dedifferentiation, which is frequently observed in gallbladder cancer when the tumor invades deeper than the muscle layer [19].

In the present study, adenomyomatosis-positive gallbladder cancer was diagnosed as advanced stage cancer by several imaging modalities. The characteristics of imaging patterns in gallbladder cancer have been reported as follows: a mass replacing the gallbladder in 40–65% of cases; focal or diffuse gallbladder wall thickening in 20–30%; and an intraluminal polypoid mass in 15–25% [20–24]. If the tumor develops sufficiently to form a mass, the tumor may invade deeper than the muscle layer through the RAS. Gallbladder wall thickening by cancer invasion may be difficult to discriminate from wall thickening due to the preceding adenomyomatosis. Given these concerns, making an exact preoperative diagnosis of early stage gallbladder cancer with adenomyomatosis seems extremely difficult, as shown in our series.

Surgical intervention for patients with asymptomatic adenomyomatosis remains controversial [3, 4, 13]. Some investigators do not consider gallbladder adenomyomatosis as a premalignant lesion and believe that delaying the treatment of asymptomatic patients will not affect morbidity [13]. Others consider this condition to be a precursor of gallbladder cancer and advise regular ultrasonographic gallbladder surveillance, and suggest that cholecystectomy

should be performed when thickening or irregularity of the gallbladder wall is detected [4]. Cholecystectomy is now commonly performed by laparoscopic surgery with a low degree of surgical invasiveness. As the clinical diagnosis of early gallbladder cancer with adenomyomatosis is quite difficult, the utility of preventive cholecystectomy should, therefore, be taken into consideration for the management of asymptomatic adenomyomatosis patients.

In conclusion, the present study revealed an unexpectedly high incidence of accompanying adenomyomatosis in resected specimens of gallbladder cancer and revealed that adenomyomatosis-positive gallbladder cancer is often diagnosed clinically at an advanced stage. Gallbladder cancer shows marked geographical and ethnic variations [25–27]. Accumulation of studies from other institutions and other countries are thus required to confirm the relationship between adenomyomatosis and gallbladder cancer. If it is confirmed that many cases of actual gallbladder cancer were clinically detected in the advanced stage because of preceding adenomyomatosis, preventative cholecystectomy for asymptomatic adenomyomatosis patients might contribute to reducing the mortality caused by gallbladder cancer.

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Disclosure The authors declare that they have no conflict of interest.

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