



# Incidental Gall Bladder Adenocarcinoma in Cholecystectomy Specimens; A Single Center Experience and Review of the Literature

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## ABSTRACT

### BACKGROUND

Gallbladder adenocarcinoma is the most common malignant tumor of the biliary tract. Most of gall bladder cancers are detected incidentally only after pathological examination of the surgical specimens. In this study we investigated the characteristics of incidental gallbladder cancers in our center and also reviewed the current literature regarding the diagnosis and treatment of such incidentally detected tumors in the gall bladder.

### METHODS

We retrospectively reviewed all of the cholecystectomy specimens in the archives of Pathology Department in the hospitals affiliated to Shiraz University of Medical Sciences in the study period (2010-2016). Clinicopathological characteristics were extracted from the patients' clinical charts, which included symptoms, radiological findings, laboratory data, and surgical procedures as well as outcome.

### RESULTS

During these 7 years we identified 18 cases of incidental gall bladder cancer, consisted of 13 women and 5 men with the age range of 32 to 85 ( $62.5 \pm 14.2$ ) years detected after pathological study of the resected gall bladders among more than 4800 resected gall bladders. During the period, only two patients were operated on with the impression of gall bladder adenocarcinoma, which was not included in the study. Ten cases were T1 and eight were T2 at the time of surgery. They have been followed up for 1-7 years, during which, six cases of T2 died. All of the T1 cases are alive and symptom free.

### CONCLUSION

By increasing laparoscopic cholecystectomies in our center we observed 0.37% incidental cases of gall bladder adenocarcinoma. Preoperative diagnosis of this cancer in early stages is very difficult and needs high degree of suspicion. The most important predictor of prognosis is the stage of the cancer at the time of surgery. To the best of our knowledge, this is the first report of incidental gall bladder cancer from Iran.

### KEYWORDS:

Incidental, Gall bladder, Adenocarcinoma, Cholecystectomy

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## INTRODUCTION

Gallbladder cancer is relatively rare but constitutes the fifth most common gastrointestinal tract cancer and the most common cancer of the biliary system. Adenocarcinoma as the most common gall bladder malignancy harbors



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a poor prognosis. There are many cases of incidental gall bladder cancers operated on with the impression of benign diseases, mostly gall stones and cholecystitis.<sup>1</sup> There are some reports from different areas of the world regarding the percentage and characteristics of incidental gall bladder cancers among cholecystectomies performed with the primary impression of benign diseases.<sup>2</sup> In this study we discuss our experience in incidental gall bladder adenocarcinomas in our university-affiliated hospitals as the largest center of hepatobiliary surgery in south of the country and the first report from Iran.

## MATERIALS AND METHODS

During 7 years (2010-2016) a total of 4872 adult patients underwent cholecystectomy in the hospitals affiliated to Shiraz University of Medical Sciences. The patients were 1827 men and 3045 women with the mean  $\pm$  SD age of  $54 \pm 12$  years (range 29-81). Of them, 18 patients were diagnosed as having gallbladder adenocarcinoma after pathological studies of the surgical specimens. There were two more cases with the preoperative diagnosis of cancer, which were not included in this study. It means that more than 89% of the gall bladder cancers in our center were incidentally detected. Both gall bladder cancers with preoperative diagnosis (non-incidentals cases) were in advanced stages with liver metastasis at the time of operation.

All the clinical characteristics of these patients (including imaging findings, laboratory findings, and patients' follow-up) were extracted from the clinical charts.

## RESULTS

During the study period (2010-2016), there were 4872 patients who underwent cholecystectomy either by laparoscopy or open surgery with the clinical impression of cholelithiasis or cholecystitis. Of them, 18 (0.37%) patients were incidentally diagnosed as having gall bladder adenocarcinoma after pathological study of the surgical specimens. They were 13 female and 5 male patients. Age of them was from 32 to 85 ( $62.5 \pm 14.2$ ) years. All of the patients presented with right upper quadrant abdominal pain. There were three patients presented with abdominal pain and jaundice, one with abdominal pain and anorexia, and another with abdominal pain and weight loss. All of the patients were non-smoker with no history of alcohol consumption.

The mean WBC count and serum hemoglobin were 1300-21100 ( $9244 \pm 4838$ ) per mL and 8.2-13.3 ( $11.4 \pm 1.4$ ) gr/dL, respectively. Alkaline phosphatase, ALT (Alanine aminotransferase), and AST (Aspartate aminotransferase) were  $293.3 \pm 120.5$ ,  $62.5 \pm 67$ , and  $46.6 \pm 48.6$  IU/L, respectively. Table 1 shows the details of laboratory findings, clinical symptoms, and surgical treatment as well as survival in these 18 incidental gall bladder adenocarcinomas.

Imaging study before operation was ultrasonography in all of the 18 patients. In most of these 18 patients the gall bladders were normal in ultrasonography except in six patients in whom ultrasonography showed mild and insignificant gall bladder wall thickening. Eight patients had cholelithiasis as well. No polyp was found.

After pathological study and diagnosis, all of them were diagnosed as being moderately differentiated adenocarcinoma. After that, staging was done, which showed T1 in 10 patients and T2 in other 8 patients. In all of the patients with stage T2 re-operation was performed in less than 40 days after the primary cholecystectomy consisted of segmental hepatectomy, roux-en-y hepaticojejunostomy with or without hilar lymph node dissection. The patients were followed-up for 1 to 7 years. During these years, six patients died secondary to widespread cancer, bleeding, and other postoperative complications and the other 12 patients are still alive and symptom-free. Of the patients, all patients with T1 stage (10 cases) are alive and only two patients with stage T2 are alive at the time of study.

## DISCUSSION

Gall bladder adenocarcinoma is the most common malignancy of the biliary tract. Increasing laparoscopic cholecystectomies as the gold standard procedure have caused more and more detection of incidental gall bladder cancers.<sup>3</sup> Incidental gall bladder carcinoma has been defined as carcinoma of gall bladder detected for the first time after cholecystectomy and accidentally found on histological examination of the gall bladder.<sup>4</sup>

There are different reports about the frequency of incidental gall bladder adenocarcinoma in the patients who have undergone cholecystectomy for other reasons mostly benign lesions i.e. cholecystitis and cholelithiasis.<sup>1</sup> Table 2 shows the different reports about the percentages

**Table 1: Clinicopathological characteristics of 18 incidental gall bladder adenocarcinomas**

Age/ Sex	Symptom	Ultrasonography	1ALP	2ALT	3AST	4WBC	5Hb	Stage	Second Surgery	Follow-up
59/M	Abdominal Pain	Stones	270	46	44	5700	10.9	T2	Segmental hepatectomy, roux-en-y hepaticojejunostomy and hilar lymph node dissection	Expired 2 months after surgery
65/F	Abdominal Pain, constipation	Stones	175	14	15	21100	12.1	T1	-	Alive
85/M	Abdominal Pain, constipation	Wall thickening, stones	261	12	14	1300	12.2	T1	-	Alive
70/F	Abdominal Pain, constipation	Normal	195	87	54	10800	10.3	T1	-	Alive
59/F	Abdominal Pain	Normal	286	30	28	8100	13.3	T1	-	Alive
65/F	Abdominal Pain, jaundice	Wall thickening	302	143	101	11300	13.1	T2	Segmental hepatectomy, roux-en-y hepaticojejunostomy and hilar lymph node dissection	Expired 1 day after secondary surgery
75/F	Abdominal pain and anorexia	Wall thickening	529	21	31	5400	11.1	T2	Segmental hepatectomy, roux-en-y hepaticojejunostomy and hilar lymph node dissection	Alive
74/F	Abdominal Pain	Wall thickening	218	85	79	16.6	9	T1	-	Alive
53/F	Abdominal pain, weight loss	Wall thickening	309	21	9	9300	11.6	T2	Segmental hepatectomy, roux-en-y hepaticojejunostomy and hilar lymph node dissection	Expired 3 months after surgery
49/F	Abdominal Pain	Wall thickening	258	25	19	7400	10.9	T2	Segmental hepatectomy, roux-en-y hepaticojejunostomy and hilar lymph node dissection	Expired 1 day after secondary surgery
80/F	Abdominal Pain	Normal	163	49	23	10800	8.2	T2	Segmental hepatectomy, roux-en-y hepaticojejunostomy	Expired 1 day after secondary surgery
67/F	Abdominal Pain	Normal	492	187	142	5300	11.5	T1	-	Alive
59/M	Abdominal Pain	Normal	269	9	10	7400	12	T1	-	Alive
56/F	Abdominal Pain	Stones	280	251	181	14300	10.3	T2	Segmental hepatectomy, roux-en-y hepaticojejunostomy	Expired a few days after secondary surgery
32/M	Abdominal pain, jaundice	Stones	589	41	21	13100	12.8	T1	-	Alive
82/M	Abdominal Pain	Stones	257	61	22	7500	10.9	T1	-	Alive
55/M	Abdominal Pain	Stones	214	19	24	3700	12.9	T2	Segmental hepatectomy, roux-en-y hepaticojejunostomy and hilar lymph node dissection	Alive
74/F	Abdominal Pain	Stones	213	25	23	6300	13.7	T1	-	Alive

1 ALP = Alkaline Phosphatase (normal &lt; 360IU/L)

2 ALT = Alanine Aminotransferase (normal &lt; 40IU/L)

3 AST = Aspartate Aminotransferase (normal &lt; 40IU/L)

4 WBC = White Blood cell (normal = 3500-10000 /mL)

5 Hb = Hemoglobin (normal = male: 14-16 gr/dL, female = 12-14 gr/dL)

of incidental gall bladder adenocarcinoma from all over the world. Overall the percentages seem to be 0.2 - 2.5%

from different parts of the world. There is not a uniform distribution according to ethnic or geographic diversity.<sup>2-11</sup>

**Table 2: Different reports about the frequency of incidental gall bladder adenocarcinoma from different geographic areas of the world**

Country	Year	Author	Incidence
Brazil <sup>2</sup>	2015	Martins-Filho ED et al	0.34%
Italy <sup>3</sup>	2013	Panebianco A et al	0.5%
UK <sup>4</sup>	2015	Emmett CD et al	0.25%
Greece <sup>5</sup>	2013	Ioannidis O et al	0.2%
Bosnia and Herzegovina <sup>6</sup>	2010	Mitrović F et al	0.54%
Turkey <sup>7</sup>	2016	Düzköylü Y et al	0.2%
Korea <sup>8</sup>	2016	Ahn Y et al	1.5%
Nepal <sup>9</sup>	2011	Ghimire P et al	1.28%
Japan <sup>10</sup>	2008	Shimizu T et al	0.83%
India <sup>11</sup>	2014	Waghmare RS et al	2.59%
Current Study (IRAN)	2017	Geramizadeh B et al	0.37%

Radiological and clinical features of benign gall bladder disease can mask gall bladder adenocarcinoma, which causes mistaken diagnosis of cholelithiasis and cholecystitis instead of gall bladder cancer. The clinical features are very similar in early stages of cancer and benign diseases.<sup>4-9</sup>

The most common ultrasonographic finding in gall bladder cancer is wall thickening and it is very rare for gall bladder cancer to create a definite mass.<sup>12,13</sup> In our study only six cases out of the 18 incidental gall bladder cancers (30%) showed mild gall bladder wall thickening and in all the others, there was just cholelithiasis or completely normal gall bladder, which makes it impossible to diagnose a cancer based on sonographic findings before surgery.<sup>14,15</sup>

The diagnosis of gall bladder cancer by computed tomography (CT) is accurate and reliable; however the ability to identify early-stage cancer on CT is still not promising and its accuracy is about 85%.<sup>16</sup> Most of the incidental gall bladder cancers are early stage and in our cases also all of the incidental gall bladder adenocarcinomas were either T1 or T2. According to the recent consensus, simple or laparoscopic cholecystectomy is an adequate procedure for T1 stage. Radical surgery is necessary for T2 and higher stages using segmental hepatectomy as well as hilar lymphadenectomy.<sup>17-20</sup>

Despite the re-operation and extended surgery in T2 cases, their prognosis was poor and only 25% of them were alive and symptom free. It was the opposite to T1 cases for whom simple cholecystectomy was performed without re-operation and further procedure, but in the

follow-up period all were alive and symptom-free. It seems that stage of gall bladder cancers is the most important predictor of surgery after cholecystectomy.<sup>21</sup>

There is a limitation in our study as we did not have the body mass indexes of the patients to assess them as a risk factor.

## CONCLUSION

Incidental gall bladder adenocarcinoma is a rare event, and there is no definitely identifiable symptom and sign for prediction of this disease in the cases operated on with the impression of benign gall bladder diseases especially cholelithiasis and cholecystitis. Radiological findings including ultrasonography and CT would not add much information before surgery, in early stages of gall bladder cancer. The most important predictor of prognosis in incidental gall bladder cancer is the stage of the tumor. T1 cases have better prognosis even with simple or laparoscopic cholecystectomy.

## ETHICAL APPROVAL

There is nothing to be declared.

## CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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