ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

Incidental gallbladder cancer diagnosed during or after laparoscopic cholecystectomy in members of the Turkish population with gallstone disease

Volkan GENÇ[1], Elvan ONUR KIRIMKER[1], Cihangir AKYOL[1], Akın Fırat KOCAAY[1], Ayça KARABÖRK[2], Acar TÜZÜNER[1], Esra ERDEN[2], Kaan KARAYALÇIN[1]

Departments of [1]General Surgery and [2]Pathology, Ankara University, School of Medicine, Ankara

Background/aims: *Gallbladder cancer is a rare neoplasm. We report our experience with gallbladder cancer that was incidentally diagnosed during or after laparoscopic cholecystectomy performed for gallstone disease.* ***Material and Methods:*** *This study included all laparoscopic cholecystectomies due to gallstone disease undertaken from May 1999 to June 2010. Exclusion criteria were suspicion of malignancy and/or existence of gallbladder polyps detected with ultrasonography preoperatively. Patients with incidentally diagnosed gallbladder cancer were recorded, and the clinical and demographic characteristics of these patients were reviewed.* ***Results:*** *Of 5,382 patients in whom laparoscopic cholecystectomy was attempted, 5,164 were included in this study. Incidental gallbladder cancer was found in five patients, with a mean age of 66.2 years. The histological tumor stages were adenocarcinoma in situ in one patient, pT1b in one patient, pT2 in one patient, and pT3 in two patients. Two patients who underwent laparoscopic cholecystectomy alone underwent no additional surgery because of the low stage of the tumors. The three remaining patients, whose laparoscopic cholecystectomies were converted to open surgeries, underwent cholecystectomy, excision of the liver bed and lymph node dissection. The overall median survival time was 32 months.* ***Conclusion:*** *The incidence of incidental gallbladder cancer has been reported to vary, up to 2.85%. In this single-center study, the rate of incidental gallbladder cancer was found to be 0.09%. Female gender and advanced age are demographic risk factors for gallbladder carcinoma. Although gallbladder cancer is well known for its poor prognosis, tumors that are incidentally diagnosed are often found at an early stage and have a better prognosis.*

Key words: Cholecystectomy, gallbladder carcinoma, incidence, laparoscopy, prognosis

Safra taşı bulunan Türk popülasyon örneğinde laparoskopik kolesistektomi esnasında veya sonrasında tanı alan insidental safra kesesi kanseri

Amaç: *Safra kesesi kanserleri nadir kanserlerdir. Biz, safra taşı nedeniyle laparoskopik kolesistektomi yapılan hastalarda operasyon esnasında veya sonrasında saptadığımız insidental safra kesesi kanseri vakalarındaki deneyimlerimizi sunduk.* ***Yöntem:*** *Bu çalışmaya 1999 Mayıs ila 2010 Haziran tarihleri arasında safra taşı nedeni ile laparoskopik kolesistektomi geçiren tüm hastalar dahil edildi. Preoperatif dönemde yapılan ultrasonografide malignite şüphesi ve/veya polip saptanan hastalar çalışma dışı bırakıldı. İnsidental saptanan safra kesesi kanserleri kaydedildi ve bu hastaların klinik ve demografik karakteristikleri değerlendirildi.* ***Bulgular:*** *Laparoskopik kolesistektomi uygulanan 5382 hastadan 5164'ü çalışmaya dahil edildi. İnsidental safra kesesi kanseri 5 hastada saptandı ve ortalama yaş 66.2 idi. Histolojik tümör evresi 1 hastada adenokarsinoma in-situ, 1 hastada pT1b, 1 hastada pT2 ve 2 hastada da pT3 olarak bulundu. İki hastaya düşük tümör evresi nedeni ile yalnızca laparoskopik kolesistektomi uygulanırken, 3 hastada açığa dönüldü ve karaciğer yatak eksizyonu ile lenf nodu diseksiyonu uygulandı. Ortanca sağkalım süresi 32 ay olarak saptandı.* ***Sonuç:*** *Literatürde insidental safra kesesi kanseri insidansı %2.85'lere kadar rapor edilmiştir. Bu tek merkezli çalışmada ise %0.09 olarak saptandı. Kadın cinsiyet ve ileri yaş, safra kesesi kanserleri için demografik risk faktörleridir. Safra kesesi kanserlerinin kötü prognozu iyi bilinmesine rağmen, insidental saptanan safra kesesi kanserleri sıklıkla erken evrededir ve daha iyi prognozludur.*

Anahtar kelimeler: Kolesistektomi, safra kesesi kanseri, insidans, laparoskopi, prognoz

Address for correspondence: Volkan GENÇ
Department of General Surgery, Ankara University,
School of Medicine, Ankara, Turkey
Phone: +90 312 508 26 76
E-mail: volkan@medicine.ankara.edu.tr

Manuscript received: 11.10.2010 **Accepted:** 10.11.2010

Turk J Gastroenterol 2011; 22 (5): 513-516
doi: 10.4318/tjg.2011.0250

INTRODUCTION

Gallbladder cancer is the fifth most common gastrointestinal cancer (1). It is well known for its poor prognosis, and 15–30% of patients show no preoperative or intraoperative evidence of gallbladder cancer (2). Gallstone disease, porcelain gallbladder, sclerosing cholangitis, and advanced age are the best known risk factors for gallbladder cancer.

Laparoscopic cholecystectomy (LC) has been the gold standard treatment for gallstone disease for over two decades. LC performed for gallstone disease rarely results in a diagnosis of unexpected gallbladder cancer. In the English-language research literature, the incidence of gallbladder cancer diagnosed during or after LC is 0.2%-2.85% (3-11). In this single-center study, we report our experience with gallbladder cancer incidentally diagnosed during or after LC performed for gallstone disease.

MATERIALS AND METHODS

We evaluated the medical records of patients with gallstone disease who underwent LC in the Surgery Department of Ankara University Medical Faculty over the past 10 years. Routine preoperative assessment was performed in all patients, including liver biochemical assessment and abdominal ultrasonography of the hepatobiliary system. Exclusion criteria were suspicion of malignancy and/or existence of gallbladder polyps detected during preoperative ultrasonography. All operations were carried out by senior surgeons or trainees under supervision using the standard four-port, two-hand technique. Following direct 10 mm trocar insertion, a 13 mmHg CO2 pneumoperitoneum was created. Intraoperative cholangiograms and drains were used when necessary.

The presence of a nodular pattern and/or irregularity in the gallbladder wall during or after dissection was evaluated as a cause for suspicion of cancer. Tumor staging was based on the 7th edition of the American Joint Committee on Cancer (AJCC) manual (12). Recorded data included patient demographics, operative procedures, perioperative outcomes, tumor histopathology, follow-up, and long-term survival. Postoperative follow-up was done with clinical examination and determination of CA19-9 and carcinoembryonic antigen (CEA) levels, and ultrasound and computed tomography (CT) scans were performed regularly. Follow-up data were obtained for all patients by establishing contact with them and their treating physicians.

RESULTS

Of 5,382 patients in whom LC was attempted, 5,164 were included in this study. Patients with pathologically proven gallbladder polyps (n=202) and suspicion of malignancy before surgery (n=16) were excluded. The mean age of patients was 49.3±11.1 years (range: 16-89 years); 3,594 of them (69.6%) were female. An abnormal gallbladder wall was found intraoperatively in 98 patients (1.9%), while in the remaining 5,066 patients (98.1%), the morphologic appearance of the gallbladder was normal. Adenocarcinoma was diagnosed histopathologically in 5 cases (4 females, 1 male) out of 5,164 attempted LCs (0.09%). The mean age in this group was 66.2±14.2 years (range: 42-76 years) and was significantly higher than the mean age in the group of remaining patients ($p<0.001$). The male to female ratios in the group of patients with adenocarcinoma and the group of remaining patients (5,159 patients) were 1:4 and 1:2.3, respectively ($p>0.05$).

Demographic features and pathological results are shown in Table 1. All patients with adenocarcinoma presented with symptoms of acute cholecystitis but no jaundice on admission. Conversion to

Table 1. Patient characteristics and follow-up

Patient No.	Age (years)	Sex	Diagnosis	Stage	Operation	Outcome
1	76	F	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease, 7 m
2	75	F	Postoperatively	pTis	LC (no additional surgery)	No evidence of disease, 22 m
3	42	M	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 52 m
4	65	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 32 m
5	73	F	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	Died of MI, 15 m

F: Female. M: Male. LC: Laparoscopic cholecystectomy. OC: Open cholecystectomy. LBx: Excision of the liver bed. LND: Lymph node dissection. M: Months. MI: Myocardial infarction.

open surgery was required due to a diagnosis of malignancy on frozen section analysis in three of five patients. They underwent cholecystectomy, excision of the liver bed and lymph node dissection. In the remaining two patients, there was no suspicion of malignancy intraoperatively and routine histopathological studies revealed the diagnosis of gallbladder carcinoma. Only LC was performed and no additional surgery was necessitated because of the low stage of the tumors (adenocarcinoma *in situ* [pTis] and pT1b) in these patients. No retrieval bag was used to extract the gallbladder and there was no port site metastasis in these two patients.

The histological tumor stages were pTis in one patient, pT1b in one patient (Figure 1), pT2 in one patient and pT3 in two patients. None of the patients had pT4 disease or evidence of metastasis. The overall survival time ranged from 7 to 52 months (median: 32 months). One patient with a T3 tumor died of acute myocardial infarction during the postoperative 15th month, and no evidence of recurrent disease was present three months before he died. The remaining four patients are still alive and have no complaints and/or evidence of recurrent disease.

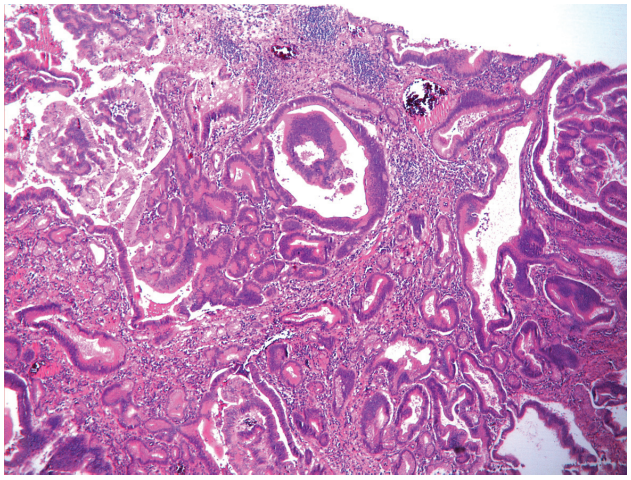

Figure 1. Microscopic appearance of gallbladder cancer (pT1b, hematoxylin-eosin, magnification x4).

DISCUSSION

Gallbladder cancer is known for its poor prognosis. The highest gallbladder cancer incidence rates have been reported in women from India, Chile and Pakistan (13). The incidence of incidentally diagnosed gallbladder cancer has been reported to vary, up to 2.85% (11). In recent years, the incidence of incidental diagnosis has increased, probably because of an increase in the number of elective cholecystectomies (14). In the present study, the rate of incidental gallbladder cancer diagnosis was found to be 0.09%. To the best of our knowledge, this is the lowest rate in the published English-language literature. The possible cause of this low incidence rate may be diagnoses at advanced stages caused by the avoidance of elective cholecystectomies in our population. Thus, all patients with adenocarcinoma presented with symptoms of acute cholecystitis. Three patients in our series had been diagnosed with gallstone disease before but had rejected elective cholecystectomies. If these patients had not had complaints caused by cholecystitis, they probably would have been diagnosed at an advanced stage.

Female gender and advanced age are demographic risk factors for gallbladder carcinoma (15). In the present study, the male to female ratio was found to be 1:4 in patients with incidentally diagnosed gallbladder cancer, and the mean age of this group was significantly higher than the mean age of the remaining patients. The median survival for the incidentally-found group has been reported to range from 8.1 to 68 months (Table 2) (3-10). In

Table 2. Patient and pathological characteristics of incidental gallbladder cancer series

Author	Year	N	Cancer (%)	Female/ Male ratio	Mean age	pTis, pT1	pT2, pT3,pT4	Median survival (months)
Sarli et al. (3)	2000	2300	9 (0.39)	6/3	62.3	4	5	12
Antonakis et al. (4)	2003	5539	11 (0.2)	8/3	57	0	11	8.1
Yamamoto et al. (5)	2005	1663	9 (0.54)	4/5	73	4	5	19
Shimizu et al. (6)	2006	1195	10 (0.84)	7/3	61.4	4	6	62.5
Kwon et al. (7)	2008	1793	38 (2.12)	21/17	66	20	18	68
Tantia et al. (8)	2009	3205	19 (0.59)	14/5	56	16	3	18.4
Choi et al. (9)	2009	3145	33 (1.05)	24/9	63	12	21	46.3
Zhang et al. (10)	2009	10466	20 (0.19)	16/4	65.7	8	12	43

the present study, the median survival time was 32 months, which compares favorably with previously reported survival times in the literature.

The therapeutic approach for gallbladder cancer was applied according to the stage of the tumors. In the present study, one patient with a pTis and one patient with a pT1b underwent simple cholecystectomies without any additional surgery. There was no suspicion of malignancy intraoperatively, and routine histopathological studies revealed the diagnosis of gallbladder carcinoma in these patients. When we examined the treatment of early stage tumors in the literature, cholecystectomy alone was a sufficient therapy for T1a tumors (7,16,17), but the possible necessity of further surgery for T1b tumors is under debate (7,16,18-23). Some authors have recommended simple cholecystectomy for T1b tumors (7,16,19,21), while others have recommended additional surgery including liver bed resection and lymph node dissection (20,22,23). Liver resection and regional lymphatic dissection should be performed for T2 tumors because nodal metastasis has been reported in up to 50% of cases (16). Furthermore, T3 tumors have also been treated in the same way as T2 tumors, but the long-term survival rate for patients with T3 tumors has been approximately 5% (22). We performed excision of the liver bed and lymph node dissection in addition to a cholecystectomy in one patient with T2 tumors and two patients with T3 tumors.

In conclusion, the incidence of incidental gallbladder cancer has been reported to vary, up to 2.85%. In this single-center study, the rate of incidental gallbladder cancer was found to be 0.09%. Female gender and advanced age are demographic risk factors for gallbladder carcinoma. Although gallbladder cancer runs a short course with a poor prognosis, incidentally diagnosed tumors are often found in early stages and have a better prognosis.

Acknowledgements: *The authors wish to extend a sincere thank you for assistance in completing this project to the staff of the Pathology Department at Ankara University. The authors did not receive any funding for this project.*

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin 2006; 56: 106-30.
2. Frauenshuh D, Greim R, Kraas E. How to proceed in patients with carcinoma detected after laparoscopic cholecystectomy. Langenbecks Arch Surg 2000; 385: 495-500.
3. Sarli L, Contini S, Sansebastiano G, et al. Does laparoscopic cholecystectomy worsen the prognosis of unsuspected gallbladder cancer? Arch Surg 2000; 135: 1340-4.
4. Antonakis P, Alexakis N, Mylonaki D, et al. Incidental finding of gallbladder carcinoma detected during or after laparoscopic cholecystectomy. Eur J Surg Oncol 2003; 29: 358-60.
5. Yamamoto H, Hayakawa N, Kitagawa Y, et al. Unsuspected gallbladder carcinoma after laparoscopic cholecystectomy. J Hepatobiliary Pancreat Surg 2005; 12: 391-8.
6. Shimizu T, Arima Y, Yokomuro S, et al. Incidental gallbladder cancer diagnosed during and after laparoscopic cholecystectomy. J Nippon Med Sch 2006; 73: 136-40.
7. Kwon AH, Imamura A, Kitade H, Kamiyama Y. Unsuspected gallbladder cancer diagnosed during or after laparoscopic cholecystectomy. J Surg Oncol 2008; 97: 241-5.
8. Tantia O, Jain M, Khanna S, Sen B. Incidental carcinoma gall bladder during laparoscopic cholecystectomy for symptomatic gall stone disease. Surg Endosc 2009; 23: 2041-6.
9. Choi SB, Han HJ, Kim CY, et al. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. World J Surg 2009; 33: 2657-63.
10. Zhang WJ, Xu GF, Zou XP, et al. Incidental gallbladder carcinoma diagnosed during or after laparoscopic cholecystectomy. World J Surg 2009; 33: 2651-6.
11. Mori T, Souda S, Hashimoto J, et al. Unsuspected gallbladder cancer diagnosed by laparoscopic cholecystectomy: a clinicopathological study. Surg Today 1997; 27: 710-3.
12. Edge SB, Byrd DR, Compton CC, et al., eds. AJCC cancer staging manual. 7th ed. New York: Springer, 2010; 347-77.
13. Goldin R, Roa J. Gallbladder cancer: a morphological and molecular update. Histology 2009; 58: 218-29.
14. Steinert R, Nestler G, Sagynaliev E, et al. Laparoscopic cholecystectomy and gallbladder cancer. J Surg Oncol 2006; 93: 682-9.
15. Furlan A, Ferris JV, Hosseinzadeh K, Borhani AA. Gallbladder carcinoma update: multimodality imaging evaluation, staging, and treatment options. AJR Am J Roentgenol 2008; 191: 1440-7.
16. Yamaguchi K, Chijiiwa K, Saiki S, et al. Retrospective analysis of 70 operations for gallbladder carcinoma. Br J Surg 1997; 84: 200-4.
17. Yildirim E, Celen O, Gulben K, Berberoglu U. The surgical management of incidental gallbladder carcinoma. Eur J Surg Oncol 2005; 31: 45-52.
18. You DD, Lee HG, Paik KY, et al. What is an adequate extent of resection for T1 gallbladder cancers? Ann Surg 2008; 247: 835-8.
19. Wakai T, Shirai Y, Yokoyama N, et al. Early gallbladder carcinoma does not warrant radical resection. Br J Surg 2001; 88: 675-8.
20. Principe A, Del Gaudio M, Ercolani G, et al. Radical surgery for gallbladder carcinoma: possibilities of survival. Hepatogastroenterology 2006; 53: 660-4.
21. Puhalla H, Wild T, Bareck E, et al. Long-term follow-up of surgically treated gallbladder cancer patients. Eur J Surg Oncol 2002; 28: 857-63.
22. Cubertafond P, Gainant A, Cucchiaro G. Surgical treatment of 724 carcinomas of the gallbladder. Results of the French surgical association survey. Ann Surg 1994; 219: 275-80.
23. Varshney S, Buttirini G, Gupta R. Incidental carcinoma of the gallbladder. Eur J Surg Oncol 2002; 28: 4-10.