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A single centre experience and literature review

Ann. Ital. Chir., 2013 84: 281-285
Published online 8 October 2012
pii: S0003469X12019781
www.annitalchir.com

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Preneoplastic and neoplastic gallbladder lesions occasionally discovered after elective videocholecystectomy for benign disease. A single centre experience and literature review

INTRODUCTION: *In this study we retrospectively reviewed data on 311 consecutive elective cholecystectomies, performed for benign disease (cholelithiasis, cholecystitis) in our institution in the last six years, in order to determine the frequency of unexpected gallbladder pre-neoplastic and neoplastic lesions and analyse their clinical, diagnostic and therapeutic features.*
MATERIALS AND METHODS: *Three hundred eleven consecutive patients underwent elective cholecystectomy for benign gallbladder disease in our Institution from January 2005 to March 2011. Clinical records and histo-pathological reports were reviewed in order to detect occult gallbladder pre-neoplastic and neoplastic lesions and describe the clinical, diagnostic and therapeutic findings. Eight patients were excluded for lacking of important clinical data.*
RESULTS: *Out of 303 patients examined, 26 (8.6%) were found to be affected by a concomitant pre-neoplastic or neoplastic lesion. Ten (3.3%) were found to have a benign lesion, 13 (4.3%) a dysplasia of the gallbladder epithelium and 3 (1%) a gallbladder adenocarcinoma.*
DISCUSSION: *Dysplasia was found in 4,3% of cases and surgery represents the interruption of an eventual malignant evolution. Adenomiomatosis and adenomas represent the most frequent benign occult lesions discovered; surgery is the definitive cure for such lesions. Occult gallbladder adenocarcinoma was detected in 1% of cases in absence of any preoperative clinical or radiological suspect. Cholecystectomy is curative in stage T1a disease, while a re-resection is necessary for more invasive non metastatic disease.*

KEY WORDS: Cholecystectomy, Cholelithiasis, Dysplasia, Gallbladder cancer, Gallbladder stones

Introduction

Cholecystectomy for benign disease represents one of the most frequent surgical operations in modern surgery. Colelithiasis is the pathology that more often leads to cholecystectomy and may mask other clinical conditions such as benign or malignant neoplasms [1]. These conditions are characterized by a non-specific clinical presentation and even the most recent imaging techniques present several limitations to detect them, especially in early stages. As a consequence it is not rare the discovering of preneoplastic or neoplastic lesions by histopathologic examination of cholecystectomy specimens of patients operated on for benign non neoplastic disease. In this study we retrospectively reviewed our experience on gallbladder surgery in order to determine the frequency of unexpected neoplasms, to analyse clinical, diagnostic and therapeutic features and to compare them with data published in recent literature.

Pervenuto in Redazione Maggio 2012. Accettato per la pubblicazione Luglio 2012
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Materials and Methods

Three hundred eleven consecutive patients underwent elective cholecystectomy for benign gallbladder disease at the Institute of Surgical Pathology of the University of Sassari from January 2005 to March 2011. The mean age of the patients was 56 years (range 13 - 90). One hundred thirteen patients were males and 198 were females (male to female ratio: 1 - 1.75). Clinical data and histopathological reports were retrospectively reviewed and 8 patients were excluded for lacking of complete clinical records.
Out of the remaining 303 patients, 257 underwent a videolaparoscopic cholecystectomy (VLC), while 46 patients underwent an open procedure.
Videolaparoscopic operations were performed by creating a pneumoperitoneum with a Verres needle or by surgical placement of the first trocar of 11,2 mm in paraumbilical position. Another trocar of the same dimension was placed in epigastrium and one or two trocars of 5mm in the right lateral region of the abdomen. Once resected eventual adhesions, the cystic duct and artery were detected, isolated and clipped and then the gallbladder was excised bottom-up. A 20F tube was placed in all cases in proximity of the gallbladder bed. Upon 46 laparotomic procedures 12 were conversions of VLC operations (tenacious adhesions, empyema, anatomical variability) while the remaining 34 cholecystectomies were performed during laparotomic surgery for other disease such as pancreatic tumors and colon cancer. Open cholecystectomy was performed with the classic anterograde technique and a 20F tube was placed in the gallbladder bed at the end of the procedure in all cases. All surgical operations were performed by senior surgeons or surgeons in training under supervision by an experienced surgeon. The specimens were routinely sent for pathological examination.

Results

Among 303 patients examined, 26 (8,6%) were found to be affected by a concomitant pre-neoplastic or neoplastic lesion. Thirteen patients (4.3%) had a dysplasia of the gallbladder epithelium and ten (3.3%) a benign lesion, while three (1%) were found to have a gallbladder carcinoma (GBC).
The mean age of patients with dysplasia was 65,6 years and the male to female ratio was 1.2 - 1. In nine cases (69.2%) low grade dysplasia was present and in four (30.8%) high grade dysplasia. Among the patients with a benign lesion occasionally discovered seven (70%) had adenomyomatosis, two patients (20%) had tubular gallbladder adenomas and one (10%) had a fibrous polyp. The mean age of these patients was 50,3 years and the male to female ratio 1 - 1.
Two of the patients found affected of GBC were females and one was male. Two of them underwent open cholecystectomy, during laparotomy for other disease. The first patient underwent a Whipple procedure for pancreatic cancer and a IA stage (T1aN0M0) gallbladder adenocarcinoma was discovered. There was no evidence of such lesion in preoperative ultrasonography (US) and Computed Tomography (CT) scan employed for the diagnosis and staging of the pancreatic tumor. The patient did not have further surgery and underwent adjuvant chemotherapy for the pancreatic tumor. He died 29 months after surgery for recurrence of the pancreatic cancer.
The second patient underwent VLC for cholelithiasis and a stage IIA (T3N0M0) GBC was found, in absence of any specific clinical or US preoperative evidence. The patient underwent surgical re-resection (wedge hepatectomy and lymphadenectomy) and she died 23 months after re-operation for relapse of the disease.
The third patient, a 80 years old lady, underwent cholecystectomy for cholelithiasis during an open right hemicolectomy for colon cancer. She had a stage IIB (T3N1M0) GBC and as in the previous cases no preoperative clinical or imaging evidence of such tumor. She refused a second surgical operation. She's alive after 9 months of follow up.

Discussion

Cholecystectomy represents one of the most common abdominal surgical operations performed, particularly after the introduction of the videolaparoscopic method. In the USA the annual incidence of gallbladder diseases is estimated about one million cases and among them more than 500.000 undergo surgery [1]. Gallstones disease is the most frequent cause of gallbladder surgery and represents even a risk factor for GBC, probably promoting a sequence of epithelial alterations due to persistent local irritation and inflammation [2].
Gallbladder epithelial dysplasia represents the most diffusely accepted pre-neoplastic lesion for gallbladder cancer. Generally it arises in a background of metaplasia and shares the same epidemiological and molecular features with carcinomas. This suggests that the natural history of gallbladder cancer starts with metaplasia, evolving to dysplasia and subsequently to cancer.
Microscopically dysplasia is classified as *low grade* when resembling a colonic tubular adenoma with cigar – shaped nuclei, while the presence of abnormally polarized, apically oriented nuclei with prominent nucleoli and nuclear contour irregularities is named *high grade* dysplasia. This condition is also named *"carcinoma in situ"* to emphasize the tendency for malignant progression. In our experience 13 patients found affected from dysplasia and among them four presented a high grade lesion. These patients may develop a gallbladder cancer and cholecystectomy eliminated this possibility. It is possible to hypothesize that the

diffusion of videolaparoscopic procedures in surgical practice may reduce the incidence of gallbladder carcinomas, interrupting the progression of a number of lesions from metaplasia to cancer.

Gallbladder adenomas are uncommon polypoid lesions which arise on normal mucosa. They occur more frequently in adult women. Adenomas are classified as tubular, papillary or tubulopapillary type. The latter is characterized by at least 20% of papillary structure with at least 20% tubular component. Dysplasia is frequently present in adenomas, more commonly in larger ones, but a genetic comparison with carcinomas demonstrates that they represent two distinct entities. For example p16 and p53 are uncommon in adenomas, but very frequent in carcinomas. These data and the epidemiological behavior of such lesions suggest that carcinomas do not arise from adenomas. Cholecystectomy represents the definitive cure for gallbladder adenomas.

Gallbladder cancer was first described in 1777 by M.Stoll who reported a small autoptic series of 3 cases and represents the most frequent malignancy of the biliary tract [3]. In some geographic areas, such as Chile, Poland, India, and Japan, it presents a consistently higher incidence [4]. In the United Kingdom and in the United Sates the incidence rates are lower than 2/100.000 [5]. However, interesting variations are registered within a country involving certain ethnic subgroups: native American females in New Mexico present an annual incidence of 14.5/100.000 [6], while in India the incidence rates are significantly higher in the north than in the south[7]. Women are more commonly affected than men with a male to female ratio ranging from 1:3 to 1:6 [2]. One study in Punjab reports gallbladder cancer as the most frequent gastrointestinal cancer in females [8]. The peak incidence of gallbladder cancer is observed in the 6th and 7th decades of life. However, sporadic cases in child or infants have been reported [9]. The prognosis of gallbladder cancer is poor in advanced stages, with less than 5% five years survival rate [10]. A great improvement in five years survival rates up to 90% -100% has been registered in recent times in early stage gallbladder carcinoma [11].

Gallbladder cancer is frequently diagnosed at an advanced stage due to its aggressiveness and atypical clinical presentation which may mimic a benign condition, such as acute cholelithiasis or chronic cholecystitis. For this reason cancer often represents an incidental finding during cholecystectomy for gallbladder stones or during laparotomy for other abdominal disease. The incidence of casually discovered GBC varies considerably in the literature, ranging from 0,17 to 47% [1,12,13]. Such variability may depend on several factors like geographic and epidemiological differences, surgical and pathological policies, retrospective data collection and study design. In our experience occult GBC was detected in 1% of cases.

In patients with clinical evidence of GBC pain, nausea and vomiting, jaundice and a mass detected on ultrasound represent the most frequent findings. Further imaging with Computed Tomography (Total Body) and/or Magnetic Resonance Cholangiography is necessary generally to determine the anatomic extension of the lesion and to evaluate for hepatic, vascular and/or biliary invasion. Other techniques such as Endoscopic Retrograde Colangiopancreatography (ERCP), Percutaneous Transhepatic Cholangiography (PTC) and Positron Emission Tomography may add useful information for the preoparative assessment of the patient. These techniques are also employed for the evaluation of occasionally discovered GBC in order to asses further surgical resection or follow up.

Once an occult GBC is discovered after cholecystectomy the patient must be informed, a staging program must be planned and the surgical strategy must be defined, eventually in the contest of a multidisciplinary treatment. The patient's general conditions must also be evaluated in the light of a greater surgical operation. This was the strategy we adopted in one case of stage IIA disease discovered after cholecystectomy; the patient underwent successfully wedge hepatectomy and lymphadenectomy immediately after the conclusion of the preoperative evaluation and staging. There is no evidence on the best timing to perform re-operation after cholecystectomy, but we advocate an early approach, once preoperative assessment is completed, in order to avoid neoplastic growth and peritoneal or port dissemination and the psychological consequences of a long waiting [14].

The possibility to find a GBC in a patient with a benign gallbladder disease, imposes some presuppositions in relation to the surgical approach: a) the surgeon must be ready and prepared to convert an initial surgical operation for benign disease in a larger resection for cancer which includes lymphadenectomy of the porta hepatis, gastro-hepatic ligament and retro-duodenal regions, b) inspection of the gallbladder walls must be performed for abnormalities such as thickening or ulceration, c) damage of the gallbladder wall during cholecystectomy must be avoided, d) once dissected, the gallbladder must be removed employing an endo-bag and any contact with the port sites must be avoided, e) the specimen must routinely be sent for pathological examination.

Some authors believe that frozen sections must be done in specimens with macroscopic characteristics suspicious for malignancy [15] but others demonstrated that this policy is not suitable [16] and only a small amount of suspicious gallbladders had cancer. Probably this depends on the criteria used to define the suspect of malignancy. When the aspect of the gallbladder or its bed or the liver itself present a morphology suggesting the presence of cancer a frozen section must be performed in order to convert the operation and complete surgery in a single stage. In the other hand a two stages approach offers the possibility for an accurate preoperative evaluation of the patient and staging of the disease, avoiding aggressive or non-complete resections in non resectable cancers.

In substance the surgical strategy is the same when diagnosis is obtained before cholecyctectomy and when the occult carcinoma is discovered after cholecyctectomy, with the exception that in the later case the gallbladder has been removed. The aim of surgery is always R0 resection. When such result is reached by the simple cholecystectomy (Tis - T1a stage) further surgery is not necessary and a careful follow up program must be planned[17]. This was the strategy we chose in our patient with early stage disease and no recurrence was observed (the patient died for recurrence of pancreatic cancer). When cholecystectomy does not guarantee an R0 resection of a resectable cancer and absence of metastasis was ruled out, further surgery must be planned, considering hepatectomy and lymphadenectomy. Controversy exists on the optimal treatment of T1b disease; some authors demonstrated that survival after simple cholecystectomy was comparable to that after radical cholecystectomy, while others demonstrate high rates of loco-regional recurrences and lower survival rates in patients treated with simple cholecystectomy [18-20]. No effective adjuvant therapies are available, but some authors report encouraging results using radiotherapy and chemotherapy combined, even if in small series[21]. Furthermore, enrollment of patient for better designed studies on adjuvant therapies is necessary.

Conclusions

Dysplasia was found in 4,3% of cases and surgery represents the interruption of an eventual malignant evolution. Adenomiomatosis and adenomas represent the most frequent benign occult lesions discovered; surgery is the definitive cure for such lesions. Occult gallbladder adenocarcinoma was detected in 1% of cases in absence of any preoperative clinical or radiological suspect.
Cholecystectomy is curative in stage T1a disease, while a re-resection is necessary for more invasive non metastatic disease.

Riassunto

La colecistectomia rappresenta oggi uno degli interventi chirurgici più frequenti in chirurgia generale. La causa più frequente è la colelitiasi, condizione che a volte maschera la presenza di lesioni neoplastiche benigne o maligne della colecisti. Queste ultime spesso si presentano clinicamente con un corteo sintomatologico aspecifico e anche le tecniche di imaging più moderne presentano diverse limitazioni nel loro riconoscimento. In questo studio abbiamo retrospettivamente esaminato i dati clinici ed anatomopatologici di 311 pazienti consecutivi sottoposti a colecistectomia per patologia benigna della colecisti presso il nostro Istituto negli ultimi 6 anni e confrontato la nostra esperienza con quanto riportato in letteratura. Sono stati identificati 26 casi (8.6%) di lesioni benigne, premaligne e maligne occulte agli esami preoperatori. Tra queste 10 (3.3%) erano benigne, con l'adenomiomatosi rilevantesi la più frequente, 13 (4.3%) erano lesioni displasiche e 3 (1%) adenocarcinomi. La chirurgia rappresenta la cura definitiva per le lesioni benigne e premaligne, come del resto per gli adenocarcinomi in situ ed in stadio T1a. Per i tumori resecabili in stadi più avanzati l'allargamento della resezione è necessario per migliorare la prognosi.

References

1. Murshid KR: *Asymptomatic gallstones: Should we operate?* Saudi J Gastroenterol, 2007; 13:57-69.

2. Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, Alonso de Ruiz P, Aristi Urista G, Nervi F: *Epidemiology and molecular pathology of gallbladder cancer.* CA Cancer J Clin, 2001; 51:349-64.

3. Solan MJ, Jackson BT: *Carcinoma of the gall-bladder. A clinical appraisal and review of 57 cases.* Br J Surg, 1971; 58:593-97.

4. Randi G, Franceschi S, La Vecchia C: *Gallbladder cancer worldwide: geographical distribution and risk factors.* Int J Cancer, 2006; 118:1591-602.

5. Miller G, Jarnagin WR: *Gallbladder carcinoma.* Eur J Surg Oncol, 2008; 34:306-12.

6. Barakat J, Dunkelberg JC, Ma TY: *Changing patterns of gallbladder carcinoma in New Mexico.* Cancer, 2006; 106:434-40.

7. Indian Council of Medical Research (ICMR). *Annual report of population based cancer registries of the National Cancer Registry Programme (1993).* New Delhi: ICMR Publication, 1996: 18.

8. Aziz Z, Sana S, Saeed S, Akram M: *Institution based tumor registry from Punjab: Five year data based analysis.* J Pak Med Assoc, 2003; 53:350-53.

9. Rudolph R, Cohen JJ: *Cancer of the gallbladder in an 11-year-old Navajo girl.* J Pediatr Surg, 1972; 7:66-67.

10. Lai CH, Lau WY: *Gallbladder cancer. A comprehensive review.* Surgeon, 2008; 6:101-10.

11. Misra S, Chaturvedi A, Misra NC: *Gallbladder cancer.* Curr Treat Options Gastroenterol, 2006; 9:95-106.

12. Ata ur Rahman, Syed Murad Ali Shah, Nadeem Khan, Attaullah Arif, Asadullah, Muzaffar uddin Sadiq: *Frequency of carcinoma gallbladder in patients undergoing surgery for chronic cholecystitis with cholelithiasis.* J Med Sc, 2006; 14:1.

13. Duffy A, Capanu M, Abou-Alfa GK et al.: *Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Center (MSKCC).* J Surg Oncol, 2008; 98:485-89.

14. Napolitano L, Artese L, Innocenti P: *Seeding from early stage gallbladder carcinoma after laparoscopic cholecystectomy.* Ann Ital Chir, 2001; 72:721-24.

15. Frauenshuh D, Greim R, Kraas E: *How to proceed in patients with carcinoma detected after laparoscopic cholecystectomy.* Langenbecks Arch Surg, 2000; 385:495-500.

16. Antonakis P, Alexakis N, Mylonaki D, Leandros E, M Konstadoulakis M, Zografos G, Androulakis G: *Incidental finding of gallbladder carcinoma detected during or after laparoscopic cholecystectomy.* Eur J Surg Oncol, 2003; 29:358-60.

17. Pilgrim C, Usatoff V, Evans PM: *A review of the surgical strategies for the management of gallbladder carcinoma based on T stage and growth type of the tumour.* Eur J Surg Oncol, 2009; 35:903-07.

18. Wakai T, Shirai Y, Yokoyama N, Nagakura S, Watanabe H, Hatakeyama K: *Early gallbladder carcinoma does not warrant radical resection.* Br J Surg, 2001; 88:675-78.

19. Kimura W, Shimada H: *A case of gallbladder carcinoma with infiltration into the muscular layer that resulted in relapse and death from metastasis to the liver and lymph nodes.* Hepatogastroenterology, 1990; 37:86-89.

20. Principe A, Del Gaudio M, Ercolani G, Golfieri R, Cucchetti A, Pinna AD: *Radical surgery for gallbladder carcinoma: Possibilities of survival.* Hepatogastroenterology, 2006; 53:660-64.

21. 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; 52:167-75.