Langenbeck's Archives of Surgery (2019) 404:573–579
https://doi.org/10.1007/s00423-019-01800-2

ORIGINAL ARTICLE

Prospective multi-center study of surgeon's assessment of the gallbladder compared to histopathological examination to detect incidental malignancy

Yurdakul Deniz Firat[1] · Ufuk Oguz Idiz[2] · Coskun Cakir[2] · Erkan Yardimci[3] · Pinar Yazici[4] · Huseyin Bektasoglu[3] · Emre Bozkurt[4] · Ramazan Ucak[5] · Zuhal Gucin[6] · Taskin Uresin[7] · Mustafa Hasbahceci[8]

Received: 10 March 2019 / Accepted: 13 June 2019 / Published online: 11 July 2019

Abstract

Purpose Routine histopathological examination after cholecystectomy for gallstones is performed despite the low rates of incidental findings of malignancy. The aim of this study was to assess predictive values of macroscopic examination of cholecystectomy specimens by surgeons in gallstone disease.

Methods A prospective multi-center diagnostic study was carried out between December 2015 and March 2017 at four different centers. All patients undergoing cholecystectomy for gallstone disease were consecutively screened for eligibility. Patients whose ages are 18 to 80 years, and preoperative imaging findings without any pathology except cholelithiasis were included. The gallbladder was first evaluated macroscopically ex situ by two operating surgeons and rated as macroscopically benign (group S1), suspicious for a benign diagnosis (group S2), and suspicious for malignancy (group S3). Thereafter, a pathologist made a final histopathological examination whose results are grouped as chronic cholecystitis (group P1), benign or precancerous lesions in which only cholecystectomy is the adequate treatment modality (group P2), and carcinoma (group P3). Diagnostic accuracy of the surgeon's assessment to the histopathological examination was evaluated using sensitivity, specificity, positive and negative predictive values, and accuracy, and correlated by a kappa agreement coefficient.

Results A total of 1112 patients were included in this trial. The specificity rates were 96.5%, 100%, and 98.7% for group S1-group S2, group S1-group S3, and group S2-group S3, respectively. Accuracy rates to detect malignancy were 100% and 95. 2% for group S1 and group S2, respectively. Kappa coefficient values were 1.0 and 0.64 for group S1-group S3 and group S2-group S3, respectively ($p < 0.001$ for both).

Conclusion Assessment of the gallbladder specimen and selective histopathological examination may be adequate after cholecystectomy for gallstone diseases. Such a procedure would have the potential to reduce costs and prevent unnecessary loss of labor productivity without affecting patients' safety. However, higher number of patients in more centers is needed to confirm this hypothesis.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00423-019-01800-2) contains supplementary material, which is available to authorized users.

✉ Ufuk Oguz Idiz
oguzidiz@yahoo.com

Yurdakul Deniz Firat
drydf@yahoo.com

Coskun Cakir
c_cakir@hotmail.com

Erkan Yardimci
drerkanyardimci@yahoo.com

Pinar Yazici
drpinaryazici@gmail.com

Huseyin Bektasoglu
hkbektasoglu@yahoo.com

Emre Bozkurt
dr.emrebozkurt@gmail.com

Ramazan Ucak
drramazanucak@hotmail.com

Zuhal Gucin
zgucin@yahoo.com

Taskin Uresin
erkinuresin@hotmail.com

Mustafa Hasbahceci
hasbahceci@yahoo.com

Extended author information available on the last page of the article

Keywords Histopathological examination · Cholecystectomy · Gallbladder Cancer · Cholelithiasis

Introduction

Cholecystectomy is a frequently performed procedure for benign biliary diseases such as cholelithiasis and biliary colic; however, instances of malignancy are rare [1]. Although gallbladder cancers are the most common biliary malignancies found worldwide, malignancy rates in patients undergoing cholecystectomy are reported to be between only 0.2 and 2% [2–5]. This already low rate falls further to 0.1–1.2% in patients with no preoperative suspicion of malignancy [6, 7]. Despite these low percentages, many centers still undertake routine histopathological examinations to exclude the possibility of malignancy [8].

Approximately half of gallbladder cancers are diagnosed in the preoperative period as a result of local symptoms and metastases, while the remainder is incidentally detected after cholecystectomy [9, 10]. However, this routine histopathological examination of materials removed during cholecystectomy has become the subject of discussion in recent years [11–13]. Conversely, other authors support routine histopathological examination as a crucial step in maximizing treatment options, especially considering the aggressive nature of gallbladder malignancies and their detection as advanced-stage malignancies [2]. On the one hand, several authors contend that routine histopathological examination is unwarranted and that only materials from selected cases should be sent to the pathology lab. They suggest that this detailed examination is only of benefit in cases where a suspicion of malignancy has already been determined in preoperative radiological evaluation [11, 12, 14]. A further recommendation is that in addition to preoperative imaging, manual examination of the matter by the operating surgeon can suffice, without recourse to systematic histopathological assessment [13]. Therefore, we hypothesize that manual inspection and examination of the specimens by the surgeons immediately after the surgery may help to detect suspicious lesions and to prevent overloading of the pathology laboratories due to the specimens that are usually considered as normal.

The aim of this study is to compare the macroscopic evaluations of cholecystectomy specimens in gallstone disease with their corresponding histopathological examinations.

Materials and methods

This prospective multi-center study was performed between December 2015 and March 2017 at four different hospitals, after approval of the local Human Ethics Committee. Informed consent was obtained from all participating patients, including those with non-inflamed cholelithiasis. Clinical trials registration was carried out (ClinicalTrials.gov Identifier: NCT02654873).

For the purposes of our study, we consecutively included patients aged between 18 and 80 years and suffering from cholelithiasis. As the main preoperative imaging finding, all reports within normal limits except cholelithiasis were considered. Our exclusion criteria comprised patients with acute cholecystitis, perforated gallbladder, malignancy, polyps in the gallbladder, increased gallbladder wall thickness, signs of gallbladder malignancy in preoperative ultrasonography, and those younger than 18 years old or pregnant.

Cholecystectomy was performed by eight different surgeons, who had already completed at least 100 cholecystectomy operations as the learning curve prior to the study using either laparoscopic or open surgical techniques consecutively. As a general policy, two surgeons attended to all operations. The pathology specimens were evaluated macroscopically by two experienced surgeons, using a longitudinal incision to the gallbladder, before being immediately immersed in formalin. The specimens were classified according to this macroscopic evaluation by two operating surgeons as macroscopically benign (group S1), suspicious for a benign diagnosis (group S2), and suspicious for malignancy (group S3). Before the initiation of the study, a schedule including criteria used for grouping of the specimens was sent to the surgeons performing surgeries. The suspicious for a benign diagnosis group included conditions such as an increased thickness of the gallbladder wall, cystic lesions, fibrotic changes on the mucosa or the wall of the gallbladder, and calcifications or polyps in the gallbladder, whereas the suspicious for malignancy group included any with detected mass or irregularities in the gallbladder wall.

The specimens were sent for histopathological examination in the center where the patient underwent surgery. Three blocks were taken, in which cross sections of the neck, the body, and the fundus of the gallbladder and their representative parts of the wall were included for microscopy. The presence of inflammation (chronic cholecystitis, xanthogranulomatous cholecystitis), non-tumoral pathologies (intestinal metaplasia, gastric metaplasia, mucocele), benign gallbladder tumors (cholesterol polyps, adenomyosis), dysplasia, and malignancy (gallbladder adenocarcinoma) were reported. The results of pathology reports were grouped as chronic cholecystitis (group P1), benign or precancerous lesions in which only cholecystectomy is the adequate treatment modality (intestinal metaplasia, gastric metaplasia, mucocele, xanthogranulomatous cholecystitis, cholesterol polyps, adenomyosis, and dysplasia) (group P2), and carcinoma

(group P3). Finally, pathology reports for the specimens were compared with the groups allocated by the surgeons.

Additionally, age, sex, and grade of gallbladder cancer, if present, were noted. The cancer staging was performed according to the 7th edition of the American Joint Committee on Cancer (AJCC) [15].

Results of the histopathological studies were regarded as the reference point for the macroscopic evaluation of the specimens by the surgeons. Identification of malignancy in the cholecystectomy specimens by the macroscopic evaluation by the surgeons was the main outcome.

Statistical analysis

Descriptive statistical methods (mean with standard deviation and frequency with percentage) were used during the assessment of the study data. Observed agreement, sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and accuracy were calculated for the macroscopic evaluation by the surgeons based on the results of the histopathological studies. For this purpose, three different analyses were performed between group S1, group S2, and group S3 as group S1-group S2, group S1-group S3, and group S2-group S3. The measure of agreement among groups was evaluated via kappa coefficient. Kappa coefficient (κ) less than 0.20 was defined as weak, 0. 21–0.40 was defined as acceptable, 0.41–0.60 was defined as moderate, 0.61–0.80 was defined as good, and greater than 0.80 was defined as very good when determining the degree of compliance. The results were evaluated by a biostatistics expert using SPSS 21.0 (IBM, Armonk, NY, USA) at the 95% confidence level and $p < 0.05$ significance level.

Results

The population of this study was drawn from 1624 patients who underwent cholecystectomy for gallstone disease between December 2015 and March 2017. A total of 512 patients (31.5%) were excluded from the study: 217 with acute cholecystitis or gallbladder perforation, 194 with previously known polyps in the gallbladder, 95 with preoperative gallbladder wall thickness, and six with a diagnosis of gallbladder malignancy in the preoperative period. The remaining 1112 patients were included in the study (Fig. 1).

The mean age of the participants was 49.3 years, and the female/male ratio was 3.21. Laparoscopic, open, and converting to open cholecystectomy rates were 97%, 0.8%, and 2.3%, respectively. Results of macroscopic examination of the cholecystectomy specimens by the surgeons and histopathological examination results are given in Table 1.

According to histopathological examination, chronic cholecystitis was the most common pathology (74%, *n* 823); intestinal metaplasia was observed in 99 patients (8.9%), and primary incidental gallbladder malignancy was observed in seven patients (0.6%). Histopathological examination revealed dysplasia at a rate of 2.8% (*n* 31). Histopathological evaluation also revealed all gallbladder polyps to be cholesterol polyps with a rate of 2.0% (*n* 22) (Table 1). The largest of these polyps was six mm in size.

The observed agreement, sensitivity, specificity, PPV, NPV, and accuracy were calculated separately for each binary groups (group S1-group S2, group S1-group S3, and group S2-group S3) (Table 2). The accuracy was the highest for group S1-group S3, and higher for group S2-group S3 than for group S1-group S2.

The κ agreement coefficient analysis showed that the correlation between the results of the histopathological studies and the macroscopic evaluation of the specimens by the surgeons were higher with group S3 compared to group S1 and group S2 (Table 3). The kappa coefficient was 1.0 (very good agreement) and 0.64 (good agreement) for group S1-group S3 and group S2-group S3, respectively. These results were significant ($p < 0.001$ for all).

In histopathological examination, malignancies were detected in seven patients as compared to the five patients identified by macroscopic examination. However, the two remaining specimens were identified as suspicious by the operating surgeons.

The histopathological examination of patients with primary gallbladder malignancy is reported in Table 2. Meanwhile, stages of incidental primary gallbladder malignancy in the seven patients were Tis in one, T1a in one, T1b in two, and

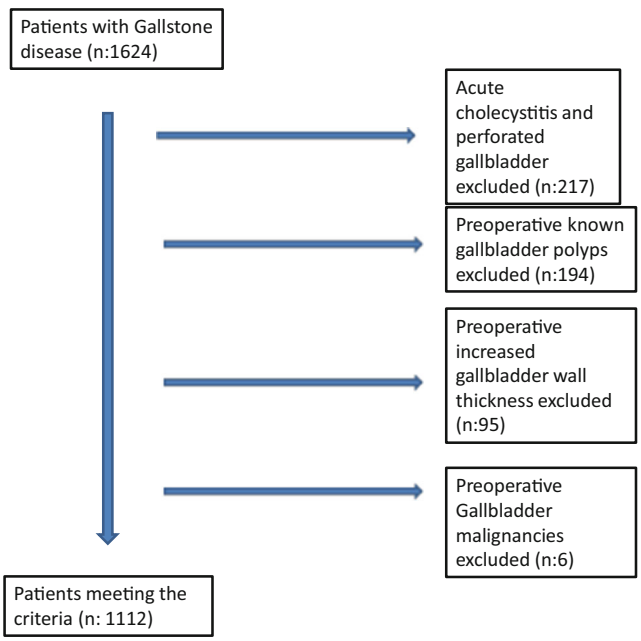

Fig. 1 Flow diagram of the study

Table 1 Distribution of the diagnoses after the macroscopic evaluation by the surgeons and the histopathological examination

Macroscopic examination by surgeon	(*n* (%))	Histopathological examination	(*n* (%))
Macroscopically benign (group S1)	1000 (89.9)	Chronic cholecystitis (group P1)	824 (74.1)
Suspicious for a benign diagnosis (group S2)	107 (9.6)	Benign or precancerous lesions (group P2)	281 (25. 3)
		Intestinal metaplasia	99 (8.9)
		Gastric metaplasia	50 (4.5)
		Adenomyosis	49 (4.4)
		Dysplasia	31 (2.8)
		Xanthogranulomatous cholecystitis	28 (2.5)
		Cholesterol polyps	22 (2.0)
		Mucocele	2 (0. 2)
Suspicious for malignancy (group S3)	5 (0.5)	Carcinoma (group P3)	7 (0.6)

T2 in three patients. Three patients underwent extended resection consistent with their pathology results. Two patients with stages T1b and T2 refused surgery and received oncological treatment, only. During the 24-month post-op period, the T2 patient who had declined resection surgery deceased, while the remaining patients continue to be monitored. Patients with Tis and T1a continue to be disease-free (Table 4).

Discussion

The majority of all diagnosed gallbladder cancers are incidental gallbladder malignancies found in cholecystectomy specimens [16]. Furthermore, a worldwide heterogeneous spread of gallbladder tumors, with variations dependent on demographic factors such as age and ethnic properties, has been well documented [17]. Gallbladder cancer is often seen in the elderly, is approximately three times more common in women than in men, and consists of aggressive tumors [18, 19].

Primary gallbladder tumors are seen incidentally in up to 2% of cholecystectomies performed for benign causes [2]. Irritation resulting from chronic gallstones is an important risk factor for dysplastic changes and carcinoma development [20], while an increase in gallstone weight, number, and volume has also been associated with an increased risk of gallbladder cancer [21]. As further surgical procedures such as hepatic resection and lymphadenectomy may be needed in patients with gallbladder tumor, early detections have great importance, according to its stage, as in other types of cancer [22]. Although our study results reflect the literature in general, our rates for incidental gallbladder cancer were lower than in many studies, probably since only patients who underwent elective cholecystectomy for gallbladder stones were included.

Intestinal metaplasia was detected in 7.4% of our patients with gallbladder malignancy; similarly, there are numerous articles documenting the precancerous nature of metaplastic changes and the relationship between metaplasia or dysplasia and carcinoma [3, 23, 24]. Simple cholecystectomy is sufficient for the management of patients with intestinal metaplasia or dysplasia, with no additional treatment required.

Although there have been many publications in recent years concerning applying histopathological examination to only selected patients, especially after benign gall bladder surgeries, the majority of these are retrospective articles [2, 7, 25]. According to some authors, patients with malignancy tend to display suspicious or abnormal appearance under macroscopic examination, and therefore only these selected cases should be subjected to histopathological examination [2, 6, 13]. Other authors recommend histopathological examination for all cholecystectomy specimens even if they are performed for benign reasons [26, 27]. These authors concur that all cases should be examined histopathologically since early stage tumors can easily be overlooked in macroscopic examination.

Table 2 Evaluation of the macroscopic evaluation of the specimens by the surgeons based on the results of the histopathological studies

Groups	Comparison	OA¥	Sensitivity¥	Specificity¥	PPV¥	NPV¥	Accuracy¥
Group S1	Group S1-group S2	78.9	27.1	96.5	72.4	79.6	78.9
	Group S1-group S3	100	100	100	100	100	100
Group S2	Group S2-group S3	95. 2	57.1	98.7	80	96. 2	95. 2

Group S1: macroscopically benign; group S2: suspicious for a benign diagnosis; group S3: suspicious for malignancy

OA observed agreement, *PPV* positive predictive value, *NPV* negative predictive value

¥ In percentage

Table 3 Correlation the macroscopic evaluation of the specimens by the surgeons with the histopathological studies

Groups	Comparison	Kappa coefficient	*p* value
Group S1	Group S1-group S2	0.30	< 0.001
	Group S1-group S3	1.0	< 0.001
Group S2	Group S2-group S3	0.64	< 0.001

Group S1: macroscopically benign; group S2: suspicious for a benign diagnosis, group S3: suspicious for malignancy

According to the guidelines, in cases of gallbladder tumors that are stage T2 and higher, segmental hepatic resection (segments IVb–V) with lymphadenectomy is required, whereas cholecystectomy alone is reported to be sufficient for T(in situ) and T1a malignancies [10, 28]. Our results showed that if at least two surgeons decide the macroscopic evaluation of the gallbladder specimens as macroscopically benign, this situation has an accuracy of 100% for not missing a carcinoma case. In addition, the decision of the surgeons for the gallbladder specimens as suspicious for a benign diagnosis has had an accuracy of 95.2% with a specificity of 98.7%. Due to the presence of significant correlations between all binary groups, the macroscopic evaluation of the gallbladder specimens by at least two surgeons may be a safe and feasible approach to perform selective histopathological examination. We may offer not to send gallbladder specimens if at least two surgeons evaluated these as macroscopically benign. Other situations as suspicious for a benign diagnosis and suspicious for malignancy should be examined histopathologically.

In fact, authors who support the need for only selected cases to be sent for histopathological assessment, in the light of this information, claim that tumors that are undetectable during macroscopic evaluation of the gallbladder are in fact early stage tumors (Tis, T1a) where simple cholecystectomy is sufficient [2].

In our study, there were only two cases where the histopathological diagnosis of malignancy was not recognized by surgeons during physical examination. They were both low-grade tumors: Tis and T1a, and cholecystectomy was the appropriate treatment. Although not positively identified by the surgeon, the cases were classified as suspicious and therefore sent for further analysis; accordingly, we consider that the surgeon's evaluation had no negative impact on the clinical course or prognosis of these patients.

In our study, the Tis and T1a patients required no intervention, while 3 of the 5 patients with stage T1b and T2 tumors underwent extended liver resection followed by chemotherapy. Surgery was refused by one stage T1b patient and one with T2. They both received chemotherapy only, but the T2 patient died at the 14th month. Meanwhile, the follow-up of all other patients is ongoing.

Survival rates in gallbladder malignancies found incidentally are reported in the literature as being no higher than in primary gallbladder malignancies that are symptomatic or preoperative [29]. Deng et al. [12] also reported that 61.4% of incidentally detected gallbladder tumors were stage T1a or T1b. In contrast, a meta-analysis by Swank et al. reported that 42.4% of the gallbladder malignancies incidentally detected in cholecystectomy materials were Tis and T1 stage tumors [30]. In our study, 57.1% of 7 patients with incidentally detected gallbladder tumor were Tis, T1a, and T1b stage tumors.

Finally, while histopathological examination of the gallbladder in European countries costs approximately 60 euros per patient, the per-case payments made by the Turkish social insurance institution is only 5 euros per patients. Despite the fact that the cost in Turkey is quite low compared to Europe, based on our study, selective histopathological examination can improve cost effectiveness in the range of 5000 euros for 1000 unnecessary histopathological evaluations, while reducing lost work time.

As the limitations, this study was designed as a prospective study. Lack of blinding for the surgeons during the macroscopic assessment of the specimens may be an important issue. In reality, this assessment would be performed by different surgeons from the operating team to reach more objective evaluations [31]. However, due to the inclusion criteria of

Table 4 Pathologic stages of patients with gallbladder malignancies, surgical and histopathological results, and survival status

No.	Age	Gender	T stage	Malignancy identified by surgeon's assessment	Malignancy identified by histopathology	Additional surgery	Chemo and/or radiotherapy	Survival at 24 months
1	57	F	Tis	–	+	–	–	Alive
2	73	F	T1a	–	+	–	–	Alive
3	64	F	T1b	+	+	Refused surgery	+	Alive
4	78	M	T1b	+	+	+	+	Alive
5	77	M	T2	+	+	Refused surgery	+	Dead
6	56	F	T2	+	+	+	+	Alive
7	65	F	T2	+	+	+	+	Alive

normal imaging reports except cholelithiasis may also limit the bias originating from the role of operating surgeons. For histopathological examinations, no blinding was performed. This is because the pathologists reported only their histopathological examinations that were the reference point for diagnostic accuracy and performed for only medical—not research—necessities.

As a conclusion, our study is the largest prospective series to evaluate the pathology of cholecystectomy surgeries caused by gallbladder stone disease in the literature. The results of our study show that in the case of patients who undergo planned cholecystectomy for gallbladder stones with no preoperative suspicion of any malignancy, macroscopic evaluation of the gallbladder specimens by the surgeons after surgery, followed by histopathological examination of selected suspicious cases, is an acceptable course of action. Not only does it not compromise the clinical course of patients, but also it can reduce overall surgical costs and prevent unnecessary loss of labor productivity. Therefore, macroscopical evaluation of the gallbladder specimens by at least two surgeons as benign may be a safe and feasible approach for not performing histopathological examination of these specimens. However, macroscopical evaluation by the surgeons as suspicious for a benign diagnosis and suspicious for malignancy should necessitate further histopathological examination.

Compliance with ethical standards

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

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Koppatz H, Nordin A, Scheinin T, Sallinen V (2018) The risk of incidental gallbladder cancer is negligible in macroscopically normal cholecystectomy specimens. HPB (Oxford) 20:456–461
2. Basak F, Hasbahceci M, Canbak T et al (2016) Incidental findings during routine pathological evaluation of gallbladder specimens: review of 1,747 elective laparoscopic cholecystectomy cases. Ann R Coll Surg Engl 98:280–283
3. Kalita D, Pant L, Singh S et al (2013) Impact of routine histopathological examination of gall bladder specimens on early detection of malignancy – a study of 4,115 cholecystectomy specimens. Asian Pac J Cancer Prev 14:3315–3318
4. Clemente G, Nuzzo G, De Rose AM et al (2012) Unexpected gallbladder cancer after laparoscopic cholecystectomy for acute cholecystitis: a worrisome picture. J Gastrointest Surg 16:1462–1468
5. Simoens S (2009) Health economic assessment: a methodological primer. Int J Environ Res Public Health 6:2950–2966
6. Bazoua G, Hamza N, Lazim T (2007) Do we need histology for a normal-looking gall bladder? J Hepato-Biliary-Pancreat Surg 14: 564–568
7. Ghimire P, Yogi N, Shrestha BB (2011) Incidence of incidental carcinoma gall bladder in cases of routine cholecystectomy. Kathmandu Univ Med J 34:3–6
8. Siddiqui FG, Memon AA, Abro AH, Sasoli NA, Ahmad L (2013) Routine histopathology of gallbladder after elective cholecystectomy for gallstones: waste of resources or a justified act? BMC Surg 13:26
9. Duffy A, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, D'Angelica M, DeMatteo RP, Blumgart LH, O'Reilly EM (2008) Gallbladder cancer (GBC): 10-year experience at memorial Sloan–Kettering Cancer Centre (MSKCC). J Surg Oncol 98:485–489
10. Machado M, Makdissi F, Surjan R (2015) Totally laparoscopic hepatic bisegmentectomy (s4b+s5) and hilar lymphadenectomy for incidental gallbladder cancer. Ann Surg Oncol 22:336–339
11. Jayasundara JA, de Silva WM (2013) Histological assessment of cholecystectomy specimens performed for symptomatic cholelithiasis: routine or selective? Ann R Coll Surg Engl 95:317–322
12. Deng YL, Xiong XZ, Zhou Y, Shrestha A, Li FY, Cheng NS (2015) Selective histology of cholecystectomy specimens–is it justified? J Surg Res 193:196–201
13. Tayeb M, Rauf F, Ahmad K, Khan FM (2015) Is it necessary to submit grossly normal looking gall bladder specimens for histopathological examination? Asian Pac J Cancer Prev 16:1535–1538
14. Dix FP, Bruce IA, Krypcyzk A, Ravi S (2003) A selective approach to histopathology of the gallbladder is justifiable. Surgeon. 1:233–235
15. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (2010) The American Joint Committee on Cancer: the 7th edition of the AJCC Cancer Staging Manual. Springer-Verlag, New York, p 211
16. Oommen CM, Prakash A, Cooper JC (2007) Routine histology of cholecystectomy specimens is unnecessary. Ann R Coll Surg Engl 89:738
17. Randi G, Franceschi S, La Vecchia C (2006) Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 118:1591–1602
18. Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, Alonso de Ruiz P, Aristi Urista G, Nervi F (2001) Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 51:349–364
19. Pandey M, Shukla VK (2002) Diet and gallbladder cancer: a case control study. Eur J Cancer Prev 11:365–368
20. Sheth S, Bedford A, Chopra S (2000) Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. Am J Gastroenterol 95:1402–1410
21. Roa I, Ibacache G, Roa J, Araya J, de Aretxabala X, Muñoz S (2006) Gallstones and gallbladder cancer-volume and weight of gallstones are associated with gallbladder cancer: a case-control study. J Surg Oncol 93:624–628
22. Cavallaro A, Piccolo G, Panebianco V, Lo Menzo E, Berretta M, Zanghì A, di Vita M, Cappellani A (2012) Incidental gallbladder cancer during laparoscopic cholecystectomy: managing an unexpected finding. World J Gastroenterol 18:4019–4027
23. Serra I, Calvo A, Baez S et al (1996) Risk factors for gallbladder cancer. An international collaborative case control study. Cancer. 78:1515–1517
24. Yamagiwa H (1989) Mucosal dysplasia of gallbladder: isolated and adjacent lesions to carcinoma. Jpn J Cancer Res 80:238–243
25. Shrestha R, Tiwari M, Ranabhat SK, Aryal G, Rauniyar SK, Shrestha HG (2010) Incidental gallbladder carcinoma: value of routine histological examination of cholecystectomy specimens. Nepal Med Coll J 12:90–94
26. Pai SA, Bhat MG (2004) Selective histopathology of gall bladders is unscientific and dangerous. Surgeon. 2:241

27. Khoo JJ, Nurul AM (2008) A clinicopathological study of nine cases of gallbladder carcinoma in 1,122 cholecystectomies in Johor, Malaysia. Malays J Pathol 30:21–26
28. Lee CP, Chertow GM, Zenios SA (2009) An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. Value Health 12:80–87
29. Tian Y-H, Ji X, Liu B, Yang GY, Meng XF, Xia HT, Wang J, Huang ZQ, Dong JH (2015) Surgical treatment of incidental gallbladder cancer discovered during or following laparoscopic cholecystectomy. World J Surg 39:746–752
30. Swank HA, Mulder IM, Hop WC, van de Vijver MJ, Lange JF, Bemelman WA (2013) Routine histopathology for carcinoma in cholecystectomy specimens not evidence based: a systematic review. Surg Endosc 27:4439–4448
31. Probst P, Zaschke S, Heger P et al (2019, 2019) Evidence-based recommendations for blinding in surgical trials. Langenbeck's Arch Surg. https://doi.org/10.1007/s00423-019-01761-6

Affiliations

Yurdakul Deniz Firat[1] · Ufuk Oguz Idiz[2] · Coskun Cakir[2] · Erkan Yardimci[3] · Pinar Yazici[4] · Huseyin Bektasoglu[3] · Emre Bozkurt[4] · Ramazan Ucak[5] · Zuhal Gucin[6] · Taskin Uresin[7] · Mustafa Hasbahceci[8]

1 Department of General Surgery, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

2 Department of General Surgery, Istanbul Training and Research Hospital, Istanbul, Turkey

3 Department of General Surgery, Bezmialem Vakif University, Istanbul, Turkey

4 Department of General Surgery, Sisli Etfal Training and Research Hospital, Istanbul, Turkey

5 Department of Pathology, Sisli Etfal Training and Research Hospital, Istanbul, Turkey

6 Department of Pathology, Bezmialem Vakif University, Istanbul, Turkey

7 Department of Pathology, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

8 General Surgery Clinic, Medical Park Fatih Hospital, Fatih, Istanbul, Turkey