

Melanoma of the gallbladder

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Abstract: Melanoma is a highly malignant neoplasm with the most typical primary locations in the skin and eyeball and rarely reported in the other organs, including the gallbladder. More commonly metastases of melanoma of various primary sites to the gallbladder are observed. However, generally melanoma of the gallbladder is a rare entity with only 217 cases reported in the literature up to date. The paper summarizes knowledge on epidemiology, symptoms, laboratory and imaging findings, morphology, treatment options, and outcome of patients with both primary and metastatic melanoma to the gallbladder.

Keywords: melanoma, gallbladder, epidemiology, imaging, morphology, outcome.

Submitted: 10-Jun-2023; **Accepted in the final form:** 30-Jun-2023; **Published:** 30-Jul-2023.

Melanoma is a malignant neoplasm with rising incidence worldwide. The most typical primary locations of the lesion are the skin and eyeball. It has been also reported in the oral cavity, anal canal, vulva, and in the esophagus, trachea and other sites. As it has unique nature it can affect and metastasize to any organ in the human body [1–5].

Melanoma of the gallbladder is a rare entity with 217 cases reported in the literature up to date. The aim of this paper is to summarize knowledge on epidemiology, symptoms, laboratory and imaging findings, morphology, treatment options, and outcome of patients with both primary and metastatic melanoma to the gallbladder.



Epidemiology

Melanoma is a malignancy developing from melanocytes with increasing incidence worldwide. Metastases of melanoma can affect every organ of the human body with a predilection to regional lymph nodes, skin, central nervous system, gastrointestinal tract, lungs, liver, and bones [1].

Gallbladder metastases can be found in 15–20% of autopsies in deceased patients that developed extra-regional metastases of melanoma [1, 2]. Backman *et al.* [3] reported that melanoma is the most common metastatic tumor in the gallbladder and accounts for 50–67% of all metastases in this location. These statistics may not be appropriate for other populations as Yoon *et al.* [4] reported higher prevalence of gastric cancer metastases to the gallbladder in the Korean population, mainly due to higher incidence of gastric cancer in this region.

The first report of melanoma of the gallbladder (GBM) as an autopsy finding in 40 years old woman was made by Wieting and Hamdi [5] in 1907. The patient died from septicemia, and there was no evidence of primary lesion in the skin or eyes, but there were other metastases present in the omentum, vertebra, meninges, and nerve roots.

Series of cases reported by Dong [6] showed male predilection, while 13 cases reported by Katz [7] showed no sex predilection. Among the rest of the reported cases, we have identified 63 male and 49 female cases of the gallbladder melanoma. The overall male to female ratio is about 1.4:1 (Table 1).

There is a wide range of age at the time of the diagnosis with the youngest reported case at 24 years of age [6] and oldest at 86 years [8], with a median age of 53 years. The disease-free interval between excision of primary melanoma to the diagnosis of GBM is ranging from 0 [9–13] to 360 months [14], with a median of 24 months.

Melanoma of gallbladder primary

Melanocytes are derived from the neural crest, and then migrate to many distant locations of the human body. They are found within the mucosa of normal gallbladder. Some authors postulated that there is a possibility of melanoma arising as a primary tumor in the gallbladder. There are 42 reports of melanoma that were considered as primary gallbladder melanoma [5, 6, 15–51].

At least a few of these cases are questionable, because of possible primary at other sites. Diagnostic criteria for primary GBM were first proposed by Allen and Spitz [52], and next reviewed in 1988 by Heath and Womack [33]. These criteria are:

- solitary tumor that arise from the mucosal surface of the gallbladder
- papillary or polypoid
- junctional activity, or any other primary site excluded.

Some of the proposed criteria for primary GBM are not specific enough for diagnosis. There are at least two cases with melanoma arising within the gallbladder, with documented junctional activity, in patients with previously excised skin melanoma [38, 42]. In both cases, authors postulate that because excision of skin melanoma was in the “in situ” stage and there was a long time interval between the onset of both lesions, there is a high possibility of another primary within the gallbladder. Late recurrences of melanoma metastases are not uncommon, so considering these two reports as primary remains questionable. Moreover, there have been reports of metastases in other than the gallbladder sites with documented junctional activity, and exclusion of other primaries, as necessary, does not cover rare cases of patients with a regressed primary lesion.

Discussion whether there is a possibility of primary origin within the gallbladder is strictly academic as it does not have any significant diagnostic or therapeutic consequences.

Characteristics of the primary site of melanoma with the gallbladder metastases

Most of the cases with gallbladder melanoma metastases have a history of skin melanoma. There are only a few cases of melanoma primary at other locations. These are eyeball [53–55], sinuses [56, 57], colon [10], and vagina [58]. The cases with skin primary are usually characterized by a high Clark level of invasion. Breslow thickness ranged from 0.3 to 12 mm, with a median of 2.1 mm.

Signs, symptoms, and laboratory findings

Gallbladder metastases can be found in up to 20% of patients with metastatic disease. They are usually asymptomatic and are rarely diagnosed in living patients [1]. With the widespread use of non-invasive imaging techniques such as ultrasonography (US), computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) for the staging of the disease, we can expect more diagnoses of the gallbladder metastases in asymptomatic patients in the future. This is supported by the fact that almost half of the cases reported, were published in the 21st century.

GBM is rarely symptomatic. If so, it usually presents with abdominal pain [6, 8, 11, 12, 17, 18, 20–23, 26–28, 33, 37–42, 46, 48, 49, 51, 53, 59–91]. Other observed symptoms are nausea and vomiting [8, 73, 75, 78, 79, 84, 86, 91, 92], jaundice [81, 83], fever [79, 83, 89], tarry stools [11, 19, 36, 93], hematemesis [19], hematuria [93], and weight loss [5, 6, 16, 22, 51, 84, 84]. Physical examination usually is unremarkable. The most common finding is tenderness in the upper right quadrant of the abdomen. There are two cases with reported liver enlargement [18, 53].

There are no characteristic laboratory findings in GBM. Anemia [10, 27, 36, 93], leukocytosis [8, 18, 28, 33, 39, 41, 62, 71, 73, 83, 86, 94], elevated erythrocyte sedimentation rate (ESR) [24], elevated bilirubin [8, 44, 46, 83, 89], and elevated liver enzymes [8, 12, 46, 51, 59, 63, 70, 75, 83, 84, 86, 89] were reported. Also the presence of occult blood in stool sample may be found in cases with haematuria or coexistence of intestinal metastases [27]. There is a single publication when the serum level of novel melanoma marker — 5-S-cysteinyl-dopa was useful in establishing the diagnosis [13]. Two cases showed minimally elevated level of Ca19.9 antigen [44, 63]. Most patients do not show any abnormalities in laboratory studies.

There are no signs, symptoms, physical examination, or laboratory findings that are characteristic of GBM. Thus, some of the patients are misdiagnosed with cholecystitis or not diagnosed at all. If there is no detailed patient history taken, the final diagnosis is made after surgical intervention and histopathological examination of excised gallbladder.

Imaging studies

Ultrasonography

Ultrasonography is the most accurate and a cost-effective method in the preoperative diagnosis of gallbladder melanoma. Typical findings are: broad base polypoid, immobile, hyperechogenic mass without or with minimal (lower than seen in cholelithiasis, hyperplastic or cholesterol polyps) acoustic shadowing [72, 95, 96]. This is due to lower density of metastases than calculi; focal thickening of gallbladder wall often involving serosa but without mucosal involvement and diffuse thickening of the gallbladder wall associated with the coexistence of cholecystitis [62, 72, 96–99]. Cholelithiasis is an uncommon finding in patients with the GBM in contrast to the gallbladder cancer. Differentiation between benign changes and malignant gallbladder carcinoma with classical US, color-doppler US, and contrast-enhanced US was described elsewhere [100].

Andreano *et al.* [98] revealed that metastatic melanoma have the same features as other malignancies in the gallbladder in contrast-enhanced ultrasonography imaging (CEUS), which are early intense heterogeneous enhancement of lesion in arterial stage with rapid washout within 60 seconds. CEUS is superior to conventional US and CT scans in the diagnosis of gallbladder melanoma/malignancy. Color-doppler shows abnormal vascular pedicle in 50% of cases with any metastatic disease in the gallbladder [99]. The combination of CEUS and color-doppler increases the sensitivity of vascular abnormalities detection within metastases. Although sonographic findings cannot distinguish between melanoma and other metastases with total accuracy, it is

helpful in distinguishing malignant from nonmalignant lesions. In one case, color-doppler failed to show blood flow within GBM [12].

Despite many detailed descriptions of metastases within the gallbladder, ultrasonographic diagnosis still depends on examiners' experience and knowledge. Baretta [99] showed that over 20% of patients with metastatic disease of the gallbladder were previously misdiagnosed with benign conditions. Holloway *et al.* [96] showed that typical ultrasonographic findings of metastatic GBM can be found in 4.1% of patients with previously diagnosed melanoma. According to the author, these cases don't require histopathologic confirmation of metastases and ultrasonographic examination is sufficient to make an accurate diagnosis. In this study all of the fatal outcomes were due to widespread melanoma, but ultrasonographic findings were not confirmed by autopsy to establish certain correlation within US finding and incidence of gallbladder metastases.

Computed tomography

CT of the abdomen in metastatic melanoma show hyperdense mass, polyp, or focal thickening of gallbladder wall with contrast enhancement in the early stage and variable enhancement in the equilibrium stage [101]. But CT does not show efficient sensitivity or specificity and can lead to misdiagnosis (as cholesterol polyp [63] or liver mass [77]) or underdiagnosis [65, 90, 98]. Sometimes CT studies can favor a diagnosis of gallbladder cancer instead of metastatic disease [53]. Still, CT scan is useful in staging of disease and evaluating treatment possibilities.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) scan has the sensitivity and specificity comparable with CT scans. MRI usually shows a hyperintense signal on T1-weighted images and hypo- or isointense in T2-weighted images (Fig. 1). This is closely related with content of melanin within the tumor and typical for melanoma metastases in other localizations. Typical to most of high cellularity and well vascularity tumors, melanoma is also characterized by restriction diffusion as on apparent diffusion coefficient — ADC map and contrast enhancement [88, 98].

Retrograde endoscopic cholangiography

Retrograde endoscopic cholangiography use in differentiation of metastatic melanoma with other causes of jaundice was confirmed in several studies [12, 13, 59]. Usually, the tumor presents as parietal and irregular filling defects of the gallbladder. It is worth mentioning that gall stones are found along with metastases of melanoma in a minority of cases [6] in contrast to gallbladder cancer.

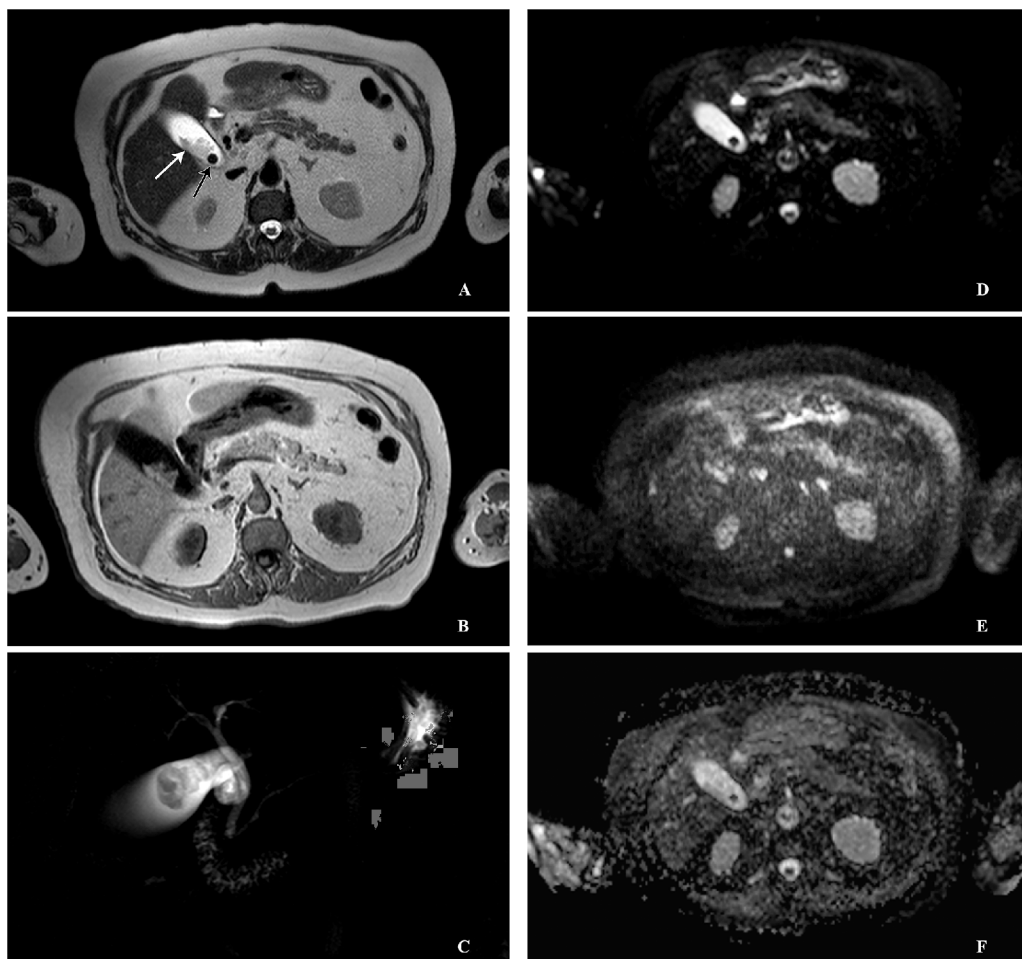


Fig. 1. Abdominal MRI of 76 female with a melanoma (white arrow) and gallstone (black arrow) of the gallbladder on T2-weighted (A), T1-weighted (B), pseudo-3D reconstruction (C), *diffusion-weighted images with 0* (D), and $1000 \text{ s mm}^{-2} \text{ b value}$ (E), as well as on apparent *diffusion coefficient* — ADC map (F). Data from authors collection.

Positron emission tomography

FDG-PET has proven useful in detecting melanoma metastases [41, 56, 57, 60, 77, 80, 98, 102, 103], but may have lower specificity when there is cholecystitis simultaneously within the gallbladder. Moreover, FDG-PET is the most useful imaging study in detecting unusual sites of metastases [56]. Still, FDG-PET remains a tool for staging neoplastic disease rather than establishing the diagnosis.

Other studies

There are some reports of cholecystogram with both oral and intravenous contrast use in the detection of the gallbladder metastases. In these cases, cholecystogram revealed mass within the gallbladder or failed to visualize the gallbladder, but the use of cholecystogram is not specific nor sensitive in the diagnosis of metastatic disease in gallbladder, and in the area of the widespread availability of US and its complex procedure the role of cholecystography declined [61, 83].

There are two reports of successful diagnosis of gallbladder melanoma with cytological techniques. One of them used naso-gallbladder drainage fluid cytology [13], and the second used fine needle aspiration with endoscopic ultrasonographic guidance [47]. In uncertain cases, in which confirmation of metastatic disease is of a superior priority than performing cholecystectomy and diagnosis is impossible to establish using noninvasive imaging studies, fine-needle aspiration biopsy (FNAB) may be helpful [6, 53, 56].

Morphological features

Macroscopically GBM typically presents as polypoid [21, 36, 39, 40, 42–44, 73, 86, 104–107] and single [5, 6, 9,15–17, 23, 25, 26, 30–40, 43, 44, 47, 57, 61, 63–67, 72, 73, 75, 77, 80–82, 85, 86, 89, 90, 94, 105, 106, 108–112], dark-colored tumor (Fig. 2). The minimal greatest dimension reported is of 5.5 mm [86], and maximal of 112 mm [54],



Fig. 2. Melanoma of the gallbladder forming exophytic dark-coloured tumor with irregular surface. Data from authors collection.

with median of 30 mm. However, many variations in the macroscopic description of GBM have been reported. Multiple lesions are not uncommon [19, 20, 22, 24, 27–29, 45, 55, 59, 62, 71, 104] and there are reports of tumors with reduced or no macroscopically visible pigmentation [57, 88].

Primary melanoma is usually composed of sheets or expansile nodules of pleomorphic epitheloid or spindle cells, with abundant eosinophilic cytoplasm. Pigmentation is a helpful finding but is variable or absent. There is usually no necrosis, described only in a single report [23]. Nuclear features are vesicular chromatin and prominent nucleoli. The feature considered to be specific to primary melanoma of the gallbladder is the presence of junctional activity (defined as the presence of melanoma cells aggregates in the epithelium or at the junction of epithelium and lamina propria) [18, 23, 33, 36, 38, 40, 41–44]. Most reports describe the location of primary melanoma limited to the mucosa and/or submucosa [19, 33, 36, 40, 44].

Histopathological examination of gallbladder metastases shows the same variety of morphological appearances as the primaries (Fig. 3A). Involvement of the gallbladder wall is more variable with only mucosal [12, 14, 26, 79, 86], submucosal [3], muscularis propria [20, 54, 80, 83, 89, 109, 111], subserosal [45, 69, 71, 91], and serosal [28] involvement all been described. It seems that the presence of necrosis is described more often than in primary lesions [6, 20, 24, 71, 79, 106, 111]. Moreover, there are single reports that mention lymphovascular [46, 69, 91], and perineural [106] invasion.

Immunohistochemistry is very useful in challenging cases. The most sensitive markers are S-100 and SOX-10, which are markers of neural crest origin. Expression of Melan A (MART1) (Fig. 3B), HMB-45, or MITF is most specific for melanocytic differentiation.

In the setting of appropriate clinical information, cytological examination (biliary cytology or FNA cytology) was sufficient for the diagnosis on several occasions [13, 47, 58].

Treatment and outcome

Patients with both primary and metastatic melanoma of the gallbladder have a poor prognosis. Follow-up is available only in few reports, with median of 10 months (range from 0 [17] to 174 months [18]). As much as 90% of deaths occurred within 26 months after the diagnosis.

Due to the scarce of reported cases, there is also little information on treatment possibilities of patients with melanoma of the gallbladder. Also because of the rarity of the gallbladder metastases, it is difficult to make an appropriate diagnosis before surgical treatment is applied and before it could be adapted to a specific patient. Some patients are misdiagnosed with acute cholecystitis, and proper diagnosis is made after surgical treatment and examination of excised GB. Nevertheless, surgical treatment is

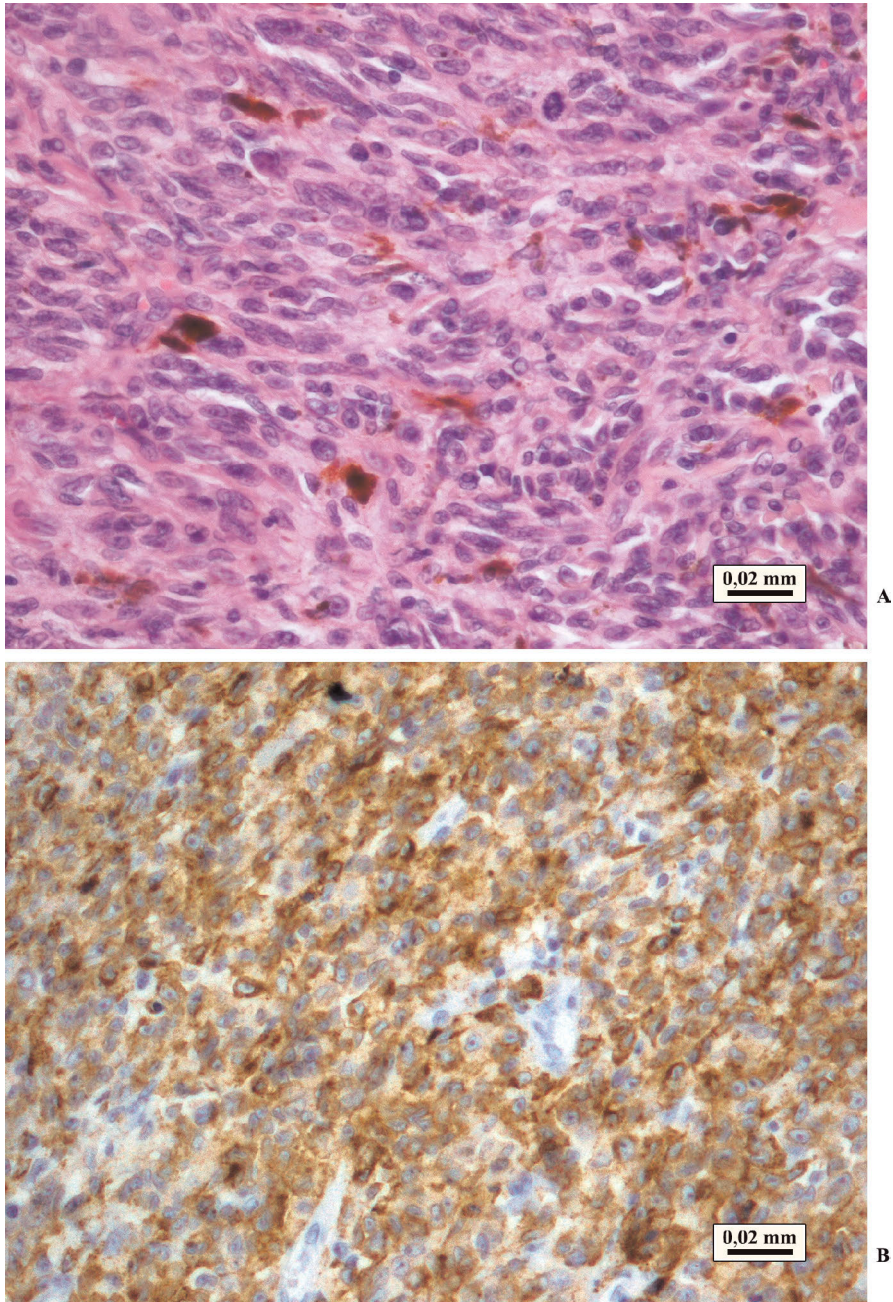


Fig. 3. Melanoma composed of sheets of epithelioid cells with abundant eosinophilic cytoplasm, oval nuclei with small nucleoli and scattered melanin pigment (hematoxylin and eosin stain) (A), and positive cytoplasmic immunostaining for Melan A (EnVision Flex/HRP, DAKO Omnis) (B). Data from authors collection.

Table 1. Characteristics of patients with gallbladder melanoma based on the literature review.

Gender	No. of cases	%	
Male	85	59.0	
Female	59	41.0	
	No. of cases	Median	Range
Age at diagnosis [years]	132	53	24–86
Interval between diagnosis and gallbladder involvement [months]	86	24	0–360
Breslow thickness of the primary [mm]	39	2.1	0.3–12
Clark level of the primary	No. of cases	%	
I	0	0.0	
II	3	7.3	
III	13	31.7	
IV	24	58.5	
V	1	2.4	
Metastases at other sites*	No. of cases	%	
Yes	78	60.9	
No	50	39.1	
Greatest dimension of gallbladder melanoma [mm]	No. of cases	%	
<10 mm	2	2.9	
10–20 mm	12	17.6	
20–30 mm	15	22.1	
30–40 mm	14	20.6	
40–50 mm	10	14.7	
≥50 mm	15	22.1	

*at the time of the diagnosis of gallbladder melanoma

an approved intervention if only applicable. Katz *et al.* [7] reported 13 cases of melanoma of the gallbladder treated surgically. They showed that there is a beneficial prognosis in patients with biliary tract symptoms disease confined to the gallbladder and if there was surgical treatment applied. Dong *et al.* [6] reported favorable outcomes in two patients with metastatic disease limited to the gallbladder, with disease-free survival of 9.2 and 13.8 years after cholecystectomy. One-year survival in patients with excisable lesions was higher (100% vs. 0%). Moreover, surgical treatment relieves biliary symptoms in all patients, and should be considered as palliative care even in disseminated disease.

There is a discussion whether laparoscopic cholecystectomy is appropriate when metastatic disease in the gallbladder is suspected. In a report by Katz [7] there were three patients with GBM treated with laparoscopic cholecystectomy, and there are many other reports of single cases treated this way [10, 37, 40, 41, 43, 54, 60, 67, 75, 79, 80, 82, 84, 85, 89, 90, 109, 111–115]. Katz [7] also reported subsequent port site recurrence of melanoma in two cases. Endobag retrieval of gallbladder should be considered to minimize the possibility of port site recurrences, however, it does not have proven preventing efficacy [80]. Tuveri *et al.* [89] described a patient with no recurrences 60 months after laparoscopic cholecystectomy, which may suggest that it could be an alternative for open cholecystectomy, but present data are not sufficient to judge whether open or laparoscopic cholecystectomy is superior in surgical management [89].

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