FOLIA MEDICA CRACOVIENSIA
Vol. LXIII, 2, 2023: 77–92
PL ISSN 0015-5616
DOI: 10.24425/fmc.2023.145915

Melanoma of the gallbladder

Paweł Bojar[1, 2], Franciszek Burdan[3, 4], Lech Wronecki[1], Justyna Szumiło[1]

[1]Department of Clinical Pathomorphology, Medical University of Lublin, Lublin, Poland
[2]Department of Pathomorphology, Beskid Oncology Centre — John Paul II Memorial City Hospital in Bielsko-Biala, Bielsko-Biała, Poland
[3]Department of Human Anatomy, Medical University of Lublin, Lublin, Poland
[4]Department of Radiology, St Johns' Cancer Center, Lublin, Poland

Corresponding author: Justyna Szumiło, Prof.
Department of Clinical Pathomorphology, Medical University of Lublin
ul. Jaczewskiego 8B, 20-090 Lublin, Poland
Phone: 48 81 448 65 30; Fax: +48 81 448 65 31; E-mail: justyna.szumilo@umlub.pl

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], hematobilia [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 haematobilia or coexistence of intestinal metastases [27]. There is a single publication when the serum level of novel melanoma marker — 5-S-cysteinyldopa 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 polypous, 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.

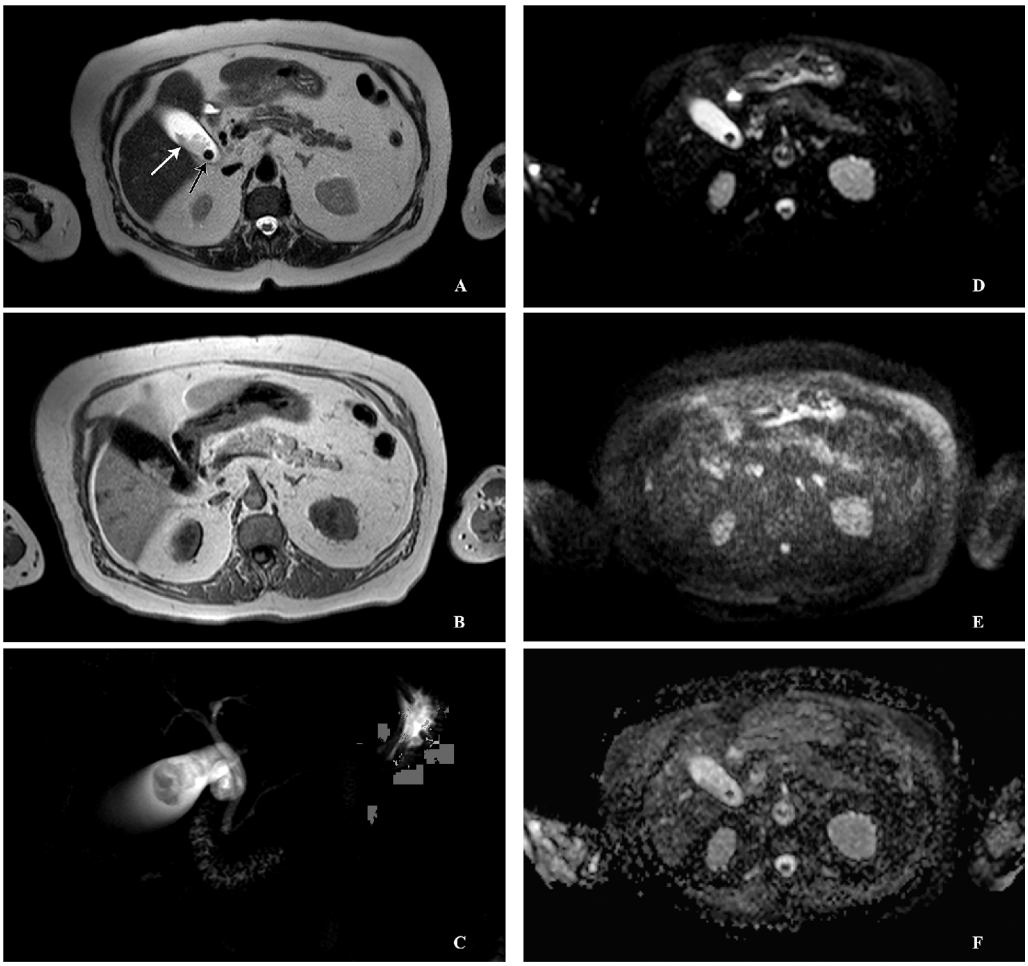

Fig. 1. Abdominal MRI of 76 female with a melanoma (white arrow) and gallstone (black arrow) of the gallbladder on T2-weighted (**A**), T1-weighted (**B**), pseudo-3D reconstruction (**C**), *diffusion-weighted imagines with 0* (**D**), and 1000 s mm^{-2} *b vale* (**E**), as well as on apparent *diffusion* 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

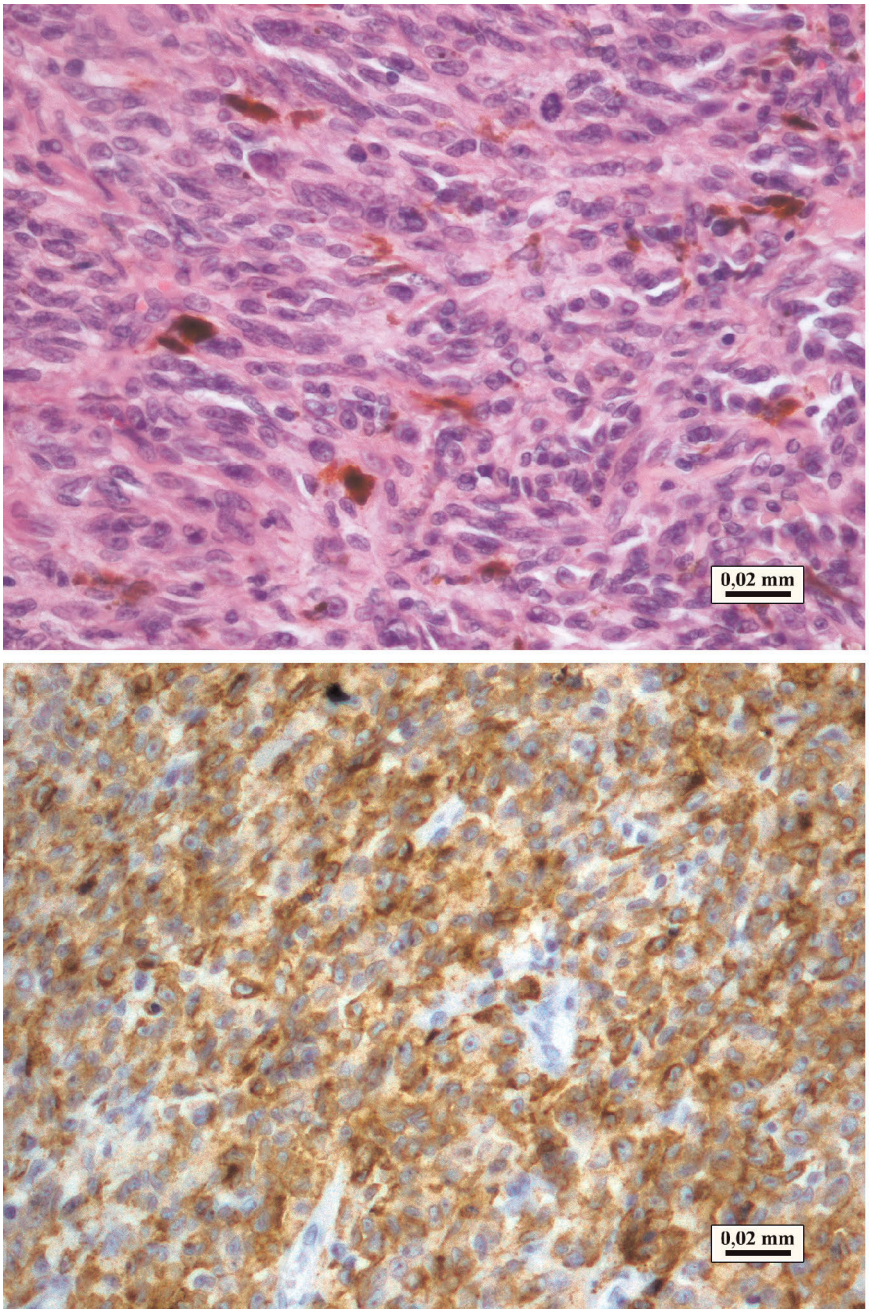

Fig. 3. Melanoma composed of sheets of epithelioid cells with abundant eosinophilic cytoplasm, oval nuclei with small nucleoli and scattered melanin pigment (hematoxylin and eosin stain) (**A**), and positive cytoplasmic immunostaining for Melan A (EnVision Flex/HRP, DAKO Omnis) (**B**). Data from authors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

References

1. *Das Gupta T., Brasfield R.*: Metastatic melanoma. A clinicopathological study. Cancer. 1964; 17: 17.
2. *Meyer J.E.*: Radiographic evaluation of metastatic melanoma. Cancer. 1978; 42: 127–132.
3. *Backman H.*: Metastases of malignant melanoma in the gastrointestinal tract. Geriatrics. 1969; 24: 112–120.
4. *Yoon W.J., Yoon Y.B., Kim Y.J., Ryu J.K., Kim Y.T.*: Metastasis to the gallbladder: A single-center experience of 20 cases in South Korea. World J. Gastroenterol. 2009; 15: 4806.
5. *Wieting J., Hamdi D.*: Uber die physiologische und pathologische Melaninpigmentierung und den epithelialen Ursprung der Melanoblastome. Ein primares Melanoblastom der Gallenblase. Path Anat. 1907; 42: 23–84.
6. *Dong X.D., DeMatos P., Prieto V.G., Seigler H.F.*: Melanoma of the gallbladder. Cancer. 1999; 14: 32–39.
7. *Katz S.C., Bowne W.B., Wolchok J.D., et al.*: Surgical management of melanoma of the gallbladder: a report of 13 cases and review of the literature. Am J Surg. 2007; 193 (4): 493–497.
8. *Riva G., Villanova M., Eccher A., et al.*: Metastatic malignant melanoma to the gallbladder. Case report and review of the literature. Pathologica. 2018; 110 (1): 68–71.
9. *Binks M., Larkin M., Palmieri D., Harrison R.*: Cholecystectomy as treatment for isolated melanoma metastasis to the gallbladder. ANZ J Surg. 2021; 91 (5): E310–E311.
10. *Endo M., Yano S., Asano H. et al.*: Long-term survival with a rare advanced primary gastrointestinal malignant melanoma treated with laparoscopic surgery/immune checkpoint inhibitor. Acta Med Okayama. 2021; 75 (2): 231–238.

11. *Ettahri H., Elomrani F., Elkabous M. et al.*: Duodenal and gallbladder metastasis of regressive melanoma: a case report and review of the literature. J Gastrointest Oncol. 2015; 6 (5): E77–81.
12. *Martel J.P., McLean C.A., Rankin R.N.*: Melanoma of the gallbladder. Radiographics. 2009; 29 (1): 291–296.
13. *Matsubayashi H., Kiyohara Y., Sasaki K., et al.*: Metastatic malignant melanoma of the gallbladder diagnosed by cytology of endoscopic naso-gallbladder drainage fluid. J Dig Dis. 2012; 13 (3): 190–194.
14. *Muszynska C., Lundgren L., Andersson R., et al.*: Incidental metastases and lymphoma of the gallbladder — an analysis of ten rare cases identified from a large national database. Scand J Gastroenterol. 2019; 54 (3): 350–358.
15. *Rosenthal S.R.*: Primary melanocarcinoma of the gallbladder. Am J Cancer. 1931; 15: 2288–2300.
16. *Pautler E.E., Gallavan E.M.*: Melanoma of brain and gallbladder. AMA Arch Pathol. 1951; 51: 238–245.
17. *Thayer K.H., Williams O.O., Rowe D.*: Malignant melanoma of the gallbladder; report of a case and review of the literature. Ariz Med. 1955; 12: 15–18.
18. *Walsh T.S.*: Primary melanoma of the gallbladder with cervical metastasis and fourteen and a half year survival; first histologically proved case. Cancer. 1956; 9: 518–522.
19. *Jones C.H.*: Malignant melanoma of the gall-bladder. J Pathol Bacteriol. 1961; 81: 423–430.
20. *Raffensperger E.C., Brason F.W., Treano G.*: Primary melanoma of the gallbladder. Am J Dig Dis. 1963; 8: 356–363.
21. *Dębiec H., Kiryłowicz K., Herba Z.*: Dwa przypadki czerniaka złośliwego pęcherzyka żółciowego. Przegl Lek. 1966; 6: 643–645.
22. *Simmard C., George P., Cautlet T.*: Les melanomes malins de la vesicule bilaire. J Chir. 1966; 92: 51–58.
23. *Peison B., Rabin L.*: Malignant melanoma of the gallbladder: report of three cases and review of the literature. Cancer. 1978; 37: 2448–2454.
24. *Sierra-Callejas J.L., Warecka K.*: Primary malignant melanoma of the gallbladder. Virchows Arch A Pathol Anat Histol. 1976; 370 (3): 233–238.
25. *Hatae Y., Kikuchi M., Segawa M., Yonemitsu K.*: Malignant melanoma of the gallbladder. Pathol Res Pract. 1978; 163 (3): 281–287.
26. *Carle G., Lessells A.M., Best P.V.*: Malignant melanoma of the gallbladder: a case report. Cancer. 1981; 48 (10): 2318–2322.
27. *Anderson J.B., Hughes R.G., Williamson R.C.*: Malignant melanoma of the gallbladder. Postgrad Med J. 1983; 59 (692): 390–391.
28. *Borja S.R., Meyer W.R., Cahill J.P.*: Malignant melanoma of the gallbladder. Report of a case. Cancer. 1984; 54 (5): 929–931.
29. *Naguib S.E, Aterman K.*: Presumed primary malignant melanoma of the gallbladder. Report of a case and a review of literature. Am J Dermatopathol. 1984; 6 (Suppl): 231–243.
30. *Seul B., Lüchtrath H.*: Malignes Melanom der Gallenblase [Malignant melanoma of the gallbladder]. Chirurg. 1984; 55 (3): 179–181.
31. *Rudolph A., Bothe J., Bonk U.*: Malignes Melanom der Gallenblase [Malignant melanoma of the gallbladder]. Chirurg. 1985; 56 (7): 469–471.
32. *Verbanck J.J., Rutgeerts L.J., van Aelst F.J., et al.*: Primary malignant melanoma of the gallbladder, metastatic to the common bile duct. Gastroenterology. 1986; 91 (1): 214–218.
33. *Heath D.I., Womack C.*: Primary malignant melanoma of the gall bladder. J Clin Pathol. 1988; 41 (10): 1073–1077.
34. *Guerini A., Gottardi D., Galassi A., et al.*: Malignant melanoma of the gallbladder. Case report and review of the literature. Arch Anat Cytol Pathol. 1990; 38 (4): 168–170.
35. *Habeck J.O.*: Primäres malignes Melanom der Gallenblase. Fallbericht und Literaturübersicht [Primary malignant melanoma of the gallbladder. Case report and literature review]. Zentralbl Pathol. 1993; 139 (4–5): 367–371.
36. *Hatanaka N, Miyata M., Kamiike W., et al.*: Radical resection of primary malignant melanoma of the gallbladder with multiple metastases: report of a case. Surg Today. 1993; 23 (11): 1023–1026.

37. *Velez A.F., Penetrante R.B., Spellman J.E. Jr., et al.*: Malignant melanoma of the gallbladder: report of a case and review of the literature. Am Surg. 1995; 61 (12): 1095–1098.
38. *Ricci R., Maggiano N., Martini M., et al.*: Primary malignant melanoma of the gallbladder in dysplastic naevus syndrome. Virchows Arch. 2001; 438 (2): 159–165.
39. *Safioleas M., Agapitos E., Kontzoglou K., et al.*: Primary melanoma of the gallbladder: does it exist? Report of a case and review of the literature. World J Gastroenterol. 2006; 12 (26): 4259–4261.
40. *Pitlović V., Latić F., Pitlović H., et al.*: Primary malignant melanoma of gallbladder. Med Glas (Zenica). 2011; 8 (1): 71–73.
41. *Haskaraca M.F., Ozsoy M., Ozsan I., Kurt K.*: Primary malignant melanoma of the gallbladder: a case report and review of the literature. Case Rep Surg. 2012; 2012: 693547.
42. *Gligorijevic J., Zivkovic V., Djordjevic B., Dimov I.*: Primary gallbladder melanoma in dysplastic nevus syndrome: report of case and literature review. Turk J Gastroenterol. 2011; 22 (6): 626–630.
43. *Virgilio E., Scorsi A., Amodio P.M., et al..*: Primary malignant melanoma of the gallbladder: an outstandingly rare tumor. Clin Exp Med. 2016; 16 (3): 479–480.
44. *Wang J.K., Su F., Ma W.J., et al.*: Primary malignant melanoma of the gallbladder with multiple metastases: A case report. Medicine (Baltimore). 2017; 96 (46): e8793.
45. *Schmidt A., Caspar C., Schmidt-Weiss E., Stadlmann S.*: Clinicohistopathological characteristics of malignant melanoma in the gall bladder: a case report and review of the literature. Case Rep Pathol. 2018; 2018: 6471923.
46. *Yu Z., Quiroz E., Shen Y., Jaiyesimi I.A.*: Pathological complete response induced by neoadjuvant treatment using BRAF and MEK inhibitors in a patient with unresectable BRAF V600E-mutant malignant melanoma of the gallbladder. Onco Targets Ther. 2018; 11: 8723–8728.
47. *Tamura K., Umemura Y., Hijioka S., et al.*: Asymptomatic malignant melanoma of the gallbladder with multiple brain metastases diagnosed with endoscopic ultrasound-guided fine-needle aspiration cytology. Clin J Gastroenterol. 2019; 12 (5): 490–494.
48. *Ujiie D., et al.*: [Primary malignant melanoma of the gallbladder]. Gan To Kagaku Ryoho, 2016; 43: 1603–1604.
49. *Longwitz D., Schulz H. G., Bosse A.*: [Malignant melanoma of the gallbladder]. Ultraschall Med. 1996; 17 (4): 195–198.
50. *Simonenko V.B., et al.*: [Primary melanoma of the gall bladder]. Klin Med. (Mosk.) 2004; 82: 69–71.
51. *Medina V., Darnell A., Bejarano N., et al.*: Primary biliary tract malignant melanoma: US, CT, and MR findings. Abdom Imaging. 2003; 28 (6): 842–846.
52. *Allen A.C., Spitz S.*: Malignant melanoma; a clinicopathological analysis of the criteria for diagnosis and prognosis. Cancer. 1953; 6 (1): 1–45.
53. *Agarwal S.R., Bhattacharya I., Patil Y.V., Amrapurkar A.D.*: Choroidal melanoma metastatizing to the biliary system: A diagnostic dilemma. Indian J Med Paediatr Oncol. 2009; 30 (4): 138–140.
54. *Cassou-Mounat T., Luporsi M., Huchet V., Jehanno N.*: Gallbladder metastasis from conjunctival melanoma. Clin Nucl Med. 2019; 44 (2): e107–e109.
55. *Shimkin P.M., Soloway M.S., Jaffe E.*: Metastatic melanoma of the gallbladder. Am J Roentgenol Radium Ther Nucl Med. 1972; 116 (2): 393–395.
56. *Basu S., Houseni M., Alavi A.*: (18)F-FDG-PET in restaging primary maxillary sinus melanoma with isolated gall bladder metastasis. Hell J Nucl Med. 2009; 12 (2): 170.
57. *Furumoto K., Miyauchi Y., Ito D., et al.*: Solitary metastatic gallbladder malignant melanoma originated from the nasal cavity: A case report. Int J Surg Case Rep. 2013; 4 (11): 965–968.
58. *Kawakami H., Kubota Y.*: Malignant melanoma metastatic to the gallbladder diagnosed by endoscopic ultrasonography-guided fine-needle aspiration. Endosc Ultrasound. 2017; 6 (6): 414–415.
59. *Abdelli N., Thiefin G., Diebold M.D., et al.*: Endoscopic retrograde cholangiography in a metastatic melanoma of the gallbladder presenting as a gallstone migration. Endoscopy. 1996; 28 (4): 402.
60. *Addeo P., Onea A., Scrivener J.-N., Bachellier P.*: Gallbladder metastasis from melanoma. Dig Liver Dis. 2020; 52: 679–680.

61. *Balthazar E.J., Javors B.*: The radiology corner. Malignant melanoma of the gallbladder. Am J Gastroenterol. 1975; 64 (4): 332–335.
62. *Bundy A.L., Ritchie W.G.*: Ultrasonic diagnosis of metastatic melanoma of the gallbladder presenting as acute cholecystitis. J Clin Ultrasound. 1982; 10 (6): 285–287.
63. *Cellerino P., Corsi F., Morandi E., et al.*: Metastatic melanoma of the gallbladder. Eur J Surg Oncol. 2000; 26 (8): 815–816.
64. *Colaneri R.P., Nunes Bdos S., Herman P.*: Melanoma of the gallbladder misdiagnosed as gallbladder cancer. Hepatobiliary Pancreat Dis Int. 2010; 9 (1): 108–109.
65. *Crippa S., Bovo G., Romano F., et al.*: Melanoma metastatic to the gallbladder and small bowel: report of a case and review of the literature. Melanoma Res. 2004; 14 (5): 427–430.
66. *Cunningham J.J.*: Atypical cholesonograms in primary and secondary malignant disease of the biliary tract. J Clin Ultrasound. 1977; 5 (4): 264–267.
67. *De Simone P., Mainente P., Bedin N.*: Gallbladder melanoma mimicking acute acalculous cholecystitis. Surg Endosc. 2000; 14 (6): 593.
68. *Ercolino G.R., Guglielmi G., Pazienza L., et al.*: Gallbladder and small bowel metastasis of regressive melanoma: a case report. BJR Case Rep. 2018; 5 (1): 20180032.
69. *Gassler N., Banafsche N., Quentmeier A., et al.*: Sekundäres malignes Melanom der Gallenblase. Ein Beitrag zur Differenzialdiagnose pigmentierter Läsionen der Gallenblase [Secondary malignant melanoma of the gallbladder. A contribution to the differential diagnosis of pigmented lesions of the gallbladder]. Pathologe. 2004; 25 (2): 155–159.
70. *Gawenda M., Franzen D., Lorenzen J., Müller U.*: Gehirn- und Gallenblasen-Metastasen 10 Jahre nach lokaler Exzision eines kutanen malignen Melanoms [Brain and gallbladder metastases 10 years after local excision of a cutaneous malignant melanoma]. Dtsch Med Wochenschr. 1995; 120 (9): 289–292.
71. *Guida M., Pisconti S., Colucci G.*: Metastatic melanoma: the new era of targeted therapy. Expert Opin Ther Targets. 2012; 16 (Suppl 2): S61–70.
72. *Hahn S.T., Park S.H., Choi H.S., et al.*: Ultrasonographic features of metastatic melanoma of the gallbladder. J Clin Ultrasound. 1993; 21 (8): 542–546.
73. *Hall N., Grenier N. L., Shah S.A., et al.*: Metastatic gallbladder melanoma presenting as acute emphysematous cholecystitis. Case Rep. Med. 2018; 2018: 5726570.
74. *Herrington, J.L.*: Metastatic malignant melanoma of the gallblader masquerading as cholelithiasi. Am J Surg. 1965; 109: 676–678.
75. *Higgins C.M, Strutton GM.*: Malignant melanoma of the gall bladder — does primary melanoma exist? Pathology. 1995; 27 (4): 312–314.
76. *Kazmann H.A., Zukaukas C.L.*: Malignant melanoma of the gallbladder. Am J Surg. 1956; 92 (3): 469–471.
77. *Khan Z.S., Huth J., Kapur P., Huerta S.*: Indications and recommended approach for surgical intervention of metastatic disease to the gallbladder. World J Surg Oncol. 2010; 8: 80.
78. *Lajolo P.P., Del Giglio A., Speranzini M., et al.*: Melanoma metastático para vesícula biliar simulando litase vesical [Metastatic melanoma of the gallbladder mimicking Bladder Calculi]. Rev Assoc Med Bras. 2005; 51 (2): 74.
79. *Langley R.G., Bailey E.M., Sober A.J.*: Acute cholecystitis from metastatic melanoma to the gallbladder in a patient with a low-risk melanoma. Br J Dermatol. 1997; 136 (2): 279–282.
80. *Marone U., Caracò C., Losito S., et al.*: Laparoscopic cholecystectomy for melanoma metastatic to the gallbladder: is it an adequate surgical procedure? Report of a case and review of the literature. World J Surg Oncol. 2007; 5: 141.
81. *McFadden P.M., Krementz E.T., McKinnon W.M., et al.*: Metastatic melanoma of the gallbladder. Cancer. 1979; 44 (5): 1802–1808.
82. *Nelms J.K., Patel J.A., Atkinson D.P., Raves J.J.*: Metastatic malignant melanoma of the gallbladder presenting as biliary colic: a case report and review of literature. Am Surg. 2007; 73 (8): 833–835.
83. *Ostick D.G., Haqqani M.T.*: Obstructive cholecystitis due to metastatic melanoma. Postgrad Med J. 1976; 52 (613): 710–712.

84. *Patel D., Sohrawardy S., Sedhai Y.R., et al.*: Metastatic cutaneous melanoma of the gallbladder. Case Rep Gastrointest Med. 2017; 2017: 8532379.
85. *Samplaski M.K., Rosato E.L., Witkiewicz A.K., et al.*: Malignant melanoma of the gallbladder: a report of two cases and review of the literature. J Gastrointest Surg. 2008; 12 (6): 1123–1126.
86. *Saraswat N.B., DeVoe W.B.*: Metastatic melanoma of the gallbladder presenting as polyp in acute cholecystitis. J Surg Case Rep. 2019; 2019 (12): rjz324.
87. *Swiatoniowski G., Mazur G., Hałoń A., et al.*: Malignant melanoma with gall bladder metastasis as a second neoplasm in the course of prostate cancer. Pathol Oncol Res. 2004; 10 (4): 243–245.
88. *Takayama Y., Asayama Y., Yoshimitsu K., et al.*: Metastatic melanoma of the gallbladder. Comput Med Imaging Graph. 2007; 31 (6): 469–471.
89. *Tuveri M., Tuveri A.*: Isolated metastatic melanoma to the gallbladder: is laparoscopic cholecystectomy indicated?: a case report and review of the literature. Surg Laparosc Endosc Percutan Tech. 2007; 17 (2): 141–144.
90. *Varsamidakis N., Panagiotou P., Yettimis E.*: Isolated gallbladder metastatic melanoma. HPB (Oxford). 2006; 8 (1): 73.
91. *Vernadakis S., Rallis G., Danias N., et al.*: Metastatic melanoma of the gallbladder: an unusual clinical presentation of acute cholecystitis. World J Gastroenterol. 2009; 15 (27): 3434–3436.
92. *Rea D.J., van Heerden J.A.*: Image of the month. Malignant melanoma of the gallbladder (primary vs secondary). Arch Surg. 2004; 139 (12): 1383–4138.
93. *De Risi D., Spier N., Holyoke E.D.*: Report of a rare case of significant hemobilia and review of this entity. J Med. 1982; 13 (4): 323–336.
94. *Avila N.A., Shawker T.H., Fraker D.*: Color-flow Doppler ultrasonography in metastatic melanoma of the gallbladder. J Clin Ultrasound. 1994; 22 (5): 342–347.
95. *Stutte H., Müller P.H., d'Hoedt B., Stroebel W.*: Ultrasonographic diagnosis of melanoma metastases in liver, gallbladder, and spleen. J Ultrasound Med. 1989; 8 (10): 541–547.
96. *Holloway B.J., King D.M.*: Ultrasound diagnosis of metastatic melanoma of the gallbladder. Br J Radiol. 1997; 70 (839): 1122–1125.
97. *Colovic R.B., Grubor N.M., Jovanovic M.D., et al.*: Metastatic melanoma to the common bile duct causing obstructive jaundice: a case report. World J Gastroenterol. 2007; 13 (5): 813–815.
98. *Andreano A., Laeseke P., Lava M., et al.*: Asymptomatic metastatic melanoma of the gallbladder diagnosed with contrast-enhanced ultrasonography. J Ultrasound Med. 2010; 29 (7): 1133–1137.
99. *Barretta M.L., Catalano O., Setola S.V., et al.*: Gallbladder metastasis: spectrum of imaging findings. Abdom Imaging. 2011; 36 (6): 729–734.
100. *Xie X.H., Xu H.X., Xie X.Y., et al.*: Differential diagnosis between benign and malignant gallbladder diseases with real-time contrast-enhanced ultrasound. Eur Radiol. 2010; 20 (1): 239–248.
101. *Choi W.S., Kim S.H., Lee E.S., et al.*: CT findings of gallbladder metastases: emphasis on differences according to primary tumors. Korean J Radiol. 2014; 15 (3): 334–345.
102. *Rehani B., Strohmeyer P., Jacobs M., Mantil J.*: Gallbladder metastasis from malignant melanoma: diagnosis with FDG PET/CT. Clin Nucl Med. 2006; 31 (12): 812–813.
103. *Ozülker T., Ozülker F., Cicin I., Ozpaçac T.*: A case of malignant melanoma with cardiac and gallbladder metastases detected by FDG PET-CT. Clin Nucl Med. 2009; 34 (12): 948–949.
104. *Alimova E., et al.* [Metastatic melanoma of the gallbladder: two cases]. Ann Dermatol Venereol. 2009; 136: 368–370.
105. *Antonini F., Acito L., Sisti S., et al.*: Metastatic melanoma of the gallbladder diagnosed by EUS-guided FNA. Gastrointest Endosc. 2016; 84 (6): 1072–1073.
106. *Christou D., Katodritis N., Decatris M.P., et al.*: Melanoma of the gallbladder: appropriate surgical management and review of the literature. Clin Case Rep. 2014; 2 (6): 313–318.
107. *Würtz H.J., Detlefsen S., Ainsworth A.P.*: [Metastasis from a malignant melanoma presenting as a gall bladder polyp]. Ugeskr Laeger. 2018; 180 (23): V01180034.

108. *Cicin I., Usta U., Sezer A., et al.*: Synchronous tonsil, gallbladder, and cardiac metastases without any other visceral metastases of malignant melanoma. Onkologie. 2009; 32 (4): 197–199.
109. *D'Urso Vilar G.G., Iriarte F., et al.*: Isolated gallbladder metastasis of melanoma: Case report. Int J Surg Case Rep. 2020; 71: 311–314.
110. *Gogas J., Mantas D., Gogas H., et al.*: Metastatic melanoma in the gallbladder: report of a case. Surg Today. 2003; 33 (2): 135–137.
111. *Hess G.F., Glatz K., Rothschild S.I., et al.*: Malignant melanoma metastasis in the gallbladder. A case report of an unusual metastatic site. Int J Surg Case Rep. 2020; 75: 372–375.
112. *Seelig M.H., Schönleben K.*: Laparoscopic cholecystectomy for a metastasis of a malignant melanoma in the gallbladder. Z Gastroenterol. 1997; 35 (9): 673–675.
113. *Di Buono G., Maienza E., Rinaldi G., et al.*: Malignant metastatic melanoma to the gallbladder: Report of a peculiar case. Int J Surg Case Rep. 2020; 77S (Suppl): S37–S39.
114. *Köhler U., Jacobi T., Sebastian G., Nagel M.*: Laparoskopische Cholecystektomie bei einer isolierten Gallenblasenmetastase eines malignen Melanoms [Laparoscopic cholecystectomy in isolated gallbladder metastasis of malignant melanoma]. Chirurg. 2000; 71 (12): 1517–1520.
115. *Ruiz Pardo J., Ruescas García F.J., Parra Cubillos A., Sagredo Rupérez M.P.*: Metastatic melanoma of the gallbladder: an uncommon finding. Rev Esp Enferm Dig. 2020; 112 (3): 236–237.