

# Surgical treatment of metastatic gallbladder cancer. Systematic review with own experience

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**Introduction.** Patients with metastatic gallbladder cancer (GBC) are generally considered incurable and compelled to palliative chemotherapy. Nevertheless, there are numerous reports of successful surgical management of metastatic GBC. The impact of such treatment is yet unclear.

**Material and methods.** We conducted a systematic literature review within Medline and Scopus databases using the following pattern: "gallbladder" and "cancer" and "dissemination". Also, our own experience with two resected metastatic GBC patients was added to the results.

**Discussion.** The literature search yielded 8 publications with a total of hundred and twelve patients fulfilling the inclusion criteria. Two additional patients were included in the analysis: one with resected GBC liver metastasis and the second with resected GBC diaphragmatic metastasis. A total of hundred and fourteen patients who underwent resection of a solid organ GBC metastasis were analyzed. The study confirmed a rare long-term survival after resection of an isolated GBC metastasis.

**Conclusions.** There is no clear indication for surgical management of gallbladder cancer metastasis. In selected cases, an aggressive surgical approach may be justified.

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**Key words:** gallbladder cancer, metastatic disease, surgery

## Introduction

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract and the fifth among cancers of the gastrointestinal tract. Risk factors of GBC include: cholelithiasis, a variety of congenital disorders and chronic inflammation. The disease has a peak incidence between the 6<sup>th</sup> and 7<sup>th</sup> decades of life [1]. It is usually diagnosed at an advanced stage, as it lacks specific symptoms at early stages [2]. At advanced stages, it is characterized by rapid progression and may frequently

spread to adjacent organs, such as: regional and non-regional duodenum, lymph nodes, peritoneum, pancreas, colon, and liver, which is the most frequent solid organ with metastasis from the GBC.

Since laparoscopy is frequently the first attempt at GBC (mainly in patients with no pre-operative suspicion of GBC), cancer implants in trocar sites can also be found by several patients [3]. The typical pre-operative staging includes: ultrasonography, computer tomography (CT) and magnetic reso-

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nance imaging (MRI). Most patients with stage IVb according to the 8<sup>th</sup> edition of the UICC TNM classification (tumor that has spread to tissues or organs far away from the gallbladder including lymph nodes) are not normally candidates for curative resection [4]. However, there are several reports, mainly from Japan, proving successful surgical management of metastatic GBC. The impact of such treatment on patients' health is unclear. The aim of this study was to evaluate the benefits of surgical approach in patients with isolated resectable solid organ metastasis from GBC.

## Methods

We have searched the available medical literature for studies reporting outcomes of surgical resection of solid organ metastasis of GBC. Since in the vast majority of patients, port-site metastasis is associated with concurrent or future diffuse peritoneal disease and death [5, 6], we have decided to limit our analysis to isolated solid organ metastases, excluding port-site metastasis.

The PubMed and Scopus databases were searched using the keywords "gallbladder" and "cancer" and "dissemination". The literature review yielded 115 results. Based on the abstracts' analysis, 43 studies were excluded due to the following reasons:

- 3 studies on veterinary surgery,
- 7 studies about metastases of cancers other than GBC,
- 19 studies about cancers other than GBC,
- 8 basic science studies,
- 3 studies that did not concern metastasis,
- 3 studies describing the operative technique.

The remaining papers were evaluated in full text version.

At this stage, studies were excluded based on the following:

- 10 studies depicting massive spread to the peritoneal cavity,
- 13 studies on peritoneal implants after laparoscopy,
- 10 studies on evaluation of inoperable tumors,
- 7 studies on basic research,
- 12 studies on patients without metastasis,
- 9 commentaries, 3 studies about other cancers,
- 1 epidemiology paper.

Of the remaining 7 studies [7–13], after a thorough analysis of the texts, we have excluded 3 further studies [8, 9, 13] because we have failed to extract the data of patients with resectable metastasis of GBC. Based on cross-referencing of the remaining 4 studies, we have added to this systematic review 5 more studies fulfilling the search criteria [14–17]. In the final analysis, we have included 8 studies.

**Table I.** The results of aggressive surgical treatment of 112 patients included in this study

Study	Number of patients	Survival	R0	Median survival (months)	Notes
1. Yagi et al.	2	1 patient – 24 months 2 patient alive with no evidence of disease after unknown time	2	Not given	Long survival possible after radical resection
2. Nishio et al.	25	3-y – 8%	Not given	Not given	The survival for patients with isolated liver metastasis was better than that for patients with other distant metastasis
3. Shimuzi et al.	16	3-y – 14.4%	Not given	Not given	Long survival possible after radical resection
4. Higuchi et al.	39	5-y – 4 patients in the R0 group	12	Not given	Long survival possible after radical surgery
5. Kondo et al. ( <i>Br J Surg</i> 2002)	10	1-y – 37% 3-y – 7% 5-y – 3% numbers calculated for all M1 patients	Not given	6.6	Limited distant metastasis is associated with worse survival
6. Yamaguchi et al.	2	No data	Not given	Not given	Perineural invasion and lymph node metastasis were identified as significant independent prognostic factors in patients with GBC
7. Chijiwa et al.	7	Approaching 0 after 20 months	Not given	Not given	Patients with resected liver metastases have a prognosis similar to nonresected stage IV patients
8. Kondo et al. ( <i>Langenbeck's Arch Surg</i> 2002)	11	Not given	Not given	Not given	No further data available. Possibly overlapping with position 5
9. Current cases	2	23 months 15 months	2	Not given	One case of synchronous liver metastasis treated with simultaneous R0 resection One case of metachronous diaphragmatic metastasis treated with R0 resection. Long survival possible

## Results

The eight papers included in this review describe altogether a hundred and twelve patients with solid organ metastasis from GBC. The results of the treatment of a hundred and twelve patients combined with data on two patients treated in Maria Skłodowska-Curie Institute – Oncology Center, Kraków Branch (MSCI-OCKB) are presented in Table I.

All 8 papers in this review come from the Japanese centers and 2 papers (17, 18) originate from the same research team. The authors of the present systematic review tried but failed to contact members of this team to confirm whether these 2 papers represent an overlapping group of patients.

In the paper by Yamaguchi et al [12], the authors reviewed their experience with 68 GBC patients that included 2 patients with liver metastasis. Based on the data from this paper, it was impossible to extract data concerning these particular 2 patients. The survival data from this paper included in Table I represent the numbers for the whole GBC group. The paper by Yagi reports only 2 patients, but with impressive survival numbers [14]. The paper by Nishio et al. reports the results of the surgical treatment of a 166 patients with stage IV GBC. The data on 25 patients with the resection of liver metastasis could be extracted from the paper [15]. Also, the paper by Shimizu et al. describing the results of the treatment of stage IV GBC, allowed for the extraction of data on 16 patients with resectable liver metastasis [16]. In the paper by Higuchi et al., the authors report 274 patients with advanced GBC. Of these, 61 patients had liver metastasis including 39 with single metastasis. The resection was possible for 12 patients from the latter allowing for 5-year survival of 4 patients [7]. From the group of 37 patients with stage IV GBC described by Chijiwa et al., 7 patients with liver metastases could be identified [10]. In the first of the 2 papers by Kondo et al. from Nagoya, the authors focused on the mode of tumor spread and its influence on prognosis in a 112 patients with advanced GBC [18]. While it was possible to identify 11 patients with hepatic metastasis in this group, no further conclusions about this particular group could be drawn from the paper. In the second paper from Nagoya team describing a 116 patients with advanced GBC, the data on 30 patients with metastatic disease was identified. This group included 10 patients with liver metastases. The survival was calculated for the entire cohort of M1 patients that included also 24 patients with metastases in para-aortic lymph nodes and 3 patients with peritoneal metastasis [17].

In Table I we have also included 2 patients fulfilling inclusion criteria, operated on in second author's institution (MSCI-OCKB). One patient underwent simultaneous radical resection of GBC and the resection of a single metastasis in segment V of the liver. She presented with disseminated disease 6 months after surgery and is alive with disease 23 months after surgery. The second patient underwent resection of the right diaphragm due to metachronous GBC metastasis 35 months after primary surgery. She presented with disseminated disease 7

months after surgery for diaphragmatic metastasis and is alive with disease 15 months after surgery.

## Discussion

Advanced gallbladder cancer (GBC) is associated with poor prognosis [19]. All stage IV GBC patients who do not undergo resection die within 20 months of diagnosis [10] and their median survival approaches 5.8 months [20]. Depending on the general status of a patient, treatment with chemotherapy, radiotherapy or palliative care is suggested [11]. Patients receiving palliative surgery and chemotherapy tend to survive less than 12 months [18]. However, there are isolated reports about longer survival following radical resection of a primary tumor and GBC metastasis. In this systematic review, we have looked at the available data on these patients. The small size of the group and the lack of data on adjuvant and neoadjuvant treatment did not allow us for the analysis of treatment options other than radical surgery.

All identified papers were authored by Japanese surgical teams and two papers came from the same team [17, 18]. This finding is probably a reflection of a more radical approach to GBC cancer in Japan, but at the same time it makes it difficult to extrapolate the results to other populations. Microscopic liver metastasis not seen on pre-operative and intra-operative imaging were found on specimen analysis of 6/44 patients with GBC and liver resection in the paper by Yagi et al. [14]. This group included 2 patients with R0 resection described in Table I. One of these patients survived 24 months and another was alive with no evidence of disease after an undefined period of time. The status of liver invasion in this group was found to be one of the prognostic factors on multivariate analysis. In the group of 25 patients reported by Nishio et al. with resected isolated liver metastasis from GBC, there were 2 patients surviving more than 5 years (8% 5-years OS). The survival of patients undergoing only the resection of liver metastasis was better than of those with other distant metastasis and better than in non-resected patients. The authors concluded that a small percentage of patients can have an important survival advantage from a radical approach to isolated liver GBC metastasis [15]. The risk factors for in-hospital mortality were advanced age, obstructive jaundice, extended hepatectomy, portal vein resection, and extrahepatic bile duct resection. The extended surgery, especially in patients with obstructive jaundice, has been found to be an important factor determining survival by increasing the risk of in-hospital mortality and morbidity in a paper by Shimzu et al. [16]. Interestingly, in univariate analysis the presence of liver metastasis detected in 16 patients was not found to influence overall survival in resected GBC patients. The 5-year survival in this group was as high as 14.4%. The authors concluded that R0 resection should be offered especially to those patients with liver metastases who have absent or minimal involvement of hepatoduodenal ligament and who are node-negative. The presence of liver metastases was found to influence survival in a paper

by Higuchi et al. In 12 patients in whom R0 resection of the liver tumors was possible, the 5-year survival was reached in 4 patients giving a stunning 33% 5-years OS. Unfortunately, the R0 resection was possible only in 12 out of 39 patients with single liver metastasis. The authors stated that radical surgery is not a viable option for patients with more than one liver lesion, but R0 resection of a single liver metastasis should always be considered [7]. Surgery should be proposed to all stage IV GBC patients as it improves survival according to the paper by Chijiwa. However, the outcomes of treatment for patients with peritoneal dissemination, liver metastasis, and distant metastasis were similar to non-resected patients. The authors concluded that all IVB patients (including patients with liver metastases) are not good candidates for surgery, which should be limited to stage IVA GBC patients [10]. In this paper, the authors excluded patients presenting with limited, resectable liver metastasis, but analyzed the whole stage IVB altogether.

In the paper by Yamaguchi et al. we were able to identify only 2 patients with resected liver metastasis. The authors were not evaluating this particular group of patients, they were rather analyzing factors influencing survival in the whole GBC cohort. Based on the analysis of 68 patients, the authors found that perineural invasion and lymph node metastasis were significant independent prognostic factors for survival [12].

The group of authors from Nagoya, Japan was the only to publish 2 papers fulfilling the criteria of the present review. In the 2002 paper, the authors described a group of 112 GBC patients, of whom 11 had liver metastasis. The paper provide only limited data on this particular group of patients. The authors stated that 2 of 47 patients with distant metastases or portal vein invasion survived for more than 5 years [18]. In the second paper by the same team, there were 30 patients with metastases included. The survival rates for this group were: 37% at 1 year, 7% at 3 years and 3% at 5 years. All patients who underwent palliative surgery died within 1 year. Based on this data, the authors suggested that radical resection should be abandoned when GBC is associated with hepatic or any other metastasis [17].

The two patients in our own encounter enjoyed relatively long survival after resection of metastatic tumors of the liver and diaphragm.

There are some important flaws in this review. The data on the precise extent of surgery (simple metastasectomy vs. anatomical resection) as well as management of gallbladder bed are missing in some papers. The management of regional lymph nodes was also not described in detail in the reviewed papers.

## Conclusions

In summary, the existing data on the surgical resection of solid organ metastases of GBC are scarce and contradictory. While some authors back radical surgery (only if R0 resection is achievable), others discourage this approach. The fact that all papers found during our review come only from 7 Japanese hospitals further obscures the results. It seems, however, that radical surgery should

be taken into account in patients with a solitary metastasis, without hepatoduodenal lymph nodes involvement, with radical primary tumor resection and without perineural invasion, as it may result in an improvement in otherwise poor survival.

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