Surgical management of breast cancer liver metastases

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We analyzed the treatment results in patients who underwent hepatic resection for breast cancer liver metastases(BCLM).
Between 1/2003 and 12/2012, 15 patients underwent hepatic resection for BCLM. All primary breast tumors were diagnosed as invasive breast cancer. Synchronous BCLM ocurred in 2 patients and 13 patients presented with metachronous BCLM.
Median age of patients at the time of BCLM diagnosis was 51 years(range from 31 to 73 years). All resections were considered as R0. From among 15 resections we performed 10 major hepatic resections according to Couinaud classification(≥3 segments) and the rest were minor ones. There was no postoperative mortality within 60 days . All postoperative complications were managed conservatively. Median hospital stay was 10,5 days, ranging from 7-14 days.
Standard therapy for patients with BCLM remains systemic chemo- and hormonal therapy. Hepatic resection as a part of multimodal treatment in tertiary HPB centers can offer in a selected group of patients a safe option for improved survival.

Key words: breast cancer, liver metastases, hepatic resection

Breast cancer is the most common malignancy among the women worldwide and the second leading cause of cancer-related deaths in the USA.[1] In 2008 the estimated number of newly diagnosed cases world-wide was 1,384,155 which represented 22,7% share of newly diagnosed cancers among women. In 2005, the number of breast cancer cases in females diagnosed in the Slovak Republic was 2,198, which represents ASR-W incidence of 52.2/100,000. [2] Metastatic breast cancer is considered as a systemic disease with pre-dominant hematogenous spread of the tumor cells. Despite of new therapeutical modalities it still could not be regarded as a curable disease. Modern systemic regimens can provide response rates up to 60%.[3] Liver is the third most common distant metastasis site in breast cancer patients.[4] The 4 most common reported anatomic sites of distant metastases are bone (41,1%), lung(22,4%), liver(7,3%), and brain(7,3%).[5] From among patients with noncolorectal nonendocrine tumors with liver metastases, patients with breast as a primary tumor site belongs to the group with favourable outcome following resection with 5-year and 10-year survival of 41% and 22%, respectively. [6] Elias et al. [7] reports that liver metastases appear in cca half of women with metastatic breast cancer. Isolated BCLM occur in 4-5% of metastatic breast cancer patients.[8,9] Presence of liver metastases indicates a very poor prognosis with median survival time of only 4-8 months if left untreated.[10] In patients with BCLM who underwent hormone therapy or chemotherapy (Doxorubicín, Docetaxel,5-fluorouracil) median survival does not exceed 24 months. [11] It remains still questionable whether surgery plays an indispensable role in overall survival improvement in patients with BCLM.

Patients and methods

Between 1/2003 and 12/2012, 15 patients underwent hepatic resection for BCLM. Diagnosis of the primary tumor was histopathologically confirmed as an invasive breast cancer in every patient. Breast cancer staging was done according to the seventh edition of the International Union Against Cancer(UICC) .[12] All of them were female patients who received either breast conserving surgery (lumpectomy,quad rantectomy) or modified radical mastectomy combined with axillar lymphadenectomy.

Statistic analysis. Data were collected prospectivelly and were retrospectively evaluated from our database. Statistic analysis was performed using XLSTAT2013 software and the Kaplan-Maier method was used for survival determination.

Results

Characteristics of primary breast cancer. All 15 patients were females with a median age at the time of BCLM diagnosis of 51 years(range from 31 to 73 years). Primary tumor was referred as an invasive ductal type in 88% (12 patients) and 12 % (3 patients) presented with invasive lobular carcinoma. High-grade cancer was identified in 47% of cases and the rest 53% were grade 2 tumors. T1/2 tumors were present in 81%, T4 tumors ocurred in 19% of patients. 50% of patients had positive axillary lymphnode status. Modified radical mastectomy combined with axillary lymphadenectomy was performed in 58% and breast conserving procedure with axillary lymphadenectomy was performed in 42%. Because of 2 cases of bilateral cancer one patient underwent bilateral modified radical mastectomy and the second one underwent unilateral mastectomy and contralateral breast conserving procedure.

Liver metastasis-specific data. Indication criteria for hepatic resection have been changing over the period of time of our study according to ability of systemic treatment (Navelbin+5FU/FA, Taxol, Avastin, Docetaxel, Femara, Herceptin, Xeloda) to stabilize the primary breast cancer disease. While some 10 years ago we had almost no patients with BCLM suitable for hepatic resection, in present we are dealing with breast cancer liver metastatic patients who are approved by multidisciplinary team for hepatic resection. Resection candidates were patients with good performance status with macroscopically safely resectable liver lesions. Before resection all the patients underwent CT, liver MRI with Primovist contrast media and bone scintigraphy. Study is a retrospective one. Written informed consent was obtained from each patient prior to hepatic resection.

Between 1/2003 and 12/2012 we performed overall 283 hepatic resections, including 15 resections for BCLM . Resections were considered as major with removal ≥ 3 segments and as minor with removal < 3 segments according to Couinaud classification. [13] Synchronous BCLM ocurred in 2 patients. In these patients hepatic resection was performed in the second step after breast surgery and adjuvant systemic treatment (Navelbin+5FU/FA, Taxol, Avastin, Docetaxel, Femara, Herceptin, Xeloda). 13 patients presented with metachronous BCLM. Median interval between breast surgical procedure and hepatic resection was 46,5 months(range 17 – 80 months). Interval between breast surgery and appearance of BCLM varied from 0(synchronous presentation of BCLM) to 178,6 months (Table 2). In this interval all patients underwent systemic treatment targeted for breast cancer and 5 patients underwent neoadjuvant chemotherapy before hepatic resection for BCLM. 5 patients with BCLM and stabilized extrahepatic disease were included in the study (1 patient with resectable pulmonary metastasis that was resected 2 months later, 2 patients with stabile skeletal lesions, 1 patient with ovarian metastasis was treated simultaneously by ovarectomy, 1 patient with triplex primary tumor: ovarian, renal and breast cancer – ovarian and renal ones treated before , she had past history of hysterectomy and bilateral adnexectomy and nefrectomy for renal cancer). Median size of liver metastases was 22 mm (range 2 – 66 mm). Number of metastatic lesions ranged from 1 to 5, solitary lesion was present in 9 patients, 3 lesions in three patients, 4 lesions in two patients and 5 lesions occurred in one patient. Distribution of the liver lesions was unilobar in 9 cases while in 6 patients was bilobar. Resection margin was more than 10 mm in all cases. Imunohistochemistry of hepatic lesions revealed steroid

Table 1. Characteristics of primary breast cancer

Patient nr.	T	N	Grade	ER	PR	HER2
1	2	0	2	0%	0%	NR
2	4	1	2	0%	0%	NR
3	1/2	0/1	3/3	50%/50%	50%/50%	NR
4	4/1	1/0	3/3	50%/75%	50%/50%	NR
5	2	2	3	90%	15%	Posit.
6	2	1	2	30%	0%	NR
7	1	0	2	70%	30%	Posit.
8	2	1	2	0%	0%	NR
9	2	2	3	75%	50%	NR
10	4	1	3	50%	0%	NR
11	2	0	2	0%	0%	NR
12	2	0	2	Posit.	Posit.	NR
13	1	0	2	0%	0%	NR
14	2	1	2	0%	0%	Posit.
15	1	1	3	0%	0%	Posit.

Abbr: ER – estrogene receptor status, PR – progesterone receptor status, IDC – invasive ductal cancer, ILC – invasive lobular cancer, NR – not recorded.

Table 2. Characteristics of metastatic liver lesions in BCLM patients

Patient Nr.	Interval to diagnosis of BCLM/months	Interval from diagnosis of BCLM to surgery / months	Extrahepatic disease	S/M
1	0	6,6	Ovarian cancer + renal cancer	S
2	0	3,2	0	S
3	55,6	0,93	0	M
4	178,6	5,4	0	M
5	73,2	2,1	lungs	M
6	85,1	1	skeletal	M
7	64,1	0,5	0	M
8	15,1	0,5	0	M
9	15	1,1	0	M
10	38,1	1,2	0	M
11	96,5	9,3	0	M
12	78,3	0,4	ovary	M
13	119,4	50,2	skeletal	M
14	33,1	4,8	0	M
15	49,3	2,3	0	M

Abbr.: S – synchronous BCLM, M – metachronous BCLM

receptor (SR) positivity in 7 patients, 5 were SR negative and in 3 patients SR status was not determined.

Hepatic resection procedures. All hepatic resections were considered as R0. From among 15 resections we performed 10 major hepatic resections according to Couinaud classification(≥3 segments) and the rest were minor ones. From among 10 major resections we performed right hepatectomy in 5 patients, right extended hepatectomy in 1 patient, left hepatectomy in 3 patients and central hepatic resection(S4, 5, 8) in 1 patient. Left lateral bisegmentectomy was performed once, anatomic segmentectomy (S3,4) in 1 patient, metastasectomy in 2 patients and in one patient we performed right portal branch ligature in combination with metastasectomy.

Mortality and morbidity. We have analysed postoperative morbidity and mortality that was defined as a complication ocurred within 60 days after operation. We did not encounter postoperative mortality within 60 days after resection. All postoperative complications were managed conservatively. Subphrenic abscess and biliary collection at the resection surface in one patient was drained under CT guidance, reactive pleural effusion resolved after drainage, 1 transient hepatic insufficiency was managed successfully in ICU. Hospital stay duration ranged from 7-14 days, with median of 10,5 days.

Overall survival – Median of overall survival in our patients was 52,7 months(range 9,2 – 79,8 months).

1, 3, a 5 –years survival was 100%, 67% and 38%, respectively.

We did not find significant difference in 1, 3 and 5-years survival in patients with synchronous vs. metachronous BCLM(p=0,606).

Concerning the time of the appearance of liver metastases we did not find significant difference (p=0,373) in 1- , 3- and
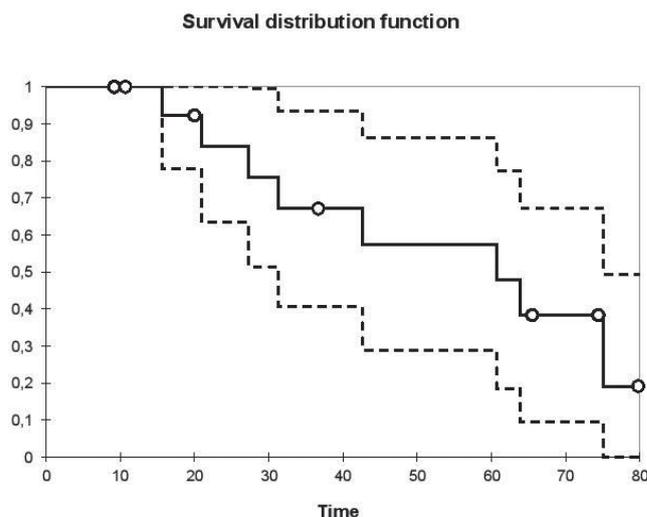

Figure 1. Overall survival curve of patients with BCLM

5-years survival between the groups of patients with BCLM development prior to 50 months (A in Fig. 3) in comparison with the one after 50 months (B in Fig.3).

Follow up/recurrence. 8 patients (53%) died during the follow up, all of them because of dissemination. During follow up we noted 6 cases with BCLM recurrence (disease free interval 6,9-15,9 months). In two patients brain and osseal metastatic lesions appeared. 7 patients are still alive with median of survival 36,7 months (range 9,2-79,8 months). In one of these patients hepatuoduodenal ligament lymphadenopathy was revealed and in one BCLM recurred. Totally 5 patients are alive without signs of disease recurrence.

Table 3. Type of hepatic resection procedure

Patient Nr.	Age/years	Procedure	Resection margin	Postop. complication	Hospital stay/days
1	51	Left lateral bisegmentectomy S2,3	>10 mm	0	11
2	57	Left hepatectomy	>10 mm	0	10
3	43	Right hepatectomy	>10 mm	0	11
4	43	Mts-ectomy S4A	>10 mm	0	7
5	51	Segmentectomy S3,4	>10 mm	0	9
6	49	Right extended hepatectomy	>10 mm	0	11
7	33	Central resection (S4, 5, 8)	>10 mm	0	7
8	31	Mts-ectomy + right portal branch ligation	>10 mm	0	8
9	66	Right hepatectomy	>10 mm	Subphrenic absces	8
10	48	Right hepatectomy 0	>10 mm	0	14
11	61	Left hepatectomy	<10 mm	0	10
12	61	Right hepatectomy	>10 mm	Fluidothorax+hepatorenal syndrome	14
13	55	Right hepatectomy	>10 mm	0	15
14	45	Mts-ectomy	>10 mm	0	8
15	45	Left hepatectomy	>10 mm	Fluidothorax, biloma	20

Survival distribution function
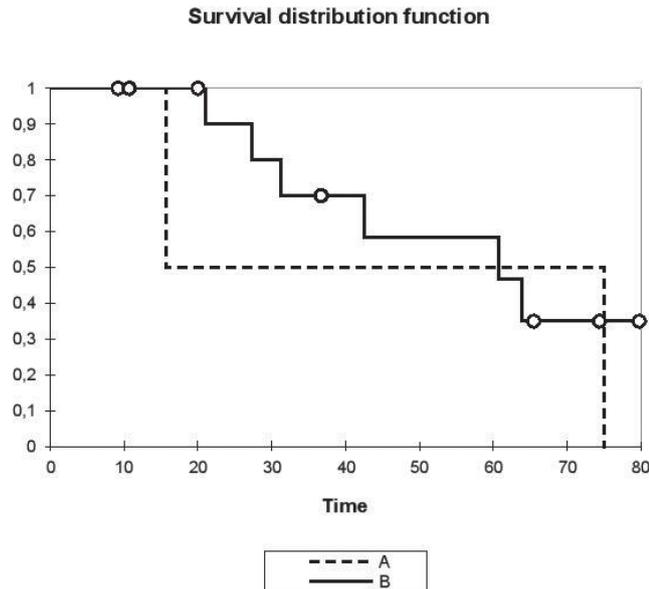

Survival distribution function

Figure 2. Synchronous(A) and metachronous(B) breast cancer liver metastases . Survival distribution function.
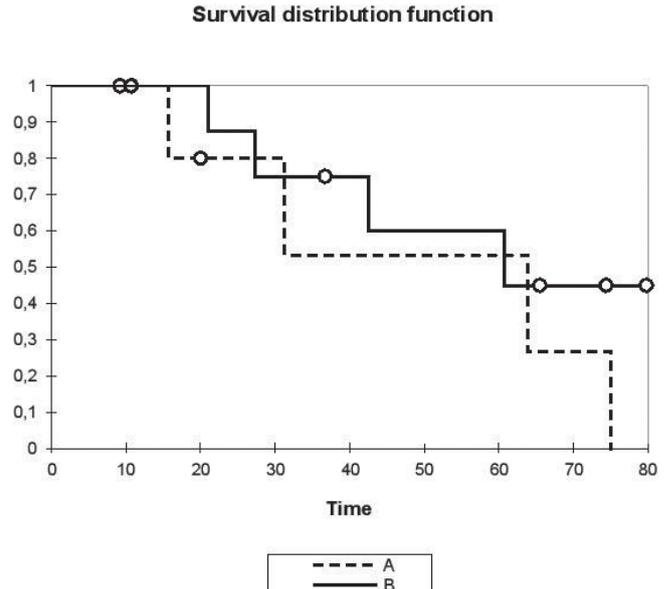
Figure 3. Comparison of survival according to the time of BCLM appearance

Discussion

According to the autopsy studies done by Lee [14], liver is the third most common site of breast cancer metastases (50-71%) after the lung (55-77%) and bone (49-74%). Breast represents the most common primary tumor site in the patients with noncolorectal nonendocrine liver metastases.[6] According to the various studies the number of patients with BCLM who underwent hepatic resection range from 6 to 85 with 5-years survival 18,4% – 61% whereby the largest study comes from Adam et al. [10] in 2006 who reports 37% 5-years survival and a median survival of 32 months in patients after surgery. Patients with BCLM are often included in the studies dealing with noncolorectal nonneuroendocrine liver metastases. In general, these studies comprise heterogenous groups of relatively small number of patients with different neoadjuvant and adjuvant treatment, with both synchronous and metachronous liver lesions. One of the parameters significantly influencing patients´ survival after hepatic resection for BCLM is time interval between breast surgery for primary tumor and development of liver metastases. Majority of the series proved the fact that the longer time interval was the better survival occurred.[15,16] Pocard et al. [17] reported 3-years survival of 55% when BCLM appeared in ≤ 48 months in comparison with 3-years survival of 85% when BCLM appeared after 48 months. Multivariate analysis showed prognostic relevance for the time interval between the primary diagnosis of breast cancer and the appearance of liver metastases (p < 0.05) .[18] However, in our study we did not find significant difference in 1- , 3- and 5-years survival between the groups of patients with BCLM

development prior to 50 months vs. after 50 months. Hepatic resection in patients with extrahepatic disease still remains controversial. In the study by Sakamoto et al. [19], presence of extrahepatic disease was the only prognostic factor of a poor outcome – no patient with extrahepatic disease survived 5 years but 5-year survival of patients without extrahepatic disease was 31%. In our study there were included 5 selected patients with stabilized extrahepatic disease: 1 patient with resectable pulmonary metastatic lesion, 2 patients with stabile skeletal lesions, 1 patient with ovarian metastasis and 1 patient with triplex primary tumor (ovarian, renal and breast cancer). Based on our opinion extrahepatic resectable disease should not be considered as an obstacle for hepatic resection. Small differences in survival were observed among patients with R0 and R1 resections.[9] According to histopathology reports all hepatic resections for BCLM in our study were considered as R0. In present breast cancer is not considered as a homogenous disease group but rather as a number of various subtypes with different features and distinct prognosis. It was reported that HER2-enriched subtype breast cancers agressively spread to the liver.[20] Gene expression studies have even identified subtype-specific predilections to distant metastatic site.[21] According to the phenotype, patients with basal-like or triple-negative breast cancers experience reduced disease-free and overall survival relative to other breast cancer subtypes.[22] Single-institution retrospective study of breast cancer liver metastases patients from Tianjin China reported 1-, 2- and 3-years survival rate 68.3, 48.0 and 34.1%, respectively with a median survival of 29 months. Results from this cohort study showed that triple-negative patients posses the worst survival when liver metastases oc-

cur in comparison with non-triple-negative subtypes . [23] In French study overal surival 1-, 3, a 5-years rate were 94, 69 and 33%, respectively. Analysis revealed that hormone receptor status, number of lesions, major hepatectomy and younger age were factors of a poor prognosis.[24] Concerning steroid receptor status in the present study 41% of the primary breast tumors were considered as ER negative and 53% PR negative. Another predictive factor is the status of hilar lymph nodes in patients with BCLM. However, studies did not revealed any significant differences in survival between hilar lymph-node positive and node-negative BCLM patients.[19,25,26]

Metastatic breast cancer, as it was emphasized above, is considered as a systemic disease and the re-appearance of liver lesions /or extrahepatic spread in previously resected BCLM patients is not rare. That is a reason why systemic treatment plays a crucial role in successful management of these patients. Unfortunately liver metastases are generally considered to be less responsive to chemotherapy than metastases at other sites and these patients with liver metastases have often worse survival in comparison with patients with metastatic spread to other organs.[27]

Standard therapy for patients with BCLM still remains systemic chemo and hormonal therapy (Navelbin+5FU/FA, Taxol, Femara, Avastin, Docetaxel,Herceptin,Aromasin). However advances in liver resection techniques, improvements in imaging tools, evolution in anesthetic and perioperative management have widely extended indication criteria for hepatic resections. Hepatic resection as a part of multimodal treatment in tertiary HPB centers has become a safe procedure with low rate of complications and can offer an option for improved survival in a selected group of BCLM patients. Liver resection is recently considered as a local adjuvant treatment of the liver in responders to systemic treatment. Pocard et al. [28] has denoted this treatment strategy as an „adjuvant surgery". On the contrary disease progression during preoperative systemic treatment is considered as a contraindiction to surgery. Limited series of patients resected for BCLM, often heterogenous groups of patients included in the series and the lack of prospective randomized trials keeps the question of impact of hepatic resection on overall survival in BCLM patients open.

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