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Review

Resection of liver metastases from breast cancer: Towards a management guideline

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ABSTRACT

In selected patients with colorectal and neuroendocrine liver metastases, the outcome of liver resection is well established with 5-year survival rates ranging from 25% to 60%. However, the role of liver resection for non-colorectal non-neuroendocrine (NCRCE) liver metastases has not been fully established. Liver metastases in breast cancer are common and a small number of those patients may be suitable for surgical resection. There have been some case series with low mortality and morbidity and prolonged survival after liver resection. We performed this review to evaluate the overall and disease free survival after liver resections for breast metastases. Extensive search of Pubmed, Medline, Cochrane database was performed and data was analysed. Although mostly case series with smaller number of patients, outcome has been comparable to colorectal liver metastases in selected group of patients with 5 years survival rate at the range of 20%–60% with main prognostic factors of being the absence of extrahepatic disease (in exception of isolated pulmonary and bony metastasis) and to achieve an R0 resection.

1. Background

Liver metastases are a common complication of cancer. Surgery to resect colorectal liver metastases has historically resulted in a 25%–30% survival at 5 years. However, only 20%–30% of patients are candidates for surgical resection.[1] The oxaliplatin based neo-adjuvant chemotherapy in combination with biologic agents are improving the survival by changing the biological behaviour, therefore, patients with unresectable liver metastases at presentation can achieve secondary resectability rates of 15–40%.[2] In addition, advances in surgical techniques of liver resection have pushed the boundary of resection. In selected group of patients with colorectal liver metastases, 5-year survival rates range from 25% to 40%[3–5] in published series; with some recent papers reporting survival rates up to 58%[6]–60%,[7–9] and 10 years survival of 23%[10] after liver resection.

In addition, there are data from neuroendocrine liver metastases with good survival benefit. Radical surgery including resection of the primary tumour and resection of liver metastases has been the main treatment for potentially resectable disease for advanced neuroendocrine tumours with five-year and ten-year survival rates of 61%,[11,12] and 35% respectively.[12]

In recent years, liver metastases from non-colorectal and non-neuroendocrine (NCRNE) tumours have increasingly been considered for surgery with evidence of improved survival.[13] The improvements are partly due to advances in surgical techniques, anaesthetic management and peri-operative patient care, reducing operative mortality from 0%[14–16] to 2%,[13,17] in referral centres. Liver metastases from non-colorectal and non-neuroendocrine origin especially from breast, kidney, teratoma, melanoma and sarcoma are increasingly being performed. However, there have been no randomised studies and no meta-analysis. Despite the increasing number of hepatectomies for NCRNE liver metastases, the indications and potential benefits remain unclear as most of the patient series are small with different primary tumours. This review evaluates indications and outcome after liver resections for metastases from breast cancer.

2. Methods

A search of Pubmed, Medline and Cochrane databases was made using the search terms: hepatectomy (Mesh term), liver resection, hepatic resection, liver metastases (Mesh term Liver neoplasm), non-colorectal non-neuroendocrine and breast cancer. All published studies on liver resection for breast liver metastases were included for consideration.

We excluded studies having less than 9 cases over 6–20 years (see Table 1), non-English based articles and the articles published by same author over the same study period from the final analysis.

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Table 1
Studies on liver resection for Breast cancer liver metastases.

Author, Journal & Year	study period	Patient Numbers & study design	Complications (m&m)	Survival & outcome
Breast only				
[32]Adam R & Aloia T et al; Ann Surg. 2006	1984–2004	85 breast ca; Single institute	Nil mortality	Median and 5-year overall survivals 46 months and 41%
[33]Pocard M et al; Eur J Surg Oncol. 2000	1988–1997	49 breast ca; Single, retrospective data	Nil mortality, 12% morbidity	Survival 86% at 12 months, 79% at 24 months and 49% at 36 months.
[34]Thelen A et al; J Surg Oncol. 2008	1988–2006	39 breast cancer	Nil mortality & morbidity 13%	overall 1-, 3-, and 5-year survival 77%, 50%, and 42%, respectively
[35]Sakamoto Y et al; World J Surg. 2005	1985–2003	34 breast ca	No mortality	Overall and disease-free 5-year survival 21% and 16%, respectively
[36]Raab R et al; Anticancer Res 18 (1998)	11 yrs	34 breast ca; R0 resection 86%.	Mortality 3%	Overall 5-year survival 18.4% (median 27 months)
[37]Vlastos G et al; Ann Surg Oncol (2004)	1991–2002	31 breast	No post-operative mortality	The median survival 63 months, Overall 2 and 5-year survival 86% and 61%, respectively
[38]Yoshimoto M et al; Breast Cancer Res Treat. 2000	1985–1998	25 breast	Nil	2 and 5-year cumulative survival 71% and 27%, respectively
[23]Lubrano J et al; Surg Today. 2008	1989–2004	16 breast	No death	Overall 1, 3, and 5-year survival 94%, 61%, and 33%, respectively. Median survival 42 months.
[39]Elias D et al; Am J Surg. 2003	1986–2000	Total 54 patients, 29 breast had surgery only, 25 patients had surgery as well as post-operative Hepatic arterial infusion chemotherapy (HAIC)	morbidity 12.9%; no mortality	3- and 5-year overall survival 50% and 34%
[24]Carlini M et al; Hepatogastroenterology 2002	Nil available	17 breast	Mortality nil and morbidity 2	Actuarial 5-year survival 46%.
[25]Caralt M et al; Ann Surg Oncol. 2008	88–2006	12 breast	Nil died, 2 bile leak	Median overall survival 35.9 months. Actuarial 1-, 3-, and 5-year survival 100%, 79%, and 33%, respectively
[26]Maksan SM et al; Eur. J. Surg. Oncol. 2000	1984–1998	9 pts breast	No death	5-year survival 51%
[27]Seifert JK et al; Hepatogastroenterology 1999	1985–1997	15 breast	No mortality	Overall median survival following liver resection was 57 months with 1-, 2- and 3-year survival rates of 100%, 71.4% and 53.6% respectively
Breast as part of non-colorectal non-neuroendocrine (NCRNE) series				
[13]Adam R et al; Ann Surg. 2006	1983–2004	Total 1452 pts Breast 460 (32%), GI 230 (16%), urologic 206 (14%) & melanoma 148 (10%); 41 French centres; Association of French Surgeons study, R_0 resection 83%, preop chemo 42%	60-day mortality 2.3% and a major complication 21.5%	5 years Overall and disease-free survival 36% and 21% and at 10 years 23% and 15%, respectively. Tumour recurrence 67% of patients
[15]Weitz et al; Annals of Surgery 2005	1981–2002	Total 141 patients; Breast 29; melanoma 17; testicular 17; gynaecological 19; (ovarian 12); renal 11; GI 12; Observational study (longitudinal type)	Post-operative mortality 0%; 46 (33%) post-operative complications	5 years survival 24%
[40]Yedibela S et al; Annals of Surgical oncology 2005	1978–2001	Total 152 patients; Stomach 31, pancreas 21, breast 24, SB 17, kidney & GU 27, melanoma 5, sarcoma 8; Single institutional retrospective cohort studies;	Morbidity 29%, mortality 9%	Overall 2- and 5-year survival 49% and 26%, respectively; Median survival up to 23 months
[41]Reddy SK et al; J Am Coll Surg 2007	1995–2005	Total 82 patients; Breast 20, ovarian 11, renal 4, sarcoma 19, melanoma 18, gastric 1; retrospective comparative	Mortality 4%, complication 30%	Actuarial 5-year overall and disease-free survival 37% and 16%, respectively.
[28]O'Rourke TR et al; Annals of Surgical Oncology 2007	1986 to 2006	Total 102 patients; GU 32 (Renal 16) ovarian 12) melanoma 15, breast 11, sarcoma 3; between 2 hospitals	Mortality and morbidity 0.8% and 21.1%, respectively	Median survival 42 months and Overall Survival at 3 and 5 years 56.1% and 38.5%, respectively.

Table 1 (*continued*)

Author, Journal & Year	study period	Patient Numbers & study design	Complications (m&m)	Survival & outcome
[17]Elias D, Lasser P et al. J Am Coll Surg. 1998	1984–1996	Total 147 patients. 35 breast, 27 neuroendocrine, 20 testicular, 13 sarcomas and 11 gastric, 10 melanomas and 7 gallbladder, 6 gynaecological; single centre	Mortality 2%.	The crude 5-year survival 36% Five-year survival 20% for 35 breast cancers
[42]Ercolani G et al; Ann Surg Oncol. 2005	1990 to 2003	Total 83 cases gastrointestinal 18, breast 21, genitourinary 15, leiomyosarcoma 10,	No mortality, 21% morbidity	The 3 and 5-year actuarial survival 49.5% and 34.3%; 3- and 5-year actuarial survival 53.9% and 24.6% from breast cancer
[29]Earle SA et al; J Am Coll Surg. 2006	1990–2005	Total 76 cases; Pancreas 12, stomach 3; sarcoma 19, breast 10, kidney 10, gynaecological 10, melanoma 4;	Mortality 2.1%, and post-operative complications 15.8%	Median survival 36 months, and 5-year survival 34.9%.
[30]Lendoire J et al; HPB, 2007	1989 to 2005	Total 106, renal 21, ovarian 14, sarcoma 23, breast 19, melanoma 6, gastric 3, other GI 4; 5 centres, Cross sectional study	Perioperative mortality 1.8%	Overall survival 1, 3 and 5 yrs is 67%, 34% and 19% respectively. 5-year survival 53% for breast origin
[31]Cordera F et al; J Gastrointest Surg 2005	1988–1998	Total 64 patients; GI 12, GU 28, soft tissue 15 (Breast 10), 3 lung; retrospective study at Mayo clinic	Mortality 1.5%	Actual 1-, 3-, and 5-year survivals 81%, 43%, and 30%, respectively
Studies not included: having less than 10 patients of breast ca				
[19]Harrison et al; Surgery 1997	1980–1995	Total 96 patients; sarcoma 27, melanoma 7, breast 7, testicular 9, adrenal 7, renal 5, ovary 7, gastric 5, 8 unknown; Cross Sectional study	No post-operative complications, but no details given on death	Survival at 1, 3 and 5 yrs 80%, 45% and 37% respectively
[20]Karavias et al; European Journal of Surgical Oncology 2002	1994–2000	Total 18 patients; Breast 4, kidney 6; gastric 4; intestinal leomyosarcoma 2; Observational (longitudinal type)	3 cases: pulmonary atelectasis and bile leakage	Median survival 3.2 years
[21]Benevento A et al; J Surg Oncol. 2000	1988–1998	Total 18 patients; breast 4, gastric 5	Nil mortality, 8 complications	Overall actuarial survival 54% at 1 year, 42% at 2 years, and 21% at 5 years
[22]Goering JD et al; Am J Surg. 2002	1991–2001	Total 42 (13 neuroendocrine); 3 renal, 8 ovarian, sarcoma 10, breast 3, melanoma 2	1 operative mortality (2%)	Overall survival rates at 1, 3, and 5 years are 82%, 55%, and 39%, respectively (median survival, 45 months).
[16]Laurent C et al; World J Surg. 2001	1980–1997	Total 39; gastrointestinal 15, genitourinary 12, breast 2, sarcoma 3	No mortality	Survival at 1, 3, and 5 years 81, 40, and 35%, respectively;
[14]Hemming et al; Liver transplantation 2000	1978–1998	Total 37 patients; 7 pts GI, 7 sarcoma, 7 renal, 5 melanoma; 2 pancreas; breast 1; Observational study (longitudinal type)	No surgical deaths. No complications mentioned	Survival at 1, 3 and 5 yrs is 85%, 55% and 45% respectively; average survival 46 months

3. Results

We analysed data from the studies tabulated below. Authors, number of participants, design of studies, and summary of study details have been detailed in the Table 1. Many of the studies published the data on the NCRNE as a group rather than the individual tumour category. Therefore, we included the data from individual tumour group where enough number of patients were published with meaningful outcomes and analysed those as an individual tumour group. Subsequently, we analysed the data on the NCRNE as a group where more than 9 breast cancer patients included. There were no randomised controlled trials or systematic reviews. Essentially all were case series or cohort studies based on single institution over 10–23 years. Results have been summarised in Table 1.

The first series reporting hepatectomy for metastatic breast cancer patients alone was published in 1991.[18] From that date, 13 studies were identified with breast cancers liver metastases only and 16 studies with NCRNE patients with breast cancer subset. Among these, 6 studies had less than 9 patients[14,16,19–22]; 9 studies had 9 or more but less than 20 patients[23–31] and 14 series referred 20 or more patients.[13,15,17,32–42] Although these studies with often confusing numerical illustration of outcome have been simplified in Table 1, we have summarised the results of larger series with 20 or more patients here to emphasise the significant findings.

Adam et al (see Table 1) analysed the data from 1983 to 2004 from 41 French centres on behalf of Association of French surgeons of 1452 patients who had non-colorectal non-neuroendocrine (NCRNE) hepatic metastases resection. Among those 32% i.e. 460 patients had the liver resections for metastases from primary breast cancer. Following surgery, these patients had 5-year and 10 year survivals of 41% and 22%, respectively, with a median survival of 45 months. Disease free survival and other complications were not analysed individually in breast tumour rather it was based on all patients.

Adam R & Aloia T et al published 85 breast patients from single institution over 20 years period with median and 5-year overall survival from the date of diagnosis of liver metastases of 46 months and 41% respectively and from the date of first hepatic resection of 32 months and 37% respectively. Eight patients were alive 5 years after their first hepatectomy and 4 of these patients were alive at 10 years. All patients have had chemotherapy and hormonal treatment.

Elias D et al, Vlastos G et al, Sakamoto Y et al,Pocard M et al; Yoshimoto M et al, Raab R et al, Thelen A et al reported 30 to 54

breast patients showing 5-year survival rate 34%, 61%, 31%, 49% (3yrs), 27%, 18%, 42% respectively.

Reddy et al, Weitz et al, Yedibela S et al, Ercolani G et al analysed relatively large data with subgroup of patients with breast primary liver metastases about 20–30 patients and reported 5 year survival of 24–37% as a group for NCRNE, whereas disease free survival was 16%–23%. However, it was not possible to infer any survival data reliably from those studies on any particular tumour. These results were for R0 resection and extrahepatic diseases were not included for surgery. In addition, most patients had hormonal treatment and chemotherapy. However, one Japanese study showed survival only 8.5 months for patients who received standard or non-surgical therapies.[43]

3.1. Prognostic indicators

Some report suggests that the disease-free interval (metachronocity) is an important prognostic indicator,[26] whereas others report on the contrary.[38] The number and size of hepatic metastases are not thought to predict the outcome,[36,38,39] There is no consensus on the effect of lymph node infiltration while some find it negatively prognostic[26] and others report it not to influence the prognosis.[39] The stage of the primary disease appears to be irrelevant.[36,39] although prior local recurrence of the primary tumour may have adverse prognostic significance.[36] Even though clear resection margins were found to be important in one study[36]; surprisingly this was not the case in one of the larger series consisting of 54 patients,[39] in which the only variable predicting the survival was found to be the hormone receptor status of the disease. However, all other authors described complete resection as the main prognostic factor. In fact, two criteria almost universally accepted for selecting patients for curative hepatic resection are firstly, the absence of extrahepatic disease (in exception of isolated pulmonary and bony metastasis) and secondly, the ability of the surgeon to perform an R0 resection with acceptable mortality.[44] Even after these two criteria are met, variations in 5-year survival after hepatic resection can vary widely as shown in the above data.

4. Discussion

Approximately 50% of breast cancer patients will develop distant metastases,[45,46] and liver metastases are present in 15% of patients newly diagnosed with metastatic breast cancer and is the only site of distant disease in one third of these patients.[47,48] Ultimately, as many as 50% of patients with stage IV disease will develop liver metastases with associated median survivals ranging from 3 to 15 months.[49–51] Systemic chemotherapy or hormonal therapy (or both) is usually indicated for these patients. The liver is the primary site of recurrence in 12–15% of patients, but metastases are confined to the liver in approximately 5% of patients.[18,52] One study found that 10% (9 of 90) of patients with hepatic metastases from breast cancer were suitable for resection.[26] Therefore, the number of patients with liver metastases from breast cancer who are currently suitable for liver resection is small. Recently with the progress in effective multimodal therapies, more patients are being referred for surgical opinion.

Treatment options available for the management of breast liver metastases are: hormonal therapy, chemo-radiotherapy, radiological or surgical radio frequency ablation, curative intent or cytoreductive surgery with or without above combinations, Selective Internal Radiation Therapy (SIRT) and palliative chemotherapy or simply palliative care. More than 100 papers have been published in English literature documenting the outcomes in patients of non-colorectal non-neuroendocrine (NCRNE) liver metastases treated with hepatic resection. Among those only the relevant papers on breast liver metastases have been considered in this review. These studies report mostly single institutional experiences with a wide variety of primary tumour types distributed with a small number of patients over a long period of time (see the Table 1). Furthermore, they were dated back to early days of liver surgery with developing technical skills, limited operative accessories and earlier versions of diagnostic modalities. Therefore, the ability to draw strong conclusions from these studies is limited.

For breast liver metastases 5 years survival after liver resection has been 16%–61% in various series. Some of these data are broadly comparable with the quoted outcome figure to those achieved following resection of the colorectal liver metastases depending upon which spectrum of data one would be comparing with.[5,53,54] However, there are some important differences in these two patients' groups. Firstly, it is likely that the patients with breast liver metastases are more selected. Secondly, whereas it is nearly impossible for patients with colorectal liver metastases to achieve 5-year survival without hepatic resection, the specific survival benefit of surgical resection for breast liver metastases is difficult to differentiate from that of hormono-oncological treatment or probably from the natural history of the disease.

In contrast to the well-defined guidelines for surgery of colorectal liver metastases, surgical decision for breast liver metastases is mainly based on institution-based experience and often with limited evidence based on a smaller number of available retrospective studies with fewer patients. For this reason, the clinical benefits of surgical resection of hepatic metastases from breast primary tumours are not widely acknowledged yet. On the contrary, non-surgical treatment does not achieve favourable outcome and survival amounts to only a few months.[55]

4.1. Role of cytoreductive surgery

cancers cells are known to produce cytokines and peptidoglycans which can precipitate immune complexes and compromise usual immunological defences. There is an argument that reducing the burden of cancerous cell volume may provide an immunologic benefit.[56,57] In addition, according to the log-kill hypothesis, chemotherapeutic agents kill a constant fraction of cells, rather than a specific number of cells after each dose.[58] Therefore, there has been a proponent of opinion that reducing the initial tumour volume increases the likelihood of chemotherapy killing the number of viable tumour cells. Reducing the total tumour volume to be treated can also reduce the possibility of drug resistance development, an event that increases with the number of cancer cells and the treatment duration.

The diverse nature of primary tumour has an influence on the inherent characteristics of liver metastases based on tumour biology, or the metastatic route or the responsiveness to chemotherapy. While selecting breast liver metastases for resection, we need to consider this inherent tumour biology and responsiveness to chemotherapy. Rapidly growing tumour tends to be more aggressive and thus have a poorer prognosis. Metachronicity is thought to be an indicator of less aggressive disease reflecting the nature of tumour biology. The way tumour behaves is very much related to histology type, as we know that adenocarcinoma is less aggressive than squamous cell cancer. This may signify that the squamous call cancer is less favourable in its cell biology.

Secondly, the liver is a common site of metastasis from various cancers; however, mechanism and the frequency of spread from various primaries vary widely. Whereas colorectal liver metastasis can be regarded as loco-regional spread through portal circulation, other tumours such as breast liver metastasis may only be first site of distant spread denoting already systemic haematogenous distant micro-metastases elsewhere. Therefore, prognosis irrespective of

liver resection would not be as good as colorectal liver metastasis. In colorectal liver metastases, extrahepatic disease spread is no longer considered as inoperable as long as chemotherapy works well and controls the disease. On the other hand, in breast liver metastasis curative resection may not achieve favourable outcome if there is extrahepatic disease except solitary lung metastasis or isolated bone metastasis; unless it is performed for cytoreductive purpose. Although the cytoreductive surgery has a proven role in certain cancers and liver metastases, there is no evidence or any published series on cytoreductive surgery in breast liver metastases to date. Unlike other NCRNE liver metastases, breast liver metastasis often respond to hormonal treatment and chemotherapy depending on the chemo-sensitivity and hormonal status. In fact, because of systemic dissemination and potential micro-metastases, combined adjuvant and neoadjuvant chemotherapy alone is often used to destroy occult cancer cells.

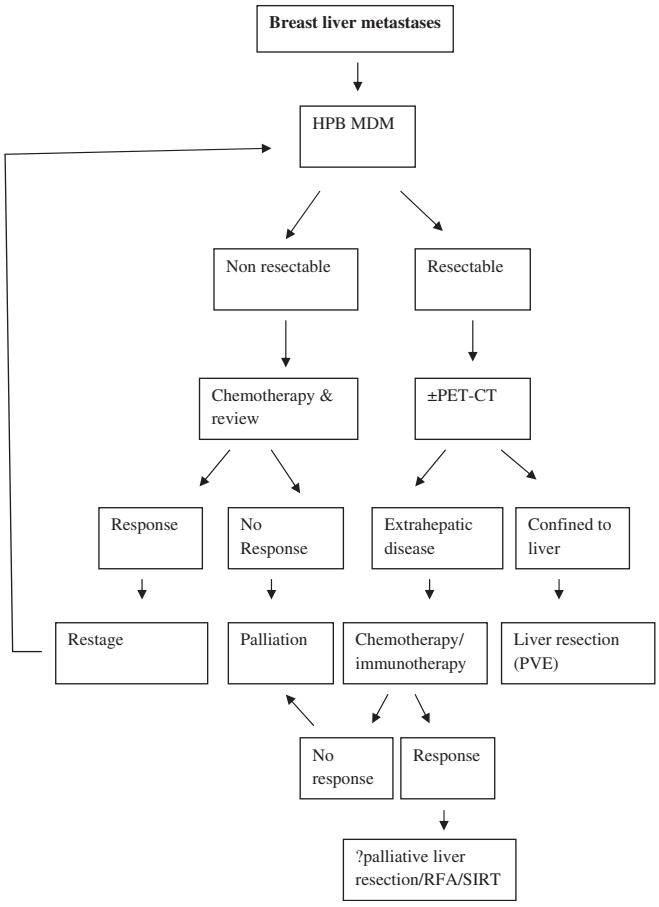
4.2. Guidelines

The question arises whether the liver resection in breast liver metastasis lead to improved survival. On balance of above studies, we believe that liver resection in selected patients with liver metastasis from breast primary improves survival. Therefore, there is a need for guidelines to determine which group would benefit from the liver resection and above all, how the patients with liver metastases from breast primary should be managed.

In reality, there is a temptation on part of oncologist to continue chemotherapy until the metastatic tumour disappears or the disease no longer responds to chemotherapy. This tendency should be abandoned for the reasons; firstly, the surgeon should see all the liver metastases before the chemotherapy to be able to resect all sites of metastasis as well-responsive liver metastasis can be difficult to locate for surgery and the available radiological tests become less sensitive[59]; secondly, chemotherapy puts enormous strain on the liver parenchyma causing steatosis and damage to hepatocyte compromising the quality of residual liver after resection.[60] Therefore, oncologists should refer all patients with liver metastasis to the surgeon before chemotherapy and all cases should be discussed in multidisciplinary meeting. Moreover, for patients who do not respond to initial systemic chemotherapy, it is now possible to say whether hepatectomy would be appropriate.

Currently, indications for liver resection and treatment protocols for breast liver metastasis differ considerably depending on the geographic location as well as the surgeon's expertise. We, therefore, propose some guidelines [see Flow chart 1] for the decision making based on the grade 3 evidences from the published cohort studies as described above as well as our own institutional experiences.

1. All hepatic metastases should be referred to tertiary centre where large volume hepatic resections are performed and have available expertise for MDM discussion
2. All patients can be candidate for neoadjuvant and adjuvant chemotherapy and hormonal therapy depending on the hormonal status
3. In patients with a normal functioning liver, up to 70% of the liver volume can be removed without risks of post-operative failure.[61]
4. Although the evidences are less clear in breast liver metastases, similar principles of liver resection for colorectal liver metastases apply
   a. Unilobar disease should be resected with hepatectomy
   b. Solitary metastasis can be ablated with radio frequency or resected segmentally or non-anatomically
   c. No clear evidence for liver resection in bilobar multiple metastases, and nor there is evidence for repeat or staged resection, however, these can be performed in trial scenario
   d. Isolated pulmonary and bony metastasis is not contraindication
5. Incomplete resection (R1, R2) of breast liver metastasis as cytoreductive surgery is not proven, although some studies suggested its role as acceptable.[62–64]



Flow chart 1. Proposed algorithm for selection and management of patients with non-colorectal, non-neuroendocrine liver metastases (NCRNELM). [HPB MDM: Hepato-pancreato-biliary multidisciplinary meeting; PET: Positron Emission Tomography; CT: computerised Tomography; PVE: Portal Vein Embolisation; RFA: Radio Frequency Ablation; SIRT: Selective internal radiation therapy].

Although the indications for resection of liver metastases (LM) from neuroendocrine and colorectal cancers are well-defined and evolving continuously with minimum of 30% non-cirrhotic liver residual being acceptable, such has not been the case for LM originating from other primaries such as breast. In the absence of known prognostic factors, long-term survival benefit following the hepatectomy can be unpredictable and may be variable among these patients. Only a randomized trial comparing surgery versus no surgery in a well-defined population with breast liver metastases will be able to demonstrate whether liver resection is at all beneficial in terms of survival and quality of life. However, this type of study will have its own ethical dilemma.

In conclusion, prolonged survival can be obtained after resection of liver metastases from breast cancer and they seem to be one of the most favourable subset of NCRNE liver metastases for surgery. It has been proposed[39] that the liver surgery can, therefore, be considered as an adjuvant treatment to systemic therapy in

selected patients, provided the conditions of a low operative risk, feasibility of complete resection, no extrahepatic disease (except for bone metastases which are easily controlled by radiotherapy or isolated pulmonary metastasis) and no disease progression under chemotherapy are fulfilled.

However, in contrast to the treatment of colorectal liver metastases where surgery has the key role and chemotherapy acts as an adjuvant treatment, it is likely that the reverse situation will be true for breast liver metastases. Multidisciplinary discussions are required to evaluate the extent of the disease, the degree to which disease has been controlled and the feasibility of a hepatectomy, the availability of expertise and skills before deciding whether a patient should undergo surgery or not. When applied surgery may be able to offer a real benefit in long-term survival in these situations in selected patients.

Conflicts of interest

None.

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None.

Ethical approval

None.

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