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The role of surgery in the management of liver metastases from non-colorectal cancers: A review of the literature

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Abstract

Surgery for non-colorectal liver metastases is nowadays indicated due to advances in surgical techniques and patients multimodal management. The objective of our study is to evaluate the surgical management of liver metastases of non-colorectal cancers in the visceral surgery department of the Mohamed V military hospital in Rabat.

This is a retrospective study on a series of 13 resections for non-colorectal liver metastases over a period of 6 years from January 2015 to December 2020.

In our series, the average age is 53 years with a prevalence of women (62%). The primary cancer was ducal breast carcinoma 6 times (46.15%). There were 2 cases of stromal tumors (15.38%), 2 cases of neuroendocrine tumors (15.38%), one case of gastric adenocarcinoma, gastric small cell lymphoma, and of adrenocortical carcinoma. Liver metastases were synchronous in 76.92% of cases, metachronous in 23.08% of cases. They were unique in 84.62% of cases, bilobar in 15.38% of cases. The type of liver resection performed was 11 metastasectomy, 3 segmentectomy, 3 bi-segmentectomy. Mortality rate was zero and the morbidity rate was 15.38%. One patient had hepatic recurrence. With a follow-up of 3 to 36 months after resection, only one patient died after 12 months.

The management of patients with non-colorectal liver metastases is based on a multimodal approach. Our results show that surgery, when feasible in selected patients, is a safe option and the only possibility for long-term survival. Future advances in chemotherapy, biotherapies and immunotherapy are likely to broaden the indications for surgery.

Keywords: Liver Metastasis; Non-Colorectal; Malignant Tumors; Hepatectomy.

1. Introduction

Hepatic metastases (HM) are foci of cancerous cells from a known or unrecognised primary tumour that have developed independently within the liver parenchyma. They are the most common malignant tumours of the liver. [1]

HM are largely derived from digestive cancers draining into the portal system. They are classified into three main groups according to the origin of the primary, prevalence and therapeutic specificities: colorectal liver metastases, endocrine metastases and non-colorectal non-endocrine metastases (HMNCRNE). Compared with colorectal metastases, non-colorectal non-endocrine liver metastases are rarer and comprise a heterogeneous group of patients, with the common feature of a high frequency of concomitant extrahepatic involvement.

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The role of surgery must always be discussed as part of a multimodal approach and in the light of local and distant control of the disease.

The aim of our study is to evaluate our practice in this area and to define the role of surgery in the management of these patients.

2. Materials and methods

Our work is a retrospective series that included patients with at least one HMNCRNE who underwent surgery for their metastasis between January 2015 and December 2020.

For each of the patients included, we studied the parameters relating to time, site, size and number of lesions, pre-operative treatment, approach, type of surgery, post-operative follow-up, post-operative treatment and survival.

3. Results

We identified 13 patients who had undergone surgical resection for HMNCRNE. The mean age of our patients was 53.8 ± 7.1 years, ranging from 44 to 68 years. The sex ratio was 0.75.

The most common primary tumour in our series was invasive ductal carcinoma of the breast, found in 6 cases (46.15%). There were 2 cases of gastric and small intestinal stromal tumours (15.38%), 2 cases of small intestinal neuroendocrine tumours (15.38%), one case of gastric adenocarcinoma, gastric small cell lymphoma and adrenocortical carcinoma.

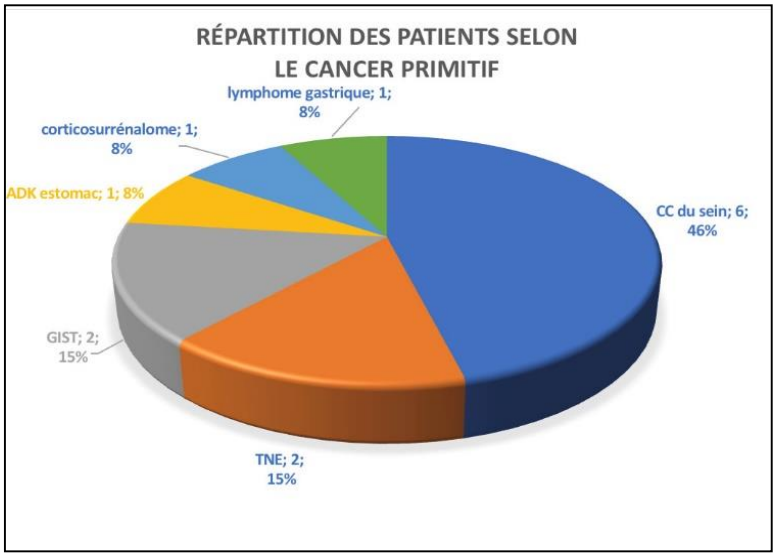

Figure 1 Breakdown of patients by primary cancer

Table 1 Summary table of the cases in our study

			Characteristics of liver metastases					Treatment of metastases			Follow-up
	Age (years)	**Primary cancer**	**Deadline**	**Headquarters**	**Size and number**	**Pre-op treatment**	**Approach**	**Type of surgery**	**Post-op suites**	**Post-op treatment**	
1	51	CCI Sein	Synchronous	Sgmt 8	1 nodule (21 mm)	CT (3 treatments)	Coelio	Metastasectomy	Simple	CT then Patey then RT	Alive (after 5 months)
2	53	CCI Sein	Synchronous	Sgmt 2	1 nodule of 30 mm	CT (3 treatments)	Laparo	Left lobectomy	Simple	Patey then RCT	Still alive (12 months)
3	48	CCI Sein	Metachronous (21 months)	Sgmt 3-4	3 nodules (10; 8; 5 mm)	CT (3 treatments)	Laparo	Metastasectomy	Simple	Currently on CT	Set back 3 months
4	49	CCI Sein	Synchronous	Sgmt 4-2	3 nodules (17; 13; 10 mm)	CT (3 treatments)	Coelio	Metastasectomy	Simple	CT then Patey then RT	Alive (after 7 months)
5	63	CCI Sein	Metachronous (1ère at 6 years and 2ème at 12 years)	Sgmt 4-5	2 nodules (10; 20 mm)	CT (3 treatments)	Coelio	Metastasectomy	Simple	CT	Set back 24 months
6	44	CCI Sein	Synchronous	Sgmt 7	1 nodule (10 mm)	CT (3 treatments)	Coelio	Metastasectomy	Simple	CT	14 months of hindsight
7	55	Antropyloric ADK	Synchronous	Sgmt 6	1 nodule (17 mm)	-------	Laparo	Partial hepatectomy S6	Simple	CT	Set back 6 months
8	68	Gastric B lymphoma	Synchronous	Left lobe	Large tumour (65 mm)	-------	Laparo	Left lobectomy + Gastrectomy	Simple	--------	Lost from sight
9	50	Hail NET	Metachronous (24 months)	Sgmt 5	1 nodule (32 mm)	G2 NET operated in 2015	Laparo	Segmentectomy 5	Simple	--------	Alive: 36 months
10	60	Differentiated Hail NET	Synchronous	Sgmt 5-6	2 nodules (32; 50 mm)	-------	Laparo	Bisegmentectomy 5-6	Simple	--------	Back 18 months

11	66	GIST Stomach	Synchronous	Sgmt 4	1 nodule (25 mm)	Imatinib	Laparo	Left lobectomy	Simple	---------	Set back 3 months
12	50	Adrenocortical cancer	Synchronous	Sgmt 5-8	2 nodules (30; 20 mm)	No	Laparo	Metastasectomy 5-8	Haematoma	Mitotane	12 months DCD
13	61	GIST Small	Synchronous	Sgmt 6	1 nodule 30 mm	No	Laparo	Segmentectomy 6	Bilome	Imatinib	24 months

3.1. Number of liver metastases

We included 20 liver metastases resected from the 13 patients. These were single in 8 patients (61.54%), 3 patients had 2 liver metastases (23.08%) and two patients had 3 liver metastases (15.39%).

3.2. Location and distribution of liver metastases

Metastases occupied the right liver in 7 patients (53.85%), the left liver in 4 patients (30.77%) and were bilobar in 2 patients (15.38%).

3.3. Size of liver metastases

The size was ≤ 20 mm for 10 metastases (50% of nodules); eight metastases were between 20 mm and 50 mm in size (40%); and two metastases exceeded 50 mm long axis (10%). The median size of HM was 20.0 ± 14.8 mm.

3.4. Circumstances of discovery

Liver metastases were synchronous in 10 patients (76.92% of cases) and metachronous in 3 patients (23.08%). There were no cases of inaugural metastases of unknown origin.

All the synchronous metastases were known preoperatively at the time of the extension work-up for the primary cancer, except in the case of the patient with a neuroendocrine tumour (NET) of the small intestine whose metastasis was discovered intraoperatively.

3.5. Approach

The most commonly used approach (nine patients, or 69.23%) was laparotomy (right subcostal and median), compared with laparoscopy, which was used in 4 patients (30.77%).

3.5.1. Liver resection

Liver resection consisted of 11 metastasectomies (55% of metastases), 3 segmentectomies (two segmentectomies 6 and one segmentectomy 5) and three bi-segmentectomies (two left lobectomies and one bi-segmentectomy 5-6). All our hepatectomies were graded R0 with a margin of 1 to 25mm.

3.5.2. Peri-operative treatments

Treatment decisions were made in multidisciplinary consultation meetings. Neoadjuvant chemotherapy ± hormone therapy was prescribed for the 6 patients with primary breast carcinoma. The patient with adenocarcinoma of the stomach also received 3 courses of neoadjuvant chemotherapy. The patient with metastatic gastric stromal tumour received 3 months' treatment with 800 mg/d of Imatinib. All our patients subsequently received specific adjuvant treatment according to histological type and immunohistochemical and hormonal profiles.

3.5.3. Treatment strategies and sequences

The patients who had breast carcinoma with synchronous liver metastases all underwent chemotherapy ± hormone therapy first if hormone receptor positive. The two patients managed in 2015 and 2016 underwent a classic sequential strategy with first radical mastectomy followed by chemotherapy then liver resection and finally radio-chemotherapy; whereas the three patients managed after 2017 underwent a so-called "reversed" or "liver first" strategy with systemic treatment followed by liver surgery then breast surgery and final radio-chemotherapy. The patient with the second recurrence of liver metastasis (six-year interval) underwent liver resection with chemotherapy. The patient with gastric adenocarcinoma underwent gastrectomy associated with a left lobectomy with peri-operative FOLFOX chemotherapy.

Patients with haemorrhagic gastric lymphoma and small bowel GIST underwent combined resection in a single operation, followed by specific systemic treatment.

The patient who had metastatic gastric GIST underwent surgery after 3 months of Imatinib. She underwent distal gastrectomy and left lobectomy at the same time, followed by treatment with Imatinib.

The two cases of NET of the small intestine were operated on immediately. The first was a combined resection of the small bowel and liver (synchronous metastasis) and the second a metastasectomy (metachronous metastasis).

The only case of metastatic adrenocortical cancer was operated on from the outset with a combined right adrenalectomy and double metastasectomy 5 and 8.

3.6. Complications

The patient who had undergone gastrectomy for lymphoma with left lobectomy at the same time had a left subphrenic biloma treated by percutaneous echo-guided drainage. The patient who underwent bi-segmentectomy 5-6 was transfused with two packed red blood cells postoperatively. We therefore noted two post-operative complications, Grade 2 and Grade 3a of the Clavien and Dindo classification [2]. The morbidity rate in our series was 15.38%.

3.7. Recurrence

Among the 13 patients operated on, one patient followed for breast cancer had two recurrences of HM at 6 and 12 years (7.69%), for which she underwent a total of 3 hepatectomies.

3.8. Survival

With one patient lost to follow-up, the median follow-up was 12 months [5.75-19.5], with extremes of 3 and 36 months. Only the patient with adrenocortical cancer died after 12 months.

4. Discussion

HMNCRNE surgery is part of a multimodal approach that includes chemotherapy, targeted therapy, surgery, selective portal embolisation and other local treatments. The initial work-up should include an assessment of the patient's general condition, the coexistence of possible extra-hepatic lesions and the resectability of the liver disease.

Over the past thirty years, the value of surgical resection and chemotherapy in the management of liver metastases from colorectal cancer has been clearly established [3]. Currently, surgical resection of HM can be performed with very low mortality and 5-year survival rates of between 25% and 44%, depending on the series [4]. However, only 10-20% of patients with metastases can be operated on [5]. To improve these results, methods have been developed to facilitate the resectability of HM and reduce the rate of recurrence after surgery. These include neoadjuvant systemic treatments and local destruction by radiofrequency or cryotherapy, particularly in cases where bilobar hepatic lesions coexist [6]. Port embolisation, which is performed prior to surgery to enlarge the remaining liver and reduce blood loss, has also been shown to reduce post-hepatectomy complications [7]. Some eligible patients use immunotherapy. Immunotherapy (known as biological therapy) helps to strengthen or restore the immune system's ability to fight cancer [8]. It can also reduce the size of advanced or metastatic liver tumours and control cancer symptoms. Anti-tumour immunotherapy has considerably improved the survival of patients with metastatic cancer [9].

In our study, thirteen (13) patients with a mean age of 53.8 ± 7.06 years underwent liver resection for metastases of non-colorectal non endocrine origin between 2015 and 2020. This series represents a very small proportion of hepatectomies performed in the same period within the hospital.

The work-up and treatment strategy should be decided in a multidisciplinary consultation involving hepatobiliary surgeons, radiologists, oncologists, gastroenterologists and anaesthetists. Surgery, whether performed immediately or after liver preparation, must be part of an overall management plan [10].

Biopsy of synchronous non-colorectal metastases is indicated if surgery is not performed, if there is diagnostic doubt or if tumour material is required to determine RAS and BRAF status in the absence of biopsy of the primary tumour is available [11].

We did not biopsy any metastases preoperatively because the context was obvious. Metachronous metastases were difficult to biopsy. We therefore relied on PET scan data, which showed intense hypermetabolism.

Hepatic digestive neuroendocrine metastases (HM of NETs):

As with colorectal metastases, the benefit of surgical treatment of neuroendocrine tumour metastases has also been proven [12]. For these metastases, resection is justified by a significantly increased 5-year survival (45-90% compared with 20-40% without resection) and by a consequent reduction in symptoms linked to hormone production [12]. Furthermore, NET HM is known for its slow progression and the ineffectiveness of chemotherapy in reducing symptoms and halting disease progression [7]. Removal surgery therefore appears to be the only potentially curative treatment.

In their study, Solorzano et al [13] reported a mean 5-year survival of 77% (62-92%) for patients whose primary tumour and metastasis were resected, compared with 16% (5-26%) for those who were not resected. Given the spread of lesions, less than 25% of patients are considered resectable [7].

Surgery is only considered for well-differentiated NETs (grade 1 or 2) [7], with a low proliferation index (Ki67 < 10%), when they are completely resectable, in the absence of unresectable extra-hepatic metastases and if the expected remaining liver volume is greater than 30%.

The two patients in our series were alive after 36 months in one case and 18 months in the other.

4.1. Non-neuroendocrine non-colorectal metastases (HMNCRNE)

While the utility of liver resection seems clear for metastatic colorectal and neuroendocrine tumours, it is much less clear for non-colorectal non-endocrine tumours. The diversity of HMNCRNEs and their potential for systemic dissemination makes it difficult to reach a consensus on appropriate treatment [14].

In 1963, Woodington and Waugh [15] first reported a 5-year survival rate of 20% in 20 patients undergoing liver resection for various colorectal and non-colorectal malignancies. Since then, there has been growing acceptance of this approach to treating liver metastases, particularly in view of the poor results obtained with other therapeutic modalities. In France, the number of hepatectomies per year for HMNCRNE rose significantly from 1983 (7 resections) to 1997, when it stabilised at between 105 and 143 resections per year [14]. The results obtained, thanks in part to advances in preoperative diagnosis, improved surgical techniques and advances in chemotherapy protocols, have demonstrated that hepatectomy for liver metastases of non-colorectal tumours can be a promising strategy for prolonging patient survival. For example, a retrospective analysis of the series by Adam et al (1452 patients) reported a five-year survival of 36% after hepatic resection of HMNCRNE [16].

Resection must be R0 and can only be considered in hyper-selected patients. In other words, patients responding to chemotherapy without progression for 6 months and in the absence of extrahepatic disease.

In the various HMNCRNE series, the best results were obtained for liver metastases of breast cancer and genitourinary origin, where there was concrete evidence of a benefit from liver resection. These were carefully selected patients integrated into a multimodal treatment concept. With regard to liver metastases from other primary sites such as adenocarcinomas (gastric and pancreatic) and cutaneous melanoma, the data are inconclusive [16].

4.2. Metastases from digestive cancers other than colorectal

4.2.1. HM from gastric cancer

For liver resection of gastric carcinoma metastases, only 10% to 20% of patients with metastases are suitable for surgical treatment, and the procedure has a median survival of 5 to 8 months, with 15% to 50% survival at 1 year and 19% survival at 5 years [17]; the American College of Surgeons series reported overall survival rates at 5 years of close to 20% after resection of synchronous metastases and 30% in the metachronous situation [18]. M. Garrancini et al [19] reported 3- and 5-year survival rates of 68% and 31% respectively in 21 patients.

In our series, the patient operated on for antral adenocarcinoma with metastasectomy in segment 6 was still alive 6 months after the end of his chemotherapy.

4.2.2. HM of adenocarcinomas of the duodenum and small intestine

The cases of resectable liver metastases reported in the literature are rare, given the poor prognosis of these cancers at the metastatic stage. Bakaeen reported a single case of cephalic duodenopancreatectomy combined with hepatectomy which resulted in survival of more than 5 years [20]. For localized small bowel adenocarcinoma, complete surgical resection is the treatment of choice, while systemic chemotherapy with liver surgery is considered indicated for tumours with hepatic metastatic spread [21].

4.2.3. HM of oesophageal cancers

MH in these cancers is almost always multiple and associated with other extrahepatic lesions. For these reasons, liver surgery is rarely indicated. In the literature, there are a few cases of resection of single metastases. In the French Association of Surgery (AFC) series [16], only 3 of the 8 patients resected survived with a mean survival of 16.2 months. The other patients died of either extrahepatic or hepatic recurrence after 10 months. There were no survivors at 5 years.

In 2011, in the study presented at the International Surgical Congress of the Association of Surgeons of Great Britain and Ireland, two of the 4 patients operated on were alive at 22 and 92 months after resection. The other two died at 10 and 21 months respectively [22]. Thus, the poor results, with frequent and rapid recurrence, do not call into question the non-surgical approach to these metastases.

4.2.4. HM of biliary cancers

Cases of hepatic resection of metastases from these cancers reported in the literature are also rare. The number of patients alive 5 years after resection of these metastases is very low. In Yamada's series, mortality was particularly high. All patients died within 10 months of hepatectomy [23].

For biliary cancer, the indication for surgery was always metachronous metastases. The results of the AFC series were poor, with 4 of the 5 patients dying and none surviving beyond 1 year after resection [16].

In gallbladder cancer, Adam et al [16] reported a survival of 30% at 3 years, including 22% without recurrence. This suggests that some patients may benefit from surgery. Survival of over 10 years has even been reported [24,25].

4.2.5. MH of exocrine pancreatic cancer

Pancreatic cancer has a very poor prognosis. Liver metastases add a further serious factor to the prognosis.

The results of resection of these metastases reported in the literature are generally unfavourable. Most patients die within a year of hepatectomy. Takada et al [26] report that survival does not exceed 10 months and remains unchanged after curative or palliative surgery. In the series by Gleisner et al [27], although the extent of liver disease was minimal (median tumour size 6 mm, 91% of patients with 1 liver metastasis), simultaneous resection of primary pancreatic adenocarcinoma and liver metastasis resulted in a median survival of only 5.9 months, no different from the control group who underwent palliative treatment only. However, rare prolonged survival of more than five years has already been reported. The AFC series of 41 patients reported an overall survival rate at 5 years of 25%, significantly better than the 6-9 months reported with chemotherapy alone [16]. The median survival for all synchronous metastases was only 18 months, compared with 37 months for metachronous metastases.

In the light of these results, we can conclude that resection of pancreatic cancer metastases can be associated with a real survival benefit when these metastases are metachronous, occur after a long free interval, are accessible to curative hepatectomy and are accompanied by chemotherapy.

4.2.6. Gastrointestinal stromal tumours (GIST)

Liver resection when feasible is the curative treatment of choice for GIST liver metastases according to several studies. Patients who undergo complete liver resection for GIST can have survival rates of 80 and 50% after 1 and 3 years respectively; whereas patients who do not have liver resection have a poor overall survival of 4% [28]. In Xiao's series, 5-year survival was 85.7% in the resected group and 59.6% in the unresected group [29].

HM resections of GISTs are generally accompanied by tyrosine kinase inhibitor treatment. Neoadjuvant treatment will allow downsizing and increase resectability. Adjuvant treatment will reduce the rate of recurrence [30].

In our series, the patient with gastric GIST had 3 months of neoadjuvant treatment followed by adjuvant treatment with Imatinib 400mg/d. The patient with metastatic GIST of the small intestine had adjuvant treatment for two years. The patient operated on for metastatic small bowel GIST received adjuvant treatment for two years. Both are alive.

4.2.7. Breast Cancer HM

At the time of diagnosis, liver metastases from these cancers are most often multiple and/or associated with extrahepatic lesions [31]. Very few patients are candidates for liver resection.

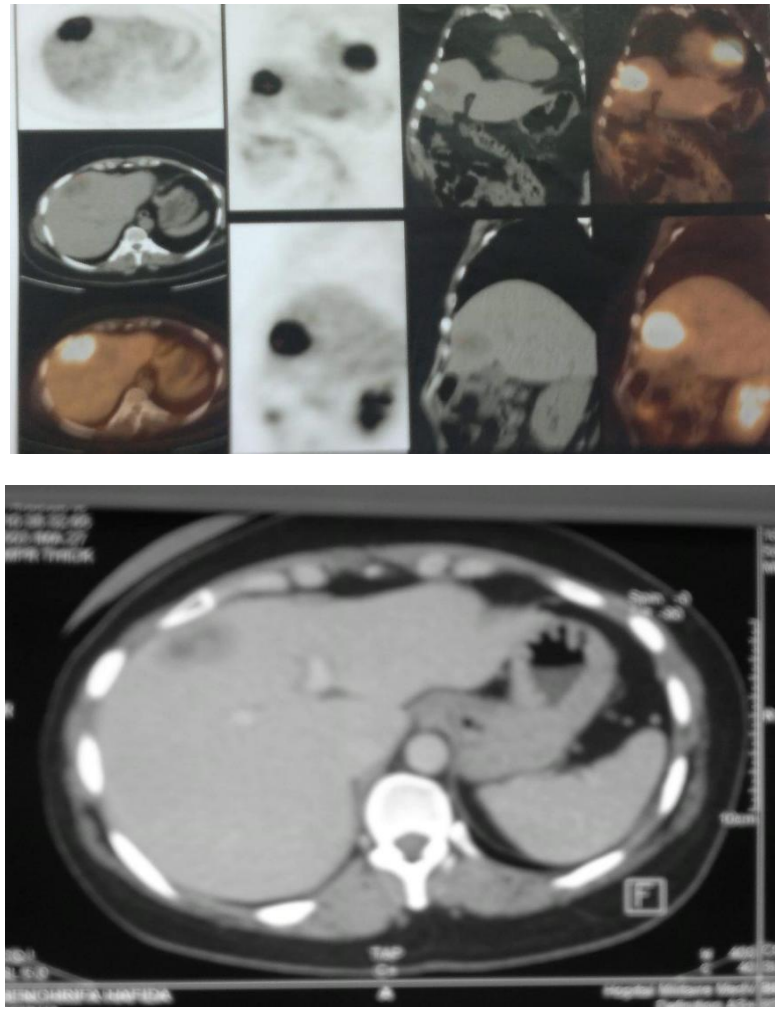

Figure 2 and 3 PET scan images of an HM in a patient in our study followed up for breast cancer, showing hypermetabolism of the metastasis in segment 4 of the liver and its correlation on the CT scan.

However, surgery combined with chemotherapy and targeted therapies may, in selected cases, be associated with a real survival benefit. The results of retrospective studies published since 2000 show that while chemotherapy and/or hormone therapy can prolong the survival of patients treated for liver metastases, the survival rate 5 years after treatment is virtually nil. Conversely, the overall survival rate of patients operated for liver metastases is 37% five years after surgery, with a median of 21% [32]. Since then, many centres have published their experience of the efficacy of liver resection for breast cancer metastases [33]. Three of our patients underwent the so-called "liver first" strategy: systemic treatment followed by liver surgery, then breast surgery and final radiochemotherapy. Reverse therapy (RT) was initially intended for patients with colorectal cancer and advanced synchronous liver metastases [34]. In a publication of 35 patients included in RT between January 1998 and December 2007, 30 patients were able to benefit from complete treatment. Survival for these 30 patients was 60% and 31% at 3 and 5 years respectively from the start of treatment [35].

HM surgery for breast cancer should be included in the guidelines for the therapeutic management of this disease. Especially in certain well-selected cases.

In our series, with a median follow-up of 10.8 ± 7.68 months [extremes 5-24 months], all our patients are alive. These were highly selected, young patients with class I hepatectomies. One of our patients was undergoing her third hepatectomy. The first metastasectomy was carried out 12 years previously (in 2006) and the second 6 years later (in 2012); these two metastasectomies are not included in our study period, but reinforce the value of hepatectomies and re-hepatectomies in the management of breast cancer metastases.

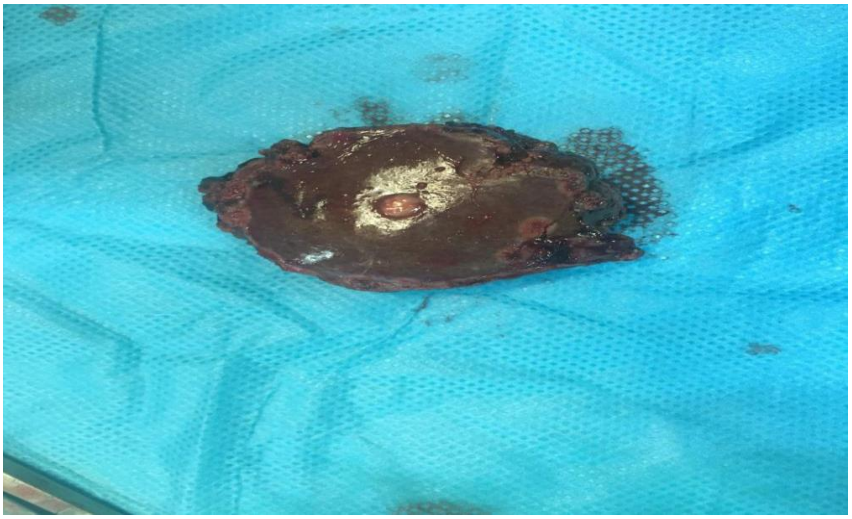

Figure 4 Laparoscopic metastasectomy specimen from a patient in our series treated for breast cancer.

Figure 5 Pieces of laparotomic metastasectomies performed on a patient in our series treated for breast cancer.

4.3. HM for gynaecological cancers

4.3.1. Ovarian cancer

The results obtained in several series show that resection of these metastases can contribute to prolonged remissions. The two studies by Yoon and Chi DS [36,37] report a median survival of 27 and 62 months. Weitz [38] states in his study that the prognosis for liver metastases from primary genitourinary tumours (testis, ovary, uterus) is better than that for primary non-genital tumours. In the series by Meribeth [39], the median survival was 26.3 months. This result was better when surgery was performed more than 12 months after the initial diagnosis and when the residual tumour mass was less than 10 mm.

4.3.2. Cancers of the uterus

Surgery is only indicated in very selected cases. As part of the overall management of advanced endometrial cancer, surgery in rare cases should be discussed, particularly in cases of locoregional relapse alone or oligometastatic disease [40]. More recently, the two patients in the series by Knowles et al. were alive at 48 and 66 months respectively after resection [41].

4.4. Liver metastases from urological cancers

4.4.1. Prostate cancer

In the majority of cases, prostate cancer metastases are multiple or associated with extrahepatic lesions, particularly bone lesions [42]. However, in highly selected patients, resection may be justified and prolonged survival may be achieved. Kawai et al [43] reported a single case of liver resection for a single metastasis 15 years after radical prostatectomy. The surgical approach in this case was justified by the singularity and very late presentation of the lesion, the low PSA and testosterone levels and the stability of the liver lesion. In the literature, cases of resection are exceptional (5 cases in total) [44]. There are currently no reliable guidelines for the resection of metastases from these cancers. Consequently, the challenge for the future is to select patients for optimal resection.

4.4.2. Kidney cancer

The prognosis of patients with liver metastases from renal cell carcinoma is generally poor [45]. In the series by Suppiah et al [46], the median survival of 186 non-operated patients was 7.8 months. Liver resection is the only potentially curative treatment, offering a chance of long-term survival in exceptional cases. Renal cell carcinomas and their metastases rarely respond to systemic chemotherapy, radiotherapy or hormonal therapy. In the series by Stief et al [47] the resectability rate was 85%. Mean survival after resection was 16 months. This result was significantly better than the 4 months observed in the case of surgical abstention. In the study by Thelen et al [48] the overall survival rates at 3 and 5 years were 54.3 and 38.9% respectively.

These long-term results are similar to the survival rates obtained after resection of liver metastases from colorectal cancer. They are also comparable to the results after resection of lung metastases from renal cell carcinoma. These metastases are therefore currently a generally accepted indication for surgery.

4.4.3. Testicular cancer

These tumours are highly chemosensitive [49]. Surgery is used as an adjuvant treatment to eliminate residual tumours after chemotherapy or to select patients who will benefit from additional chemotherapy. In the study reported by You et al [50], 11 of the 15 patients were still alive 8 years after hepatectomy.

4.5. Adrenal tumours

4.5.1. Adrenocortical cancer

The surgical approach to these HM is justified by a survival gain that can exceed 10 years in selected patients [51].

4.5.2. Liver metastases from lung cancer

Liver metastases from these cancers are rarely isolated. This explains the lack of significant series in the literature. Most articles report minor resections for one or two lesions. The study by Oshiro et al [52] reported only one resection of lung cancer HM in the overall series of HMNCRNE. In Ercolani's cohort of 144 HMNCRNE [53], three patients underwent surgery for lung cancer HM. Only one patient survived for more than 5 years.

4.5.3. Liver metastases from ENT cancers

The HM of these cancers is most often multiple, associated with other extrahepatic lesions and therefore inaccessible to liver surgery. Chemotherapy is the mainstay of treatment for metastatic nasopharyngeal cancer [54]. However, in rare cases of isolated and limited numbers of HM, liver surgery may be discussed, especially when the metastases are well controlled with radiochemotherapy. The patient in Alexander's study [55] died 25 months after resection of his metastases.

4.6. Morbidity - Mortality

4.6.1. Hepatic metastases of neuroendocrine tumours

The results reported by several specialised centres show that hepatic excision of HM from NETs is a safe procedure with very low mortality and an acceptable morbidity rate [56,57,58]. Sarmiento et al [56] reported a morbidity rate of 30% in their series of 23 patients who underwent pancreatic and hepatic resection. In this series, the main complications were fistulas (pancreatic and biliary). In the series by Norton et al [57] the overall morbidity rate was 19%, with an average hospital stay of 14 days. Mortality was zero. Reddy et al [59] directly compared the length of hospital stay between patients. Although no difference was found between patients with HMNCRNE (median: 7 days, range: 3 to 48

days) and colorectal metastases (median: 7, range: 3 to 55), patients with neuroendocrine liver metastases had a significantly longer hospital stay compared with the previous two groups (median: 10 days). In our series, none of the two patients operated on for hepatic metastases of NET had any specific post-operative complication. The mean length of hospital stay was 07 days.

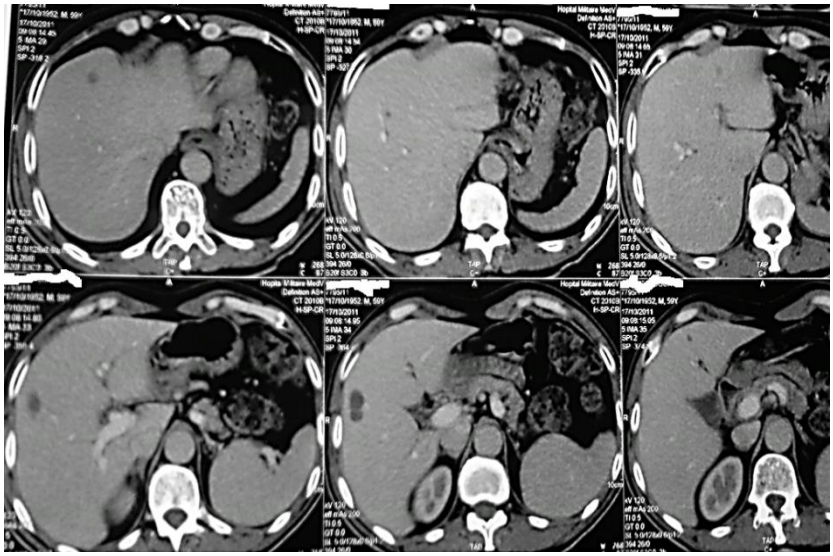

Figure 6 Pseudocystic NET liver metastases from a patient in our series

4.6.2. Liver metastases from non-colorectal, non-endocrine tumours

In recent series, peri-operative mortality ranged from 0 to 4% [60,61], while the morbidity rate varied from 8 to 30%. [62,63] These low morbidity and mortality rates can be explained by the development of new surgical techniques, the use of hepatic pedicle clamps, the increasingly frequent and regular practice of hepatectomies, very often in specialised centres, and above all by a better selection of young patients with a future liver that is still quantitatively and qualitatively sufficient and not diminished by too many courses of chemotherapy.

In our study, there was only one Clavien grade 3A complication.

Table 2 Comparative table of morbidity and mortality rates after resection of non-colorectal liver metastases between the different studies

Studies	Year	No. of patients	Mortality	Morbidity
Hamy et al [18]	2000	27	3%	-
Van ruth et al [77]	2001	28	0%	25%
R. Adam et al [19]	2005	1452	2,3%	29%
Groeschl et al [270]	2012	420	1,9%	20%
Our study	2020	13	0%	15,38%

4.7. Oncological results

4.7.1. Recurrences

Despite rigorous selection, resection of HM is followed by tumour recurrence in almost two-thirds of cases [64]. Rarely, the liver is the only site of recurrence. As in patients with colorectal liver metastases, repeat hepatectomy may be considered in the absence of extrahepatic disease and if the patient's condition and liver reserve allow. Technically, they are more difficult because of the numerous adhesions formed and the fragility of the liver induced by post-resection regeneration and previous courses of chemotherapy. Slotta et al [65] reported a recurrence rate of 25.7%. The 10-year recurrence rate in the series by Elias [55] was 70%.

4.7.2. Survival

Hepatic metastases of neuroendocrine tumours

In the homogeneous group of NET HM, resection prolongs survival compared with other treatments. The 5-year overall survival rate varies between 45 and 90% [56].

In 2010, Mayo et al [66] published the results of a cohort of 339 patients operated on for HM of NETs (40% primary pancreatic and 25% primary small bowel). Overall survival rates at 5 and 10 years were 74% and 51% respectively. The median survival of 125 months was more than 3 times greater than the median survival observed in untreated patients. In the series by Elias et al [58] curative hepatectomy of 47 HM of well-differentiated NETs performed between 1985 and 2000 resulted in a mean survival of 91 months.

Hepatic metastases of non-colorectal non-endocrine tumours

Estimated at around 25% in the 1980s, the 5-year survival rate gradually increased to 47% in 2008 [67]. The most recent multicentre series report survival rates ranging from 27.9% to 50% [51,65]. Beyond the heterogeneity of these series in terms of primary cancers, the improvement in survival rates for patients operated on reinforces and demonstrates the usefulness of liver resection. The large series (1452 patients) by Adam et al [16] showed an overall survival at 5 years and 10 years of 36% and 23% respectively after hepatic resection. Recurrence-free survival at 5 and 10 years was 21 and 15% respectively. Although there was an improvement in survival between the pre-1995 period and the post-1995 period, the difference was not significant. The authors classified the outcome in terms of 5-year survival after liver resection into:

- Favourable: adrenal, testicular, ovarian, small intestine, ampulla of Vater, breast, renal and uterine tumours;
- Intermediate: gastric adenocarcinoma, exocrine pancreas, cutaneous melanoma, choroidal melanoma and duodenal tumours;
- Poor: oesogastric junction, pulmonary, oesophageal and ENT tumours.

Over a period from 1990 to 2009, Groeschl et al [51] performed 420 resections for MHNCR. Patients operated on between 2000 and 2009 had a median survival of 66 months (p=0.003). Survival rates at 3 and 5 years were 55% and 38% for resections performed during this second decade.

In their study reported in 2014 on a cohort of 101 patients, JE Slotta al [65] obtained a 5-year and 10-year survival rate of 43% and 30% respectively. Patients with liver metastases of non-gastrointestinal origin had significantly prolonged survival after resection compared with those not resected ($p < 0.05$).

In our study, after an average follow-up of 12 months (extremes 3 to 36 months), there was only one death: the patient who underwent surgery for hepatic metastatic adrenocortical cancer. She developed several extrahepatic metastases.

4.7.3. Prognostic factors

The poor prognostic factors for non-colorectal liver metastases identified in the various studies (survival < 30% at 5 years) are the presence of extrahepatic metastases, progression on chemotherapy, non-urological and non-gynecological cancers and a recurrence-free survival interval of less than 12 months.

The good prognostic factors reported in several series are curative resection and hepatic metastases of non-digestive origin [68,69,70]. A single metastasis may also be associated with a good prognosis [71]. A metachronous metastasis occurring at least 12 months after the primary tumour has also been identified as a good prognostic factor [72], although in some series survival is better in the case of synchronous metastasis [73,74].

The factors associated with better survival were [75]:

For patients: age < 60, female;

For the primary tumour: the site of the primary tumour (breast cancer or urological and gynaecological cancer), its non-squamous histology, and its initial treatment by excision;

For hepatic metastases: metachronous appearance, at best > 12 months after treatment of the primary, uniqueness, maximum size < 5 cm, unilateral location, good response to chemotherapy and absence of any extrahepatic location;

For hepatectomy: its limited nature, R0 and the possibility of iterative hepatectomy.

The influence of the primary tumour site on survival has also been demonstrated by JE. Slotta et al [65] who found that patients with liver metastases from primary non-gastrointestinal tumours had significantly longer survival than those with metastases from gastrointestinal tumours ($p<0.05$).

In the group of neuroendocrine HM, Chamberlain et al [76] proposed a predictive survival score ranging from 0 to 4 points. These were:

Whether the primary tumour is functional (=0 point) or non-functional (=1 point);

Absence (=0 point) or presence (=1 point) of extrahepatic disease;

The unilobar (=0 points) or bilobar (=2 points) nature of HM;

Finally, the percentage of tumour invasion of the liver parenchyma (0 points if <75%) and (2 points if >75%).

For example, a patient with a score of 0 has a 100% probability of survival to 5 years, whereas a patient with a score of 4 has a 0% probability of survival to 2 years.

In the series by Elias [58], the poor prognostic factors found were: incomplete excision (R2) (5-year survival 47% compared with over 70% in the case of R0 or R1); bilobar or multiple HM (> 10) and pancreatic origin of the primary.

Abbreviations

- HM: Hepatic metastases
- HMNCRNE: non-colorectal non-endocrine liver metastases
- CT: Chemotherapy
- RT: Radiotherapy
- RCT: Radiochemotherapy
- ICC: Invasive ductal carcinoma
- NET: Neuroendocrine tumour
- GIST: Gastrointestinal stromal tumour
- ADK: Adenocarcinoma
- Sgmt: Segment
- DCD: Deceased
- AFC: French Association of Surgery
- RT: Reverse therapy

5. Conclusion

Interest in the resection of non-colorectal liver metastases continues to grow, as evidenced by the significant increase in publications over the last 30 years. This trend can be explained on the one hand by the improved results of liver surgery in terms of mortality and morbidity, advances in oncology and the efficacy of cytotoxic agents, the significant contribution of immunotherapy and the strengthening of multidisciplinary management of patients.

By operating only on patients with a limited number of liver lesions (≤ 3 lesions), totally resectable (R0), with a time to onset ≥ 12 months for metachronous metastases, without extrahepatic lesions, without comorbidities, and responsive to chemotherapy, our series of 13 resections of liver metastases from non-colorectal cancers achieved satisfactory results with only one death occurring 12 months after resection.

Multidisciplinary decision-making remains the cornerstone of treatment for these patients, who must benefit from the full range of therapies available to bring a general illness to an end.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

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