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Original Article

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Will Patients With Liver Metastasis From Aggressives Cancers Benefit From Surgical Resection?

Abdallah Al Farai[a], Jonathan Garnier[a], Anais Palen[a], Jacques Ewald[a], Jean-Robert Delpero[a], Olivier Turrini[b, c]

Abstract

Background: We aimed to evaluate the outcomes of resections for liver metastases (LMs) originating from pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer (NSCLC), and esophagus/gastric cancers (EGCs), which we label as major killers (MKs; overall survival (OS) under 10%). We hypothesized that LM resection must provide the patient with almost a year of OS postoperatively that is considered beneficial.

Methods: From January 2005 to December 2020, 23 patients underwent resection for isolated LM from MKs. These patients underwent surgery after a multidisciplinary discussion about their performance status, disease evolution during prolonged medical treatment, and the existence or absence of extrahepatic metastases.

Results: LM originated from an PDAC, EGC, or NSCLC in 10 patients (43%), nine patients (39%), and four patients (18%), respectively. The median delay between primary cancer and LM diagnoses was 12 months, and the median delay between LM diagnosis and liver resection was 10 months. Most patients, who had objectively responded to medical treatment (57%), had a solitary (61%) and unilobar (70%) LM. Severe morbidity and 90-day mortality rates were 13% and 4.3%, respectively. Margin-free resection was achieved in 16 patients (70%). After liver resection, the median OS was 24 months without a statistical difference when considering the primary tumor site; 1, 3-, and 5-year OS were 70%, 23%, and 23%, respectively.

Conclusion: Selection based on criteria such as good clinical condition, response to treatment, and long observation period helped identify patients with LM of MKs who seemed to benefit from resection.

Keywords: Pancreatic cancer; Lung cancer; Gastric cancer; Liver metastasis

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[a]Department of Surgery, Institut Paoli-Calmettes, Marseille, France
[b]Department of Surgery, Aix-Marseille University, Institut Paoli-Calmettes, CRCM, Marseille, France
[c]Corresponding Author: Olivier Turrini, Department of Surgical Oncology, Institut Paoli-Calmettes, 232 Boulevard Sainte Marguerite, 13009 Marseille, France. Email: turrinio@ipc.unicancer.fr

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Introduction

Some metastatic cancers show an estimated overall survival (OS) below 10% [1] and can be defined as major killers (MKs): pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer (NSCLC), and esophagus/gastric cancers (EGCs). Upfront surgery is not recommended in patients presenting with synchronous metastatic MK; however, resections after induction treatment can be performed, as several studies report an advantage in resecting metastases in selected patients [2-4]. However, no criteria have been reported, and patients are selected for surgery based on mixed factors such as performance status (PS), a delay in the initial surgery, disease evolution during medical treatment, number of metastatic sites, ability to obtain complete (R0) resection with the balance of the expected postoperative morbidity, and serum tumor marker evolution, with a final decision made by a multidisciplinary staff.

At the time of surgery, these selected patients have a favorable medical history, which estimates at least 1 year of survival with continuous medical treatment.

This study aimed to determine whether selected patients will benefit from resection of liver metastasis (LM).

Materials and Methods

From January 2005 to December 2020, 23 patients (0.9%) who underwent resection for LM from MKs were identified from our databases (NCT02871336 and NCT03686137). The study design was approved by the appropriate ethics review board. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Patient selection

The multidisciplinary staff proposed a liver resection based on the medical history, the patient's good PS (0 or 1), an exhaustive imaging workup (body computed tomography (CT) scan associated with diffusion-weighted magnetic resonance imaging (MRI) and positon emission tomography-CT (PET-CT) according to the period of treatment) that did not show metastatic sites other than the liver, the disease stabilization/regression

after a prolonged (> 6 months) medical treatment, serum tumor marker stabilization/regression during medical treatment (i.e., carcinoembryonic antigen and/or carbohydrate antigen (CA) 19-9 for PDAC and EGC, squamous cell carcinoma (SCC) for NSCLC), the absence of supplementary metastasis identified during medical treatment, and the surgical team that was estimated to achieve R0 resection without excessive expected postoperative morbidity. Consequently, all these factors were considered, but one could not prevent surgery by itself, and not all were considered for resection. No patients with percutaneous destruction of LM were included in the present series as we wanted to focus on the most "aggressive" treatment (i.e., the surgical approach).

Variables studied and primary endpoints

Various routine variables were evaluated, including American Society of Anesthesiologists (ASA) score; primary tumor etiology; number, size, and location of the LM; type of surgery; morbidity [5]; margin resection status (R0 or R1); and tumor recurrence site assessed every 4 months by clinical examination, serum tumor markers, and thoracoabdominal CT scan.

The primary endpoint of the study was the OS after liver resection.

Statistical analysis

Continuous data were expressed as the mean (± standard deviation) or median (range). Survival duration was measured from the liver resection date until death or the sensor date (June 1, 2020). Survival curves were generated using the Wilcoxon method. Statistical significance was set at $P < 0.05$.

Results

None of the patients were lost during a mean postoperative follow-up period of 28 months. LM originated from an PDAC, EGC, or NSCLC in 10 patients (43%), nine patients (39%), and four patients (18%), respectively (Table 1). The median delay between primary cancer and LM diagnoses was 12 months (range, 0 - 67 months), and the median delay between LM diagnosis and liver resection was 10 months (range, 8 - 61 months). The majority of patients had a solitary (61%) and unilobar (70%) LM and objectively responded to medical treatment (57%). Most patients (61%) underwent intraoperative local destruction (n = 2) or a minor hepatectomy (n = 8) possibly associated with local destruction (n = 4). Severe morbidity and 90-day mortality rates were 13% and 4.3%, respectively (one patient died from postoperative liver failure during the early period of the study). R0 resection was achieved in 16 patients (70%). Four patients (17%) received adjuvant chemotherapy.

Recurrence was diagnosed in 13 patients (56%) with a median delay of 11 months (range, 6 - 27 months); recurrences were located in the liver in 11 patients, and one patient with EGC developed a unique lung metastasis that was treated by local destruction. Overall, 12 patients (52%) died of disease recurrence (Table 2). After the liver resection, the median OS was 24 months without a statistical difference when considering the primary tumor site; 1, 3-, and 5-year OS were 70%, 23%, and 23%, respectively (Fig. 1).

Discussion and Conclusions

Our study showed that selected patients with LM of MKs benefit from resection as the median OS after liver resection was 2 years.

Oncologists and surgeons are reluctant to consider liver resection in patients with metastatic MKs because of two reasons. First, MKs are rarely confined to one organ and medical teams are worried of metastasis in other organs despite an exhaustive preoperative imaging workup. Therefore, the benefit of surgery for LM is considered questionable; it could even cause rapid metastasis of the disease in the event of a poor postoperative course. Second, the therapeutic arsenal in MKs is not evolved as other solid tumors (i.e., colorectal cancer, breast cancer, etc.).

However, few patients with metastatic MKs seem to have a less aggressive disease course. These patients probably have a particular tumor biology that could not be detected early due to the lack of current knowledge. Consequently, we could only discuss liver resection based on criteria that are a surrogate of this favorable tumor biology and that answer the oncologists on their reluctance as mentioned above.

When considering the first reason, PS is a major criterion in our decision-making process. Obviously, the patient's clinical status has to be optimal to minimize the risk of poor postoperative courses. However, the clinical status also reflects the impact of the disease on the patient: a poor PS (> 1) and/or a significant weight loss (> 10%) probably underestimates the spread of the disease even if the imaging did not show any metastatic site other than the liver. Consequently, we argue that the clinical status is the first criterion to be considered to further discuss liver resection in patients who have an exhaustive imaging staging that excluded extrahepatic disease. Together with the clinical status, "prolonged" (unknown cut-off) follow-up helps identify other metastatic locations in most patients. In our series, only one patient developed a solitary extrahepatic recurrence that reinforced our preoperative supposition of a disease solely located in the liver. However, most patients showed a recurrence in the liver that highlighted our poor ability to identify very small LM despite the improvement of liver imaging, mainly with MRI and PET-CT.

If the patient is surgically fit according to its PS, comorbidities, and follow-up, several factors could help answer the second reason. Tumor response to chemotherapy is crucial to discuss in all patients with solid tumors as resection in patients with tumor progression during chemotherapy remains exceptional even for favorable etiologies [6]. Thus, in patients with MKs, stabilization or progression during chemotherapy is frequent, and good responders are rarely identified, representing only 1% of our liver resection procedures over two decades.

Table 1. Characteristics of the 23 Patients

Sex ratio (M/F)	2.8 (17/6)
Median age (range)	67 (26 - 80)
Mean BMI (± SD)	23.1 (± 4.63)
Performance status (before liver surgery) (%)	
0 - 1	23 (100)
≥ 2	0
ASA score (%)	
1	3 (13)
2	18 (78)
3	2 (9)
Primary tumor etiology (%)	
Pancreatic ductal adenocarcinoma	10 (43)
Esophagus/gastric cancer	9 (39)
Non-small cell lung cancer	4 (18)
Synchronous LM (%)	9 (39)
Median delay initial diagnosis - LM diagnosis (months) (range)	12 (0 - 67)
Median delay LM diagnosis - liver surgery (months) (range)	10 (8 - 61)
Liver metastasis	
Median number (range)	1 (1 - 10)
Mean size of the biggest LM (mm) (± SD)	38.3 (± 22.03)
Unilobar (%)	16 (70)
Chemotherapy prior to surgery after LM diagnosis	
Median number of lines (range)	1 (1 - 3)
Objective response to chemotherapy (>10%) (%)	13 (57)
Surgery	
Major hepatectomy (%)	9 (39)
Minor hepatectomy (%)	8 (35)
Minor hepatectomy + local destruction (%)	4 (17)
Local destruction (%)	2 (9)
Primary tumor resection combined with LM resection[a] (%)	5 (56)
Mean intraoperative blood loss (mL) (± SD)	216.7 (± 163.8)
Mean operative duration (min) (± SD)	201 (± 115.8)
Overall morbidity (%)	8 (35)
Severe morbidity (%)	3 (13)
90-day mortality (%)	1 (4.3)
Median lenght of hospital stay (days) (range)	11 (4 - 34)
Readmission (%)	3 (13)
Adjuvant chemotherapy (%)	4 (17)

[a]Calculated on patients with synchronous metastatsis. BMI: body mass index; SD: standard deviation; LM: liver metastasis; ASA: American Society of Anesthesiologists.

This small sample size prevents any strong conclusions or recommendations. However, these patients can have an interesting survival as previously reported [7-18].

The appropriateness of resection cannot be determined without comparison with a group of patients with similar conditions who are pursuing medical treatment. This represents the major limitation of our study as we cannot compare the prognosis with patients who received medical treatment in a matching analysis or discuss the approximate duration of the expected prognosis if the medical treatment is continued un-

Table 2. Oncological Outcomes of the 23 Patients

Patient	Etiology	Recurrence	Liver recurrence	Status	Survival* (months)	Cancer-related death
1	EGC	No	No	Dead	1	No
2	EGC	Yes	No	Alive	19	-
3	NSCLC	No	No	Alive	19	-
4	EGC	No	No	Alive	160	-
5	EGC	Yes	Yes	Dead	16	Yes
6	NSCLC	No	No	Alive	87	-
7	EGC	Yes	Yes	Dead	24	Yes
8	EGC	No	No	Dead	4	Yes
9	EGC	Yes	Yes	Dead	32	Yes
10	EGC	Yes	Yes	Dead	17	Yes
11	PDAC	Yes	Yes	Dead	31	Yes
12	PDAC	Yes	Yes	Dead	10	Yes
13	PDAC	Yes	Yes	Dead	28	Yes
14	PDAC	No	No	Alive	36	-
15	EGC	Yes	Yes	Dead	16	Yes
16	PDAC	Yes	Yes	Dead	6	Yes
17	PDAC	Yes	Yes	Dead	10	Yes
18	NSCLC	No	No	Alive	8	-
19	PDAC	Yes	Yes	Dead	5	Yes
20	NSCLC	No	No	Alive	22	-
21	PDAC	No	No	Alive	7	-
22	PDAC	Yes	No	Alive	18	-
23	PDAC	No	No	Alive	14	-

*From liver surgery. NSCLC: non-small cell lung cancer; PDAC: pancreatic ductal adenocarcinoma; EGC: esophagus/gastric cancer.

der the same conditions. Indeed, patients in whom continued medical treatment or resection can be considered are very few. Therefore, 1) there is no randomized study that has compared the two approaches, and 2) as we routinely propose a surgical attitude, we cannot provide data on patients with same criteria that received only medical treatment. However, the literature reports series of fit patients receiving exclusive medical treatment and whose survival is less than the 24 months that we observed with our interventionist attitude [19-21]. We can therefore maintain that the survival of resected patients is not inferior to that reported in these series.

But the advantage of resection is to allow a break in medical treatments which undeniably generate significant side effects and alter the quality of life. Our study is also limited by its retrospective design and the heterogeneity of the perioperative medical treatments delivered during the long inclusion period. Despite these drawbacks, it is reasonable to suggest liver resection in the qualified patients. While genetic markers can identify the disease accurately and at an early stage, criteria such as good clinical condition, response to treatment, and long observation period can help multidisciplinary staff perform local resection or destruction in patients. Oncologists must consider this strategy as it can avoid prolonged medical treatment that is often poorly tolerated.

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Financial Disclosure

None to declare.

Conflict of Interest

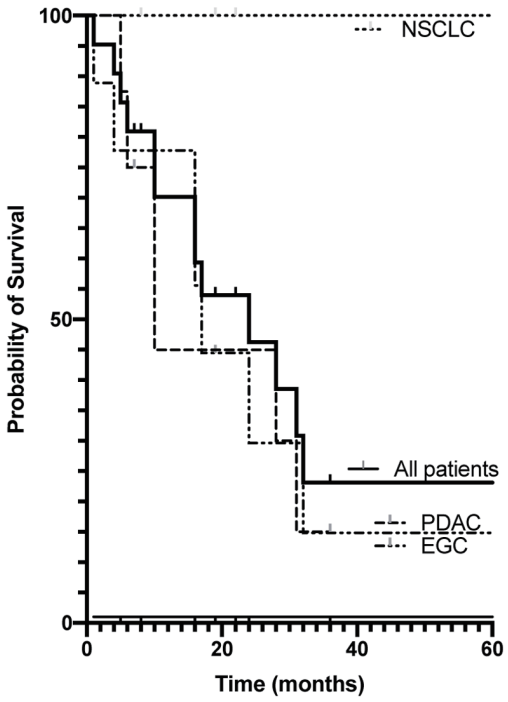
None to declare.

Informed Consent

All study participants provided informed consent.

Author Contributions

AAF contributed to the study design and wrote the manuscript.



(NSCLC: Non-Small Cell Lung Cancer; **PDAC**: Pancreatic Ductal ADenoCarcinoma; **EGC**: Esophagus/Gastric Cancer)

Wilcoxon Test: 0.38

Subjects at risk

Time	**0**	**12**	**24**	**36**	**48**	**60**
All	23	17	7	3	3	3
PDAC	10	7	5	1	1	1
EGC	9	9	3	2	2	2
NSCLC	4	4	2	2	2	2

Figure 1. Overall survival of the 23 patients, and according to primary tumor site, since liver surgery.

AP contributed to data collection and data analysis. JE contributed to data analysis and reviewed the manuscript. JG contributed to data collection and reviewed the manuscript. JRD reviewed the manuscript. OT contributed to the study design and wrote the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

MK: major killer; PDAC: pancreatic ductal adenocarcinoma; NSCLC: non-small cell lung cancer; EGC: esophagus/gastric cancer; LM: liver metastasis; OS: overall survival; PS: performance status; MRI: magnetic resonance imaging; PET-CT: positon emission tomography-computed tomography

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