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Combined liver surgery and RFA for patients with gastroenteropancreatic endocrine tumors presenting with more than 15 metastases to the liver.

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ABSTRACT:

Aim: The aim of this study was to report the feasibility and early survival results of liver metastasis (LM) resection combining cytoreductive surgery and radiofrequency ablation (RFA) during a one-step procedure, in patients presenting more than 15 bilateral LM from well-differentiated endocrine carcinoma. It is an extensive application of the current guidelines.

Methods: In this retrospective review of a prospectively collected database, we used a combination of hepatectomy to treat large or contiguous LM, and extensively used multiple RFA to treat the remaining LM which were smaller than 2.5 cm. Patients were selected based on a low natural tumor burden slope, and the technical feasibility of treating all the detectable LM.

Results: From January 2002 to May 2007, 16 patients with a median of 23 LM per patient (mean number: 25.7 ± 12 ; range 16–89) underwent this procedure. A mean of 15 ± 9 LM per patient were surgically removed and a mean of 12 ± 8 (median of 10) LM per patient were RF-ablated. No mortality occurred. Morbidity was observed in 11 patients (69%). The 3-year overall survival and disease-free survival rates were similar to those observed in our preliminary series of 47 hepatectomized patients with a median of 7 LM per patient.

Conclusion: This new one-step combined technique allowed us to apply an “upgraded” therapeutic approach to a selection of patients presenting a median of 23 LM per patient and to improve their prognosis, putting it on a par with that obtained by conventional hepatectomy.

Key-words:

Endocrine tumor, liver metastases, hepatectomy, radiofrequency ablation.

Gastroenteropancreatic endocrine carcinomas (GEPEC) are classically defined as exhibiting positive immunohistochemical staining for secretory granule or secretory vesicle markers. This simple definition distinguishes a subgroup of rare tumors characterized by common features including hormone secretions, association as part of inherited syndromes, hypervascularized stroma, and the expression of multiple peptide receptors. From a prognostic standpoint, GEPEC are characterized by a variable course among patients including the subgroup with indolent progression. Finally, a high prevalence of hepatic metastases (LM) and their major impact on survival has made the liver a major target for therapy in well-differentiated endocrine carcinoma (1).

All the guidelines for the management of neuroendocrine tumors recommend the removal of LM, when possible and resection of at least 90% of the disease (19-21) and liver surgery is considered a major tool in the therapeutic arsenal against GEPEC. A reason to support this approach is that liver surgery is potentially capable of achieving a complete response of LM which cannot be otherwise obtained. Indeed, several studies have reported 5-year survival exceeding 70% and improved survival in the subgroup of patients with LM amenable to resection (2-7). However, the lack of randomized studies precludes any definite conclusions. There are two limitations of this approach which merit discussion. Firstly, it applies to a limited number of patients who, most of the time, have a small number of LM, and secondly, 75% of these patients relapse at 10 years (2-7). Recent progress achieved in the prognostic classification of GEPEC as well as in imaging studies has enabled a better definition of the different patient subgroups. From a prognostic point of view, we recently highlighted the major role of the number of LM and the natural tumor burden slope (8). We also emphasized the sensitivity of liver MRI in detecting tiny LM (9). Paradoxically, however, the progress which enabled the detection of tiny LM has generally resulted in a restriction of the indications for hepatectomy because the resection of more than 10 or 15 bilateral LM is usually considered surgically unfeasible.

The recent introduction of liver radiofrequency ablation (RFA) allowing intraoperative destruction of small-sized LM, may be a new tool for the liver surgeon with the main advantage of sparing normal liver parenchyma. The percutaneous approach is minimally invasive but only 3 or 4 limited sized LM can be treated. The per-laparoscopic use of RFA allows treatment of a few additional but also limited

sized LM, and is still a palliative approach (10). To date, the putative role of RFA integrated into the surgical setting has not been evaluated.

The aim of this retrospective review of a prospectively collected database was to report on the feasibility and the early survival results of a maximally cytoreductive hepatectomy combined with multiple RFA in one session to treat patients presenting more than 15 bilateral LM. This approach is a logical extent of the guidelines concerning maximal cytoreduction of GEPEC metastases.

Patients and methods:

Selection Criteria

All the data concerning patients with more than 15 LM from a GEPEC who underwent surgical resection or RF ablation of LM, were prospectively collected in a database. All LM seen on imaging were considered (but not lesions discovered in the pathological specimen).

The preoperative work-up included pathological confirmation of the diagnosis of well-differentiated GEPEC, and staging of the primary tumor. All patients underwent somatostatin analog receptor scintigraphy, a CT-scan of the thorax, abdomen, pelvis and determination of relevant blood markers. The number, size and location of the LM were determined on liver ultrasound, MRI and CT-scan including the hepatic arterial phases (9). Volumetric CT-scan was also used to estimate liver volumes. When the estimated remnant liver volume was less than 30% of the total liver volume, preoperative portal vein embolization was performed (11,12).

The treatment was decided at a multidisciplinary team meeting during which all imaging studies were reviewed with the radiologists. All the patients were operated on during the 4 weeks following the last imaging work-up. Only patients with a good general status (WHO Performance Status < 2) and therefore, able to undergo major liver resection, were included in this study. The spontaneous slope of tumor growth before liver surgery was low [less than 20% of progression over 6 months] (8), which excluded patients with rapidly progressive disease. Small extra-hepatic metastases limited to bone were not considered an exclusion criterion (given that the short-term prognosis of the patient was based on the liver tumor burden). The detection of LM

on ultrasound was a further requirement. No chemotherapy nor biotherapy was given before surgery, nor as adjuvant treatment after surgery.

Surgical procedures

The aim of the surgical procedure was to resect all LM but also extra-hepatic tumor sites including the primary tumor (which could have necessitated a pancreaticoduodenectomy, splenopancreatectomy, or intestinal resection), and lymph nodes. After complete exploration of the abdominal cavity, the liver was meticulously explored following complete mobilization of the two lobes and an ultrasound examination enabled us to produce a precise drawing of the lesions (locations and sizes of the LM).

All LM exceeding 2.5 cm had to be resected as they could not be safely RF ablated. LM smaller than 2.5 cm could be resected or RF ablated. Hepatectomy was systematically performed under intermittent complete vascular exclusion of the liver, without interrupting inferior vena caval flow (13), after intermittent vascular clamping of the hepatic pedicle and all the hepatic veins (excepted those of the Spiegel lobe). The definition of an extended hepatectomy was applicable when at least four Couinaud liver segments were resected. RFA was performed with Valleylab cool-tip RF electrodes (Gosport, PO, USA) which come in 3 sizes (1 cm, 2 cm, and 3 cm) and are used according to the diameter of each metastasis. RFA was performed after the hepatic resections, under ultrasonographic guidance, working clockwise, from right to left, first ablating deep-seated LM and finishing with the superficial lesions. The surgeon constantly referred to drawing indicating the sites and sizes of LM produced following ultrasound detection before RFA. Simple RFA sessions were performed (14), but when necessary, the central bile ducts were also cooled to protect them from heat (a technique we described in 2001) (15,16), or a trans-RF hepatectomy was performed after RF destruction of one or several LM located along a suitable transection line, in order to spare as much normal parenchyma as possible (a technique we described in 2002) (17,18). Patients underwent a postoperative CT-scan before being discharged from hospital.

Statistics

Usual arithmetic was use for medians and means. Survival curve was done with the Kaplan-Meyer method.

Results

Patients

Sixteen patients underwent this one-step extensive surgery including the treatment of a minimum of 15 bilateral LM, from January 2002 to May 2007. There were 7 males and 9 females with a mean age of 48 ± 10 years (median: 52, range: 30-61). The primary was located in the pancreas or duodenum in 10 patients (including 2 gastrinomas, 1 insulinoma, 1 glucagonoma and 1 vipoma), in the small bowel in 4 patients, and in the bronchus in 2 patients. During the preoperative work-up, the primary tumor was present in 9 patients, residual invaded lymph nodes were present in the area of the previous primary tumor resection in 3 patients, and asymptomatic small bone metastases were present in 3 patients (but not considered as contraindication to the liver procedure, the short term prognostic being based on the liver tumor burden)..

Procedures

Four patients underwent preoperative selective portal embolization. Nine major hepatectomies were performed. Extra-hepatic resections were associated with six of the 9 major hepatectomies, and with all the minor hepatectomies. Thus, associated resections were performed in 13/16 patients. Of note, extra-hepatic resections were mainly performed on the duodenopancreas (table 1). A mean of 2.3 supplementary LM per patient were discovered through palpation or ultrasonography at laparotomy. The surgical and RFA procedures are described in **table 1**. In brief, surgical resections with anatomical and non anatomical liver surgery treated a mean of 15.3 ± 8.9 LM (median: 12, range:3-59), while RFA treated a mean number of 11.6 ± 8.4 LM (median 10, range 0-30) per patient. The mean size of RF-ablated LM was 13 ± 11 mm (range: 4-27). Three bile duct cooling procedures and 5 trans-RFA hepatectomies were required.

Finally, a median of 23 LM per patient (range 15-89; mean 25.7 ± 12) were treated with surgery combined with RFA. Approximately 60% of the LM were surgically excised, and 40% were RF ablated. The mean duration of surgery was 5h32 min, and median intra-operative blood loss was 510 ml.

Postoperative course (table 2)

No mortality occurred. Morbidity was observed in 10 patients (62.5%). The following surgical complications were recorded : hemorrhage (n=1), biliary peritonitis requiring re-operation (n=1), pleural effusion requiring drainage (n=4), pancreatic fistula (n=3), transient liver insufficiency with ascites (n=2), subphrenic hematoma (n=1) and inferior vena caval thrombosis (n=1). The following medical complications were documented : lung infection (n=3), urinary infection (n=4), and myocardial infarction (n=1). This resulted in grade 4, grade 3 and grade 2 complications (NCI classification) in 2, 4 and 5 patients respectively. Among the 13 patients who underwent hepatic and extra-hepatic resections, 8 experienced at least one postoperative complication. Postoperative complications were equally divided between the 2 groups of major and minor hepatectomies. Lately, no stenosis of the central bile ducts has been observed for the three patients in whom the bile duct cooling was used.

The mean duration of hospitalization was 16.6 ± 4.8 days (median: 15, range: 10-24). The five patients who presented symptoms in relation with tumor secretion were free of symptoms after surgery.

Follow-up, survival rate

Follow-up was not the chief objective of this feasibility study. It was conducted every six months with a liver ultrasound and MRI, associated with somatostatin analog receptor scintigraphy. After a median follow-up of 27 months, 12 patients relapsed (8 of them inside the liver) and two patients died. The overall survival rate was 84% at 3 years (**figure 1**).

Discussion

Rational. To date, it has not been possible to conduct a randomized study focused on the place of hepatectomy in the treatment of LM from well-differentiated GEPEC. So, following the results of numerous non randomized studies which showed that surgical therapy is still the most efficient way to treat metastatic disease, offering the longest-lasting benefits and the best quality of life (2-7), all the guidelines for the management of neuroendocrine tumors recommend the removal of LM, when possible and resection of at least 90% of the disease (19-21). The crucial point about

surgery of LM from well-differentiated GEPEC is patient selection. A multivariate study of 118 patients with metastatic GEPEC treated in our institute taught us that the three main prognostic factors are age (>65 year), more than 10 LM, and a low natural tumor burden slope (8). Most teams propose surgery to patients presenting only a few LM or unilobar LM. Different surgical teams use diverse selection criteria and resection techniques. Finally, liver resection series exclusively concern small groups of highly selected patients, and the majority of the other patients presenting with numerous and bilateral LM are not selected for surgery.

The first objective of our work was to expand the indications for liver surgery and to operate on a greater proportion of patients in the subgroup exhibiting a low natural tumor burden slope and a good general status. Our series represent only an extensive application of the international guidelines concerning the survival benefit of maximal cytoreduction of the metastatic disease for GEPEC (19-21).

Feasibility and preliminary survival results. Our feasibility study shows that partial hepatectomy resecting large or contiguous LM combined with extensive use of optimized RF ablating the remaining small LM, allowed us to treat 16 selected patients bearing a median of 23 LM per patient, in a single surgical session, with 40 % of the LM being treated with RFA. No mortality occurred, however, significant but still acceptable morbidity was observed. It is too early to determine a possible benefit in terms of long-term survival, but early results are encouraging. Effectively, when the survival curves of these 16 patients bearing a median of 23 LM per patient are compared with those of the 47 hepatectomized patients with GEPEC LM bearing a median number of 7.4 LM per patient that we published in 2003 (7), the overall survival (**figure 2**) and disease-free survival rates (**figure 3**) are similar. To date, this median number of 7.4 LM resected per patient is the highest reported in the literature (7). In the present series of highly selected cases, the median number was 23. In other words, with this new approach we succeeded in obtaining the same survival rates for patients bearing more numerous and bilateral LM, whose disease extent was not initially amenable to resection. So, it was possible to upgrade treatment for these patients and ultimately improve their early survival. It also seems that, being able to turn the clock back to zero for all detectable tumor disease, results in a similar survival duration, whatever the number of LM from GEPEC. The major criticism to

our series is to do not present a control group. However, until now, none randomized study could be conducted concerning the treatment of LM from GEPEC.

The high postoperative complication rate in our series could be considered debatable. However, it includes all grades of complications, there were no postoperative deaths, and this approach allowed these selected patients to leave the poor prognosis group of unresectable patients whose 5-year survival rate was only 22% in the US Modlin and Sandor database (22).

Technical aspects. Various surgical approaches have been proposed to treat a high number of LM, in one or two sessions. A two-step surgical procedure was recently described to treat a higher number of LM (23,24), but only a few cases were reported and the mean number of LM resected during the two steps never exceeded fifteen (23,24). It is noteworthy that these two-step procedures incur a cost in terms of risk, pain, hospitalization and have social and economic repercussions. An alternative approach is to use the entire range of tools currently available to treat these patients in one step, as presented in our series. In our opinion, the only indication for the above-mentioned two-step surgical procedure is when both a major hepatectomy and a duodenopancreatectomy have to be performed since this surgical situation is known to be associated with high morbidity (91%) and mortality (14 to 47%)(25,26). In such cases, we first resect the primary and the LM in the less tumorous part of the liver, while the second step is devoted to removing the LM remaining in the more tumorous part of the liver.

This report presents an integrated approach aimed at improving the number of treatable hepatic metastases. We use a great number of different tools currently available in the liver surgery setting : preoperative interventional therapy, intraoperative imaging and intraoperative RFA with new techniques like bile-duct cooling or the trans-LM liver section (these LM are ablated with RF before surgery). Our experience, based on more than 1300 hepatectomies for malignant tumors and more than 250 intraoperative uses of RFA, has taught us the following technical points. First, complete mobilization of the liver is necessary to perform a meticulous exploration of the organ and to operate under safe conditions. Second, bloodless hepatectomy is a prerequisite before using multiple RF ablations in the remaining liver in order to decrease the risk of liver failure. We systematically perform this

bloodless hepatectomy achieved through transient intermittent total vascular exclusion of the liver without interrupting inferior vena caval flow. Third, the extensive repeated use of intraoperative ultrasound is mandatory. When multiple RF ablations are required, a precise drawing indicating the sites and sizes of the LM is useful to guide repeated RFA. Each of the previously ultrasound identified LM are ablated, one by one, and noted as “treated” on the drawing. When a part of the liver is temporarily saturated with gaseous micro-embols, we leave it for 10-15 min before resuming RF ablation in that part, and another part of the liver is treated during that interval. Particular techniques like bile-duct cooling or the trans-RF hepatectomy passing through an ablated LM (in order to spare parenchyma for volumetric reasons) are useful. Their safety and efficacy have already been proven (16,18) and the location of LM is no longer a limit to RFA. Fourth, due to the high number of RF ablations in the remaining part of the liver, maximum sparing of normal parenchyma is critical : RFA must be as limited as possible in volume and optimally adapted to the size of the LM. Fortunately, numerous LM from endocrine tumors are small, round, and easily detectable because they are strongly hyperechogenic. This is why in most cases, we only used probes with an electrode length limited to 10 mm or 20 mm. The liver volume reduction resulting from these multiple RF ablations, even when limited in size, is difficult to predict. Our inability to precisely predict this reduction explains the occurrence of two cases of transient liver failure and we are awaiting a 3-D volumetric reconstruction program usable on MRI in order to be able to appraise the real volume of functional liver parenchyma with greater safety margins.

In conclusion, by combining bloodless hepatic resection with the extensive use of RFA, selected patients presenting a median of 23 LM per patient can be curatively treated in a single-step surgical procedure. Thus, the therapeutic approach is “upgraded” and patient early survival rates are improved, and similar to those obtained by conventional hepatectomy.

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Conflict of interest statement:

The authors state that they have no conflict of interest.

Statement of the contribution of each author:

Elias: original concept, clinic, writing and supervising

Goere: clinic

Leroux: collecting data , statistics

Dromain: imaging

Lebouleux: imaging

De-baere: imaging

Ducreux: review

Baudin: review

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Table 1 – Surgical and RFA Procedures

	Hepatectomy (Type)	RFA (number)	Extra-hepatic resection	Blood loss (ml)	Operative time (min)
Major hepatectomy	Left Hep. + 2 LM¶	7	Splenopancreatectomy	200	330
	Left Hep	10	Diaphrag m+ Bilat Oophorectomy + appendicectomy+ lymphadenectomy SMA*	400	360
	Right Hep	11	Appendicectomy	950	450
	Left Hep	28	Splenopancreatectomy	500	315
	Right Hep + 2 LM	3	Splenopancreatectomy	300	310
	Right Hep	7	Appendicectomy	300	300
	Right Hep	3	-	500	270
	Extended Right Hep + 1LM	7	-	600	330
	Right Hep	4	-	750	300
	Bisegment V-VI	16	Right colectomy	250	300
Minor hepatectomy	2 LM	16	Paraganglioma	300	315
	Bisegment II - III	30	Splenopancreatectomy	270	1000
	Segment II + 1 LM	19	Duodenotomy	350	420
	4 LM	16	Duodenopancreatectomy	600	450
	Bisegment II – III + 2LM	11	Appendicectomy	600	180
	1LM	9	Duodenopancreatectomy	200	450

¶LM : limited resection of liver metastases

*SMA : Superior Mesenteric Artery

Table 2 – Postoperative outcome in 16 patients

	Major hepatectomy		Minor hepatectomy		Total
	With Extra-hepatic resection	Without Extra-hepatic resection	With Extra-hepatic resection	Without Extra-hepatic resection	
Medical complications	1	1	2	0	4
Surgical complications	3	1	2	0	6
Total complications	4	2	4	0	10
No complications	2	1	3	0	6
Total	6	3	7	0	16

Figures

Figure 1: Overall and disease-free survival rates of the 16 patients.

Figure 2: Comparison of the overall survival curves of a personal historical group of hepatectomized patients (with a median of 7 LM per patient)⁷ and the present group of patients (with a median of 23 LM per patient).

Figure 3: Comparison of the disease-free survival curves of a personal historical group of hepatectomized patients (with a median of 7 LM per patient)⁷ and the present group of patients (with a median of 23 LM per patient).

Figure 1

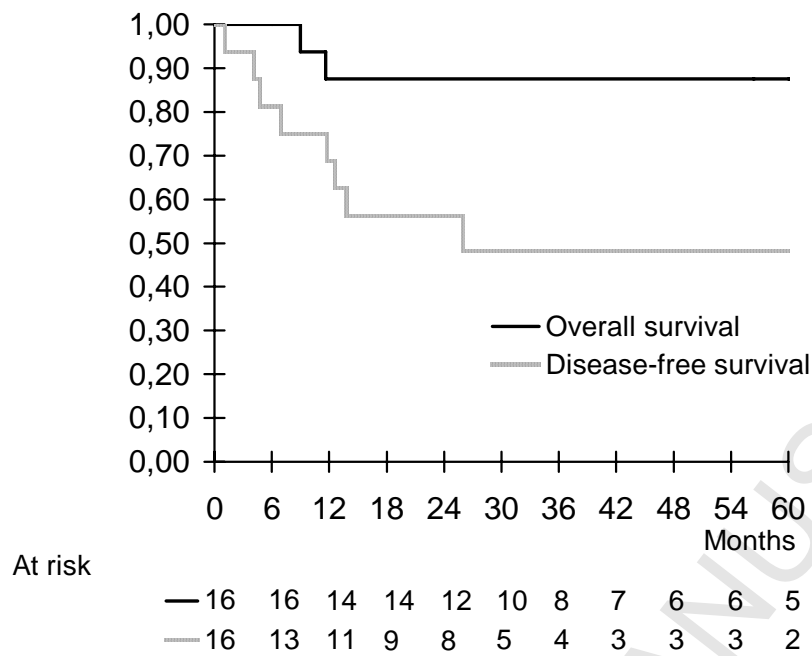


Figure 2

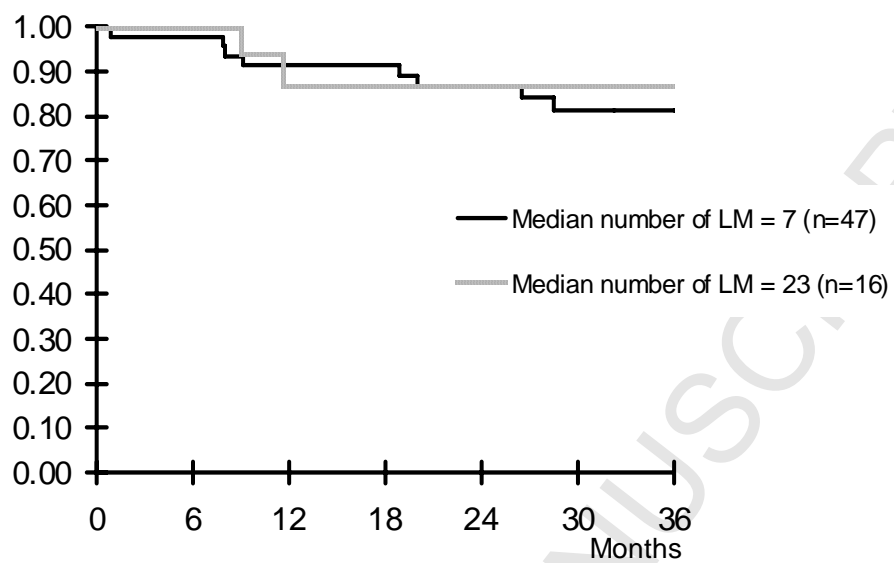


Figure 3

