Outcome of combined partial liver resection and intraoperative radiofrequency ablation in colorectal liver metastases

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Received: 18 October 2019
Revised: 12 November 2019
Accepted: 6 December 2019
Published: 27 April 2020

The Egyptian Journal of Surgery 2020, 39:289–296

Background
Liver metastases occur in 40% of patients with colorectal cancer. A minority of the patients are eligible for resection, with 5-year survival rates of 18–38%. Intraoperative radiofrequency ablation (IRFA) could be an alternative for resection to reduce loss of liver remnant. A median survival of 36 months was achieved by using multidisciplinary approach, doubling the survival rate.
Patients and methods
This is a prospective consecutive study. Between June 2016 and June 2018, 32 patients with colorectal liver metastases (CRLM) were divided into group A, comprising 15 patients with unilateral CRLM that can be resected with adequate residual volume, and group B, comprising 17 patients with unilateral CRLM that cannot be resected, but they are still eligible for complete hepatic clearance using combined liver resection and IRFA. All were followed up for 6 months.
Results
Fifteen patients underwent anatomical liver resection and 17 patients had partial resection combined with IRFA. The Clavien's complication rate was significantly lower in group B (35%) vs 60% in group A, and most complications were minor. Only two patients in group A had a grade III complication, where they underwent pigtail insertion for biliary leakage. Liver progress in IRFA group was seen in one patient. Liver recurrence was seen in 13 and 17.5% in groups A and B, respectively. During the first 3 months, complete hepatic response was observed in 14 patients in group A and 15 patients in group B (93 and 88%, respectively). After 6 months, all patients were alive, without liver tumor burden in 11 (73%) patients in group A and 17 (70%) patients in group B, but three patients developed colonic tumor recurrence.
Conclusion
Combined IRFA and liver resection augments the number of patients who can be treated surgically.

Keywords:
colorectal cancer liver metastases, liver resection, radiofrequency ablation

Egyptian J Surgery 39:289–296

1110-1121

Background

Liver metastases occur in 40% of patients with colorectal cancer. Only a minority of patients who develop colorectal liver metastases (CRLM) are eligible for upfront liver resection, which is associated with reported 5-year survival rates between 18 and 38% [1]. At the time of presentation, most of the patients are not candidate for partial liver resection, which may be attributed to many reasons such as extrahepatic disease, tumor site, and inadequate future liver volume or nearby major vascular structures [2].

Modern chemotherapy treatment associated with biological therapies is now frequently able to make previously unresectable liver metastases resectable. Despite this combined medical and surgical strategy, only 15–25% of patients are ultimately able to undergo surgery with curative intent [3].

Surgical treatment for CRLM has evolved over the past few years from major to minor hepatectomies, from anatomical to nonanatomical resections, and from single to planned staged operations [4]. At least two alternative surgical approaches aim for R0 resection by means of a two-stage procedure using portal embolization [5] and introducing tumor ablation in combination with resection [6,7]. The latter alternative is considered much safer yet efficient. Intraoperative radiofrequency ablation (IRFA) is considered a low-risk procedure, with low mortality rate of ~0.5%, and complication rates of ~6.9–9.8% [8,9]. On the contrary, local recurrence following percutaneous

 DOI: 10.4103/ejs.ejs_190_19

radiofrequency ablation (RFA) as reported in many large series is up to 40% [10,11].

In patients with technically unresectable CRLM, a median survival of 36 months could be achieved by using multidisciplinary approach, including hepatic resection, IRFA, and chemotherapy [12]. These combined approaches could double the survival rate compared with other treatment strategies (single modality) in this group of patients [13].

IRFA could be performed as an alternative for resection to reduce the loss of future liver remnant reducing postoperative morbidity and mortality owing liver failure. IRFA was performed in case of bilobar disease after resection of one liver lobe and residual tumor deep in the parenchyma of the remaining; superficial lesions were rather resected. Furthermore, IRFA may extend the feasibility of surgery in case of multiple tumors [14].

Evrard *et al*. [15] reported the safety and effectiveness of the use of IRFA as a complementary technique to resection and had encouraging outcomes in a specialized center.

The present prospective consecutive double-arm study was designed to evaluate the result of combined surgical resection and IRFA in comparison with classic surgical resection in the term of complete hepatic response (CHR) at 3 and 6 months. Secondary end points included morbidity, mortality, time required for recovery presented as ICU and hospital stay, and time to resume chemotherapy.

Patients and methods

Between June 2016 and June 2018, 32 adult patients with CRLM who were diagnosed according to the triphasic abdominal computed tomography (CT) or MRI scan criteria and were confirmed with postoperative histopathology of the resected liver specimen were included in a prospective consecutive study and treated with either a combination of partial liver resection and IRFA or classic surgical resection in two medical centers: Eldemerdash University Hospital and Ain Shams Specialized Hospital, Ain Shams University, Cairo, Egypt.

Patients included in the study were aged 18–75 years, with an Eastern Cooperative Oncology Group performance status of 0–2 [16]. All patients had pathologically confirmed colorectal adenocarcinoma with resection of the primary tumor. Metastases had to be confined to the liver and were synchronous or metachronous. Patients were eligible whether or not they had received chemotherapy previously.

Patients are divided into two groups: group A, with unilateral CRLM that can be resected surgically with adequate residual liver volume (35% residual liver volume), intact inflow and outflow, and biliary drainage (Fig. 1), and group B, which cannot be resected owing to lack of one of the aforementioned criteria but still eligible for complete hepatic clearance using combined partial liver resection and IRFA.

Patients with bilobar tumor distribution, inadequate functional hepatic reserve, proximity to major vascular structures, or with underlying liver disease were excluded from the study, as well as those with liver recurrence after previous resection. Patients with progressive disease following chemotherapy or extrahepatic metastases were not considered eligible for the study. Any case that was diagnosed as having bilobar CRLM by intraoperative ultrasound (IOUS) was excluded as well.

Preoperative workup consisted of a baseline history and physical examination, serum laboratory tests reflecting liver function, triphasic CT or MRI abdomen, and pelvic and hepatic ultrasonography. CT volumetry was requested if major resection was suspected. Additional distant metastases were excluded by renewed staging before liver surgery: bone scan, CT chest, and sometimes positron emission tomography.

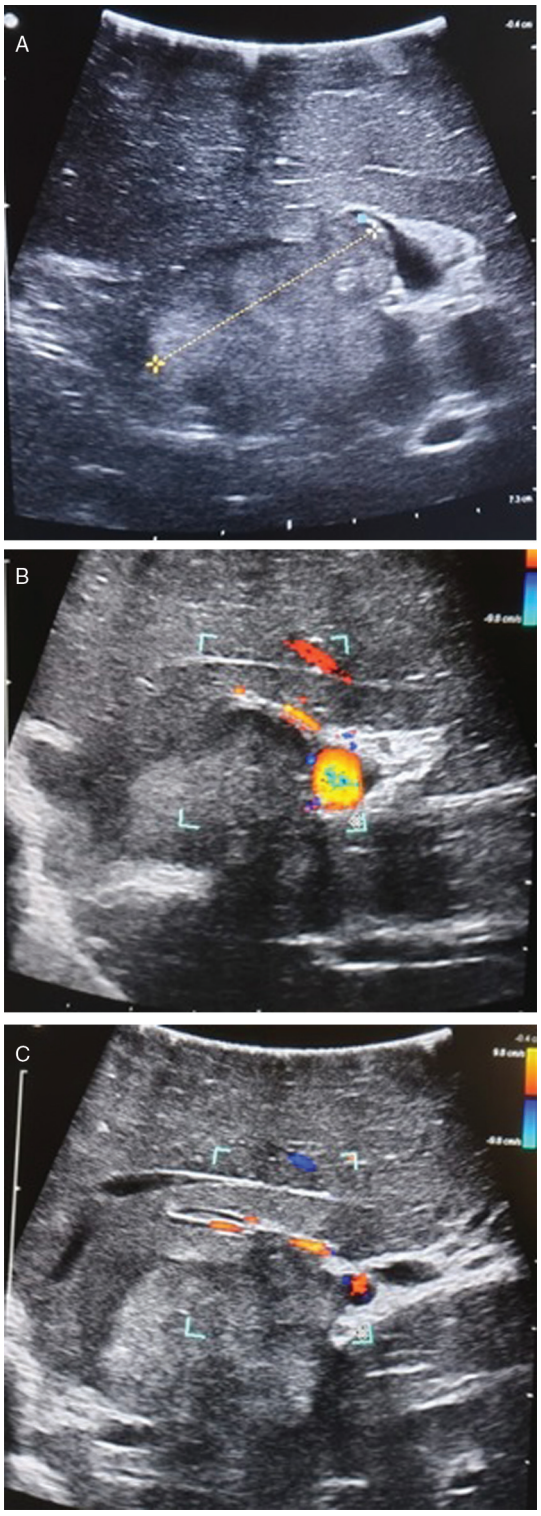
Clinical and pathologic parameters evaluated included age at diagnosis of CRLM, primary colonic surgery, chemotherapy of the primary, interval from diagnosis of the primary tumor to the discovery of metastases, number, size, location and histology of the metastases, and type and extent of resection.

The study was approved by the Ethics Committee of Ain Shams University Hospitals. Signed, written, informed consent was obtained from each patient.

All patients underwent partial liver resection by liver surgeon and IRFA by interventional radiologist during laparotomy. IOUS was performed before the resection and IRFA to document and target the lesions (Fig. 2).

During IRFA, IOUS (BK medical flexfocus 800 machine, BK Medical, Mileparken, Denmark; with an intraoperative T-shaped probe 8816 with frequency range 10–4.3 MHz) was used to guide placement of the RF needle (cool-tip single needles) into the center of the lesion and to monitor the ablation. Overlapping ablation

Fig. 1



(a) A large 4 cm irregular lesion at the bifurcation of the right main portal vein. Radiofrequency cannot be done owing to proximity to large vessel (heat sink) and possibility of major bile duct injury; (b and c) portal vein Doppler image for the same lesion.

areas were considered in tumor sizes exceeding 4.0 cm. A safety margin of 0.5–1.0 cm was aimed for IRFA.

The same IRFA systems were used in the two medical centers (Radionics Medical Systems, Valleylab, Boulder, Colorado, USA). Specific IRFA protocols, designed by the manufacturer, were used according to the manufacturer's recommendations.

Fig. 2

A colorectal liver metastases 1.6 cm for intraoperative radiofrequency ablation.

Routinely, ultrasonic dissection technique was used to perform liver resection using standard techniques for either anatomic or nonanatomic resection aiming at 1 cm safety margin. Cavitron ultrasonic surgical aspirator (Excel^{+} system, Integra Life Sciences Corporation, Tullamore, Ireland) was available whenever needed (Fig. 3). Selective vascular clamping or Pringle maneuver was used to control intraoperative blood loss according to the intraoperative findings. Depending on the duration of induction chemotherapy, all patients underwent laparotomy 4–6 weeks from the last dose.

Type of the surgical procedures, postoperative complications, ICU and hospital stay, and time to resume chemotherapy were recorded. Postoperative chemotherapy was used at the discretion of a multidisciplinary tumor board.

These patients were followed in clinic 2 weeks postoperatively to record early postoperative complications, besides basic clinical examination, blood samples, chest radiography, and abdominal US (screening method of choice) were done as supplementary in case of suspicious ultrasound findings by CT or MRI study. In subsequent follow-up visits, the full set of clinical and pathological

Fig. 3

Right posterior hepatectomy with preservation of portal vein branches; cavitron ultrasonic surgical aspirator was used in this case.

evaluations as described above was repeated 3 months after IRFA and then every 3 months during the first year. Histopathological confirmation of tumor recurrence was not mandatory.

Definitions

Complications were classified according to Clavien-Dindo classification of surgical complications [17]. All complications following a procedure were registered. When complications were clearly caused exclusively by the ablation procedure, they were considered IRFA related. All deaths within 30 days of surgery were considered perioperative mortality.

Curative resection was defined as removal of all macroscopically detectable disease and microscopically clear resection margin of the excised liver. Hepatectomies were classified into major and minor resections, as defined by resection of up to three segments for minor and corresponding more than three segments for major hepatectomies [18].

Curative management of colorectal primary is considered if no vital tumor was evident at the site of previous tumor by CT. In our study, we defined liver recurrence as newly developed metastases in residual liver volume. Local liver progression was defined as progression of residual unablated tumor or recurrence of tumor in the RFA lesion. CHR was defined as the absence of new hepatic lesions or contrast enhancement at the ablation and resection sites on CT after 3 and 6 months [19].

Liver failure was defined as a progressive increase of serum bilirubin and the prothrombin time within 30 days of surgery [20].

Statistical analysis

Data were analyzed using Student's *t*-test. All the data was presented as mean±SD. Statistical analyses were performed with SPSS version 17 for Windows computer software (IBM Corporation, Armonk, New York, USA). A value of P 0.05 was considered statistical significance.

Results

From 2016 to 2018, 32 patients with CRLM was subjected to therapy, 15 patients underwent liver resection, and 17 patients had been combined with IRFA. Two patients in group A needed colonic resection in combination with liver resection to control the primary owing to the synchronous nature at time of presentation, in contrast to a single case in group B.

Age and sex of the patients were comparable in both groups (Table 1). Patients experiencing left lobe metastases were eight in each group, and right lobe metastases were seven and nine, respectively. All patients presented with unilobar but multifocal tumor disease.

However, the interval between diagnosis of primary and diagnosis of liver metastases was not significant between the two groups. Six out of fifteen patients in group A had a tumor burden more than 3 cm compared with five out of seventeen in group B (Table 1), reflecting a higher tumor burden in group A, necessitating more aggressive anatomical surgical resection. All patients had received chemotherapy before the surgical procedure.

Major resection was done in eight patients in group A (Table 2). Extended resection was not performed in this series. Other resections included left lateral bisegmentectomies (n=2) and lateral hepatectomy (n=5), both in group A, or non-anatomical resections (n=17), all in group B (Fig. 4).

IRFA was performed to ablate one (n=10) or two (n=7) nodules, all in group B. Ablated tumor

diameter ranges from 1 to 4.5 cm. Five RFA tumors had a diameter of 3 cm or larger (Table 3).

Patients were discharged after an average hospital stay (Table 4) of 7 days in group A and 5 days in group B.

Table 1 Demographic and characteristics of colorectal liver metastases

Characteristics	Group A (*N*=15)	Group B (*N*=17)	*P* value
Sex			
Male	8	10	NS
Female	7	7	NS
Age (years)			
Mean±SD	54.7±1.8	52.5±2.6	NS
Range	41–61	36–63	
Primary colorectal tumor			
Right colon	4	5	NS
Transverse colon	3	2	NS
Left colon	5	5	NS
Rectum	3	5	NS
Time of presentation in relation to primary			
Synchronous	2	1	S
Metachronous	13	16	NS
Interval between primary and diagnosis of liver metastases (months)			
Mean±SD	13±2.2	10±3.3	NS
Range	0–27	0–24	
All over tumor size (cm)			
≤3	6	5	NS
>3	9	12	S
Number of lesions			
2	2	3	NS
3	6	5	NS
4	7	9	NS
Lesion site, nodule (*n*)			
Left lobe	8	8	NS
Right lobe	7	9	NS

S, significant.

Patients in group A were all admitted to the ICU postoperatively, with a mean stay of 2 days. On the contrary, only six (35%) patients in group B (*n*=6) needed ICU and for a shorter duration.

According to the classification of Clavien, a major part of the complications (Table 5) were classified as grade I (three in each group; 20% in group A vs 17.6% in group B) and an equal number with grade II complications [one patient in group B (6%) with urinary tract infection, and three and two patients (20 vs 11.7%) in groups A and B, respectively, were diagnosed with biliary leakage, which was managed conservatively]. In contrast, two patients in group A (13%) underwent ultrasound-guided aspiration and pigtail insertion for treatment of biliary leakage, recorded as grade III complication, with uneventful further clinical course.

One grade IV complications occurred in group A, which needed ICU readmission for 8 days for liver failure. No grade V complications, that is, death of the patient, occurred.

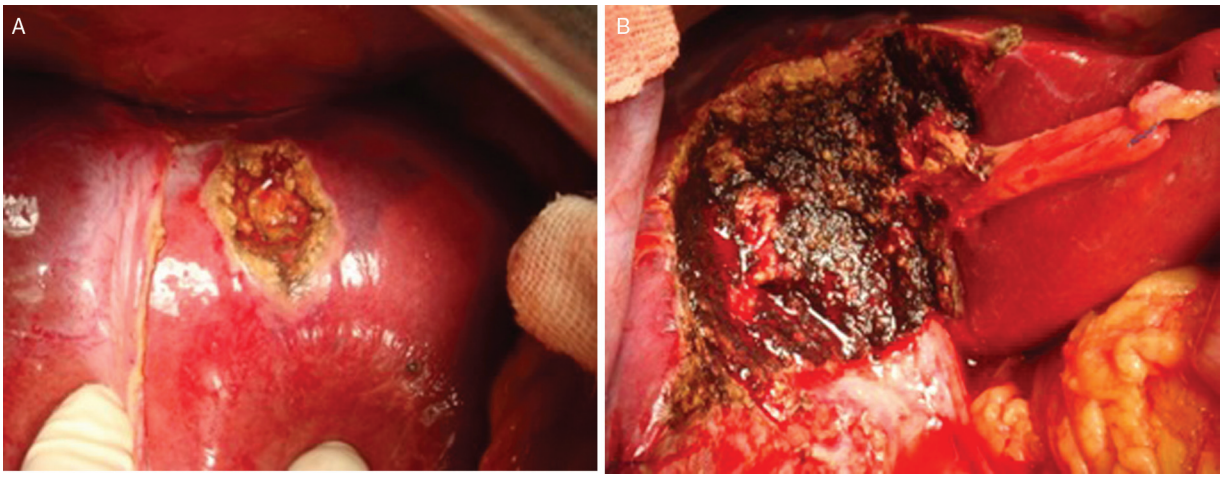
Outcome and CHR are shown in Table 6. Tumor recurrence was observed in six patients. True liver progress (recurrence at the same site of ablation) in

Table 2 Type of operative procedure adopted

Type of operation	Group A (*N*=15) [*n* (%)]	Group B (*N*=17)
Right hepatectomy	8 (53)	0
Left hepatectomy	5 (33)	0
Left lateral hepatectomy	2 (14)	0
Combined resection and IRFA	0	17

IRFA, intraoperative radiofrequency ablation.

Fig. 4



(a) Nonanatomical resection for a nodule in left lobe; (b) partial liver resection for a nodule in segment 4.

Table 3 Criteria of intraoperative radiofrequency ablation in group B

	Group B (*N*=17)
Size of nodule (cm)	
Mean±SD	2.2±0.8
Range	1–4.5
Nodule >3 cm	5 (30)
Number of nodule	
1	10
2	7

Table 4 Recovery

Recovery	Group A (*N*=15)	Group B (*N*=17)	*P* value
ICU stay (days)			
Number of patients	15 (100)	6 (35)	S
Mean±SD	2±0.5	1±0	
Hospital stay (days)			
Mean ±SD	7±2	5±2	S
Range	5–20	3–17	
Time to return to chemotherapy (months)			
Mean±SD	1±0.5	0.7±0.2	NS
Range	1–2	0.5–1.4	

S, significant.

Table 5 Surgical morbidity and mortality

Type of complication	Group A (*N*=15) [*n* (%)]	Group B (*N*=17) [*n* (%)]
Pleural effusion (grade I)	1 (6.6)	0
Wound infection (grade I)	2 (13)	3 (17.6)
UTI (grade II)	0	1 ()
Bile leak (conservative) (grade II)	3 (20)	2 (11.7)
Bile leak (pigtail) (grade III)	2 (13)	0
Liver failure (grade IV)	1 (6.6)	0
Mortality (grade V)	0	0
Total	9 (60)	6 (35)

UTI, urinary tract infection.

Table 6 Follow-up period and recurrence

	Group A (*N*=15)	Group B (*N*=17)	*P* value
Follow-up period (months)			
Mean±SD	12±3.8	13±2.7	NS
Range	6–20	7–22	
Recurrence (*n*)			
Colonic	2	1	S
Liver	2	3	NS
Progression (*n*)			
Liver	0	1	S
CHR (months) [*n* (%)]			
3	14 (93.3)	15 (88.2)	S
6	11 (73.3)	13 (70.5)	NS

CHR, complete hepatic response; S, significant.

IRFA group was seen in one (6%) patient diagnosed by CT criteria after 2 months of the procedure. Liver recurrence with new tumor nodules in other parts of the liver was present in five patients [two in group A (13%) and three in group B (17.5%)].

During the first 3-month follow-up, CHR was observed in 14 patients in group A and 15 patients in group B, giving a CHR rate of 93 and 88%, respectively. After 6-month follow-up, all patients were alive; eleven patients in group A (73%) and thirteen in group B (70%) were without liver tumor burden, but three had local colonic tumor recurrence (two in group A and one patient in group B) (Table 6), and all were treated with chemotherapy.

Discussion

Liver resection for colorectal metastases seems to provide a 5-year survival of 25–40%. The most important factor is to achieve a tumor-free status after resection [13].

RFA of liver tumors is a well-established treatment option for irresectable liver tumors, with technical consideration regarding size and location (proximity from major bile duct and bowel). The RFA may be done through different approaches: percutaneous, laparoscopic, or via laparotomy. The selection of the approach is based on tumor site, number of nodules, and general health condition [21,22].

Several series have been published on combined resection and IRFA via laparotomy that offers many advantages compared with the percutaneous and laparoscopic approach. IRFA gives the privilege of more accuracy and safe needle placement than other approaches (percutaneous or laparoscopic), which may improve tumor control [13].

In selected cases, irresectability can be converted into an operable condition using IRFA additionally to hepatic resection. Our study is a trial for the extension of the feasibility of surgical treatment of liver tumors using the combination of liver resection and IRFA.

The study presented here demonstrates significant reduction in ICU and hospital stay as well as faster recovery period till return to chemotherapy between the two groups.

In our current series, we observed a morbidity rate of 53% in group A and 35% in group B, among which

major complication rate was 6.6 and 0%, respectively, as there was a single case of postoperative deterioration of liver function and no mortality recorded in both groups. The most frequent complication was biliary leakages inherent in hepatic resection. Most of them were managed conservatively. The study revealed that morbidity and mortality rates of combined partial liver resection and IRFA were better than those of anatomical liver resection alone.

In the prospective trial observing IRFA done by Evrard, who used the Clavien–Dindo system, the overall complication rates were 44.8%, and when considering grade III or higher, it was 12.2% [19].

Complications after IRFA in a study done by Desolneux was 39.5%, and the complication rate for grade III or higher as classified according to the Clavien system was 18.4%. However, when IRFA is combined with resection, grade III complication rates increased to reach 12.1–31.0%, and mortality increased to 0–5.2%. These results must be compared with the morbidity and mortality rates of liver resection alone, which are estimated at 20–50 and 0–5%, respectively [23].

On examining series with a similar protocol in comparison with group A results, Pawlik *et al.* [11] reported in 172 patients better figures regarding postoperative complication rate of 19.8% (among which 54% were major hepatectomies), but with 2.3% mortality rate, whereas similar results as ours were published by Mulier *et al.* [24], reporting a morbidity rate of 31.8%, but with a mortality rate of 4.5%. Elias *et al.* [12] did not observe any hospital deaths in 63 patients and found a morbidity rate of 27%.

These findings resemble complication rate reported in the literature [12,25] on the feasibility of this treatment approach with limited complications, but not as in a series of partial liver resection presented from the University Medical Centre Utrecht, where mortality and morbidity rates recorded were 5.8% and 23%, respectively [2].

According to Xiao *et al*. [26], IRFA may not seal biliary radical efficiently, and postoperative sloughing of necrotic bile duct stumps may be responsible for bile leakage and biloma. Notably, thermal injury of nearby structures, major biliary duct injury, and intrahepatic abscess formation did not occur in the second group.

Most research groups describe complication rates of RFA to be 0–16% and mortality rates of 0–1.8% [27]. According to Jansen *et al*. [9], 87 patients who were treated by IRFA showed morbidity and mortality rates of 9.8 and 0%, respectively. This finding can be explained by the authors because of the more precise placement of the RFA electrode, and they indicating that IRFA can be performed safely and without adding intolerable risk to the patient.

Three months were chosen as a minimal reference point, which is approximately equivalent to between four and six cycles of chemotherapy. As the local liver recurrence is considered to be the main goal of surgical oncology, the present study provided prospective data for patients undergoing IRFA with resection for low residual nonresectable CRLM. With a CHR rate at 3 months of 93 and 88% in groups A and B, respectively, and CHR at 6 months of 73 and 70% in groups A and B, respectively, it is confirmed that extensive liver resection can achieve prolonged survival but CHR in group B and is still not considered inferior in comparison with chemotherapy alone, which has a higher event-free survival rate .

Local liver recurrence rate after ablation of unresectable lesions should not be compared with that for anatomically resectable CRLM, as the larger the liver remnant the larger area for metastatic deposit. Moreover, on comparing the local liver recurrence rate, it was 13% in group A vs 17% in group B. These may be owing to stimulation of micrometastatic growth through the hepatic regeneration process that follows IRFA and resection and owing to the larger residual liver volume. Elias *et al*. [28] reported a local recurrence rate of 5.7% after IRFA, 7.1% for wedge resections, and 12.5% for segmental anatomical resections.

Tumor size exceeding 3 cm is known to be a significant risk factor for increased local progress rates. For metastases larger than 3 cm, the local progress rate can be as high as 21.7%, but for lesions smaller than 3 cm, it is considerably lower and varies between 1.6 and 3.8% [2]. In this study, it was 12% regardless of the size and 20% if larger than 3 cm.

It is preferable to use IRFA with small nodules as tumor diameter is considered the main risk factor for local recurrence after IRFA when combined with resection. A cutoff point of 3-cm diameter has been proposed [19]. The higher local liver recurrence rate in group B is partly explained by the presence of large nodules ($\geq$3 cm, n=5), which represents approximately one-third of all RFA nodules treated with IRFA.

We should take into consideration that long-term outcome was not measured in the current study

owing to limitation in keeping a complete registry of the patient follow-up for a long period. However, according to the literature, in a series of Elias and colleagues, the strategy of combined partial liver resection and IRFA with perioperative chemotherapy appeared favorable by doubling the median survival (from 18 to 36 months), when compared with chemotherapy alone in similar patients with unresectable colorectal tumor [19].

Conclusion

Combined IRFA and partial liver resection appears to augment the number of patients with CRLM who can be treated surgically, as IRFA can be performed accurately and safely with efficient results, reducing the loss of a large part of functional liver parenchyma and oncological outcome to that of classic surgical resection, which cannot be performed in patients with low residual liver volume.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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