Chirurgia (2014) 109: 500-506
No. 4, July - August
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Radiofrequency Ablation Device Assisted Liver Resection for Hepatocellular Carcinoma

N. Vlad[1], C. Gouillat[2], R. Moldovanu[1,3], C. Lupaşcu[1], Ş. Georgescu[1], E. Târcoveanu[1]

[1]First Surgical Unit, Department of Surgery, "Gr.T. Popa" University of Medicine and Pharmacy Iaşi, Romania
[2]Digestive and General Surgery and Liver Transplant Unit, Croix-Rousse Hospital, Lyon, France
[3]Department of Surgery and Oncology, Les Bonnettes Hospital, Arras, France

Rezumat

Rezecția hepatică pentru carcinomul hepatocelular folosind dispozitive de ablație cu radiofrecvență

Lucrarea îşi propune să evalueze rezecțiile hepatice pentru carcinomul hepatocelular (CHC) efectuate cu ajutorul dispozitivelor de radiofrecvență.
Pacienți şi Metodă: Au fost analizați 35 de pacienți la care s-a practicat rezecție hepatică pentru CHC. Ca dispozitiv de radiofrecvență s-a folosit Habib®4X. Pacienții au fost grupați în două loturi: lotul A (45,7%; n=16), pacienți la care rezecția hepatică a fost efectuată cu ajutorul radiofrecvenței şi respectiv, lotul B (54.3%; n=19), în care rezecția hepatică s-a realizat classic, fără radiofrecvență.
Rezultate: Pacienții au avut o vârstă medie de 62.6±11.6, iar raportul bărbați/femei a fost de 25 / 10. Volumul tumoral mediu a fost de 161.8±35.5mL; nu s-au constatat diferențe din punct de vedere al volumului tumoral între cele două loturi de pacienți. Timpul operator şi pierderea intraoperatorie de sânge au fost mai mici în lotul A, dar diferența nu a fost semnificativă statistic [132,5±61,5 vs 167,9±46,3 min, (P=0,061) şi respectiv 459±342 vs 716±648 mL (P=0,135)]. De asemenea, nu au fost constatate diferențe semnificative statistic nici între accidentele intraoperatorii (P=0,508) şi nici din punct de vedere al morbidității generale (P=0,782); cu toate acestea a fost notată o incidență mai crescută a complicațiilor postoperatorii tardive în lotul A (56,3% vs. 16.7%, P=0.016). Mortalitatea postoperatorie global a fost de 2,8% iar recidiva locală de 32,4%. Supraviețuirea la 3 ani a fost de 60%.
Concluzii: Folosirea dispozitivelor de radiofrecvență în efectuarea rezecțiilor hepatice este asociată cu o morbiditate şi mortalitate redusă; de asemenea, dispozitivele de radiofrecvență tind să scadă durata operatorie şi pierderea de sânge intraoperatorie.

Cuvinte cheie: rezecții hepatice "bloodless", carcinom hepatocelular, radiofrecvență

Abstract

The present study aim was to evaluate radiofrequency (RF)-assisted liver resection for hepatocellular carcinoma (HCC).
Patients and Methods: 35 consecutive patients were enrolled in this study. A Habib®4X RF ablation device (RFAD) was used for liver resection. The patients were divided into two groups: in group A (45.7%; n=16) liver resection was performed using the RFD, whereas in group B (54.3%; n=19), liver resection was performed without RFD. The data were analysed for statistical significance.
Results: The study population had a male/female ratio of 25/10 and a mean age of 62.6±11.6 years old. The mean overall tumor volume was 161.8±35.5 mL and there were no differences in tumor volume between groups. The operative time and intraoperative blood loss were lower in group A, but without statistical significance [132.5±61.5 vs 167.9±46.3 mins, (P=0.061) and 459±342 vs 716±648 mL (P=0.135)]. No differences were reported between the two groups in operative accidents (P=0.508) and postoperative morbidity (P=0.782); a higher rate of late postoperative complications was found in group A (56.3% vs. 16.7%,

Corresponding author: Radu Moldovanu MD, PhD
Department of Surgery and Oncology,
Les Bonnettes Hospital,
2 Rue Dr. Alfred Forgeois, 62012, Arras
France
E-mail: rmoldovanu@gmail.com

P=0.016). The overall postoperative mortality rate was 2.8%. Local recurrence was noted in 32.4%. The three-year cumulative survival rate was 60%.
Conclusions: RFAD allows liver resection with low postoperative mortality and morbidity rates; RFD tends to decrease the operative time and blood loss.
Abbreviations: AFP - alpha fetoprotein, ALT - alanine amino transferase, ASA - American Society of Anesthesiologists, AST - aspartate amino transferase, CT - computed tomography, HCC - Hepatocellular carcinoma, MELD - Model for End-Stage Liver Disease, RF – Radiofrequency, RFAD - Radio-frequency ablation device

Key words: bloodless hepatectomy, hepatocellular carcinoma, liver resection, radiofrequency ablation

Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequent type of cancer and the third leading cause of cancer death worldwide, with about 500,000 deaths annually (1-3). Although it is most common in Asia and Africa, the incidence of HCC has increased over the last several decades in Western Countries (1). In Romania, the actual incidence of HCC is 4–10 new cases per 100,000 inhabitants per year (4).

Surgical resection is considered the gold standard curative treatment for HCC (5-8); there is a tendency to increase the indications for liver resection in more advanced stages of the disease (5-8). In selected cases, liver transplantation is also a therapeutic option for HCC (9-11). However, liver resection remains a major surgical procedure with a high risk of intra-operative blood loss and perioperative transfusions, which directly influence postoperative morbidity and mortality (12). To increase the safety of liver resection, different bloodless techniques have been developed over the last several decades (13-17). Radiofrequency (RF)-assisted liver resection has been shown to result in a virtually bloodless procedure without the need for vascular exclusion maneuvers (18-20).

The present study was performed to evaluate the use of a radiofrequency ablation device (RFAD) in performing liver resection for HCC. The primary outcomes were intraoperative blood loss and surgical time. In addition, postoperative morbidity and mortality rates and survival time were analysed.

Patients and Methods

Patient population

Thirty-five consecutive patients who underwent liver resection for HCC were then enrolled in the study. The patients were divided into two groups; in group A, liver resection was performed using the radiofrequency ablation device (RFAD) (45.7%; n = 16), whereas in group B, liver resection was performed without the RFAD (54.3%; n = 19).

Surgical procedure

All surgical procedures were performed by highly skilled surgical teams. A Habib®4X bipolar handheld RFAD and RITA 1500 radiofrequency generator were used (18). RFAD-assisted liver resection was performed according to the technique described by Weber JC et al. (17) (*Fig. 1, A,B*). We did not perform any vascular exclusion maneuvers in group A patients. In group B the liver resections were performed by parenchymal transsection approach using harmonic scalpel; Pringle's maneuver was routinely used in all group B patients. In two patients from group B, liver resection was performed using laparoscopic approach (tumors smaller than 5 cm located in segments III and V). Different liver resection procedures were performed, from atypical resection and segmentectomy to right hepatectomy. To simplify the analysis, we coded the surgical

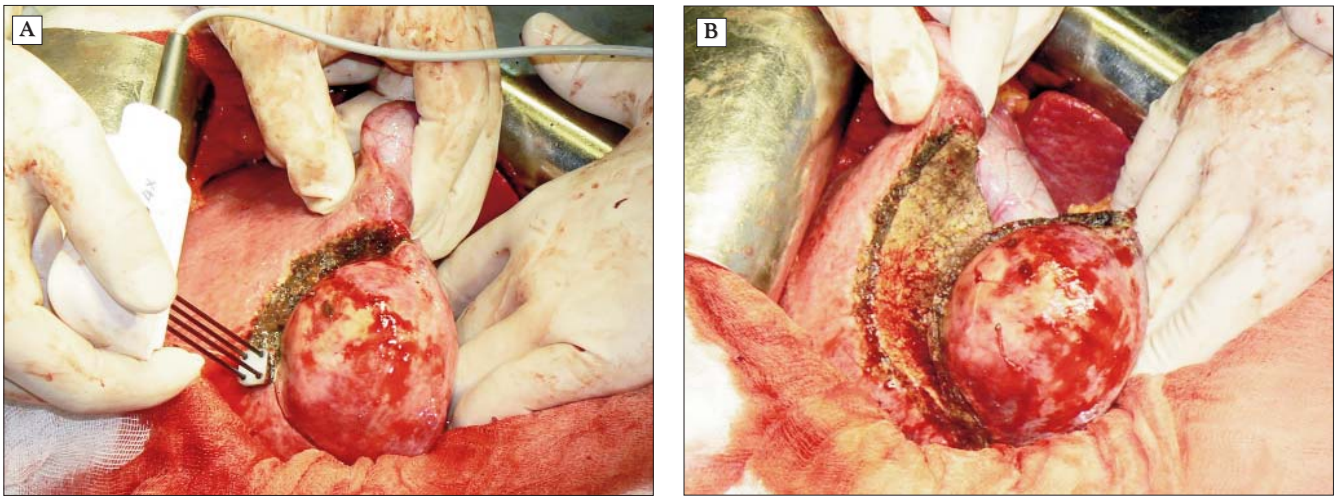


Figure 1. ***(A)*** *Atypical liver resection for hepatocellular carcinoma (HCC) in a cirrhotic patient using the HabibTM 4X device.* ***(B)*** *Liver transection after use of the radiofrequency device (RFD).*

procedures into minor liver resection (atypical resection, segmentectomy, bisegmentectomy) and major resection (trisegmentectomy, left or right hepatectomy).

Data analysis

Different demographic, clinical, imaging, biological, and intraoperative data were analysed. Complete lab tests (e.g., aspartate amino transferase (AST), alanine amino transferase (ALT), albumin, bilirubin, prothrombin time ratio, and alpha fetoprotein (AFP)) were performed preoperatively; the same tests were also performed postoperatively. The patients were assessed using the Child classification, ASA (American Society of Anesthesiologists) scores, and MELD (Model for End-Stage Liver Disease) scores. The tumor volume was estimated by computed tomography (CT) volumetric computing. Operation time as well as blood loss were included, recorded, and analysed. Blood transfusion was performed when hemoglobin decreased to below 8 g/dL. The resected specimens were analysed histopathologically to confirm the R0 status. Postoperative morbidity was reported as immediate (during the first 30 days) and late (during the first year). The median postoperative follow-up was 17 months (range: 7–70 months). Recurrence, metastasis, and mortality rates were also recorded. Deaths that occurred during the first 30 postoperative days were referred to as postoperative mortality.

Statistical analysis

All of the data were encoded, included in a database (MS Access), and analysed statistically using SPSS ver. 15.0 for Windows. Data are presented as number and percentages. Descriptive and bivariate statistics (t test and Pearson χ^2) were used. The average values were noted as means ± standard deviations (SD). The survival time was computed using the Kaplan–Meier function. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

The study population had a male to female ratio of 2.5 (25/10) and mean age of 62.6 ± 11.6 years old (range: 26–88; median: 61). There were no significant differences in demographic data between the two groups (*Table 1*).

Comorbidities were noted in 91.4% (n = 32) of patients, with no difference between the two groups (*Table 1*). Cirrhosis was noted in 40% (n = 14) of the patients, most of whom (62.5%) were in group A (P = 0.013). Most of the patients (64.3%; n = 9) were Child A, while the remaining 44.7% (n = 5) were Child B. Ascites was detected in 20% (n = 7), and there was no significant difference between the two groups. Esophageal varices were found in 11.4% (n = 4) of patients, all of whom belonged to group A (P = 0.021). Most of the patients (91.4%; n = 32) had "symptomatic" HCC, and the tumor was incidentally diagnosed during a routine ultrasound exam in only three cases (8.6%).

The biological data are shown in *Table 2*. The preoperative prothrombin time was significantly lower in group A (82.1% (range: 50-113) vs 94.4% (range: 72-120); P=0.025. All the other variables were not significantly different between the two groups. AFP, which is considered to be relatively specific for HCC, was found pathological (over 10 ng/mL) in only 54.3% of cases (n = 19), with a similar distribution in the two groups (P = 0.787).

The estimated operative risk was higher in group A than in group B; the MELD score was 10.37 ± 376 (range: 6–19) in group A vs. 7.84 ± 1.8 (range: 6–12) in group B (P = 0.014) and the ASA score was 2.81 ± 0.72 (range: 2–4) in group A vs. 2.16 ± 0.69 (range 1–3) in group B (P = 0.027).

A single tumor was detected in 77.1% of cases and multiple (multicentric) tumors were observed in the other 22.9% (n = 8). Specifically, there were two tumors in 14.3% (n = 5), three tumors in 5.7% (n = 2), and four tumors in 2.9% (n = 1). Group A showed a higher incidence rate of multiple tumors, but the difference was not statistically

Table 1. *Demographic and clinical data*

	Group A (n = 16)	Group B (n = 19)	P
Mean age (years)	63.4 ± 9.5 (range: 47–78)	61.8 ± 13.4 (range: 26–88)	0.692
Sex (male/female)	12 (75%)/4 (25%)	13 (68.4%)/6 (31.6%)	0.668
Comorbidities	15 (93.8%)	17 (89.5%)	0.517
Cirrhosis	10 (62.5%)	4 (21.1%)	0.013
Child A	7 (70%)	2 (50%)	0.265
Child B	3 (30%)	2 (50%)	0.458
Ascites / Micro ascites	3 (18.8%)	4 (21%)	0.865
Esophageal varices	4 (25%)	0	0.021
Diabetes	6 (37.5%)	9 (47.4%)	0.557
Obesity	6 (37.5%)	9 (47.4%)	0.557
Hypertension	8 (50%)	13 (68.4%)	0.268
Symptomatic HCC*	16 (100%)	16 (84.2%)	0.096

* HCC – hepatocellular carcinoma

Table 2. *Preoperative and postoperative biological data*

	Group A (n = 16)	Group B (n = 19)	P
AST (IU/L) preoperative	49.31 ± 17.21 (28–83)	47.73 ± 29.52 (16–127)	0.852
AST (IU/L) postoperative	164.31 ± 129.32 (30–468)	143.4 ± 94.82 (34–378)	0.578
ALT (IU/L) preoperative	49.37 ± 23.53 (22–107)	54.05 ± 44.12 (19–197)	0.706
ALT (IU/l) postoperative	235.68 ± 170.51 (68–659)	189.68 ± 127.43 (34–506)	0.368
Albumin (mg/dL) preoperative	39.3 ± 4.37 (33.1-47.3)	39.7 ± 4.46 (29-47.1)	0.795
TB (μmol/L) preoperative	13.43 ± 6.78 (4–27)	12.16 ± 6.63 (3–30)	0.577
TB (μmol/L) postoperative	19.44 ± 14.69 (7–68)	25.68 ± 28.65 (5–105)	0.436
PTr (%) preoperative	82.12 ± 17.23 (50–113)	94.36 ± 13.61 (72–120)	0.025
PTr (%) postoperative	57.06 ± 15.32 (30–78)	65.78 ± 16.64 (36–86)	0.119
AFP > 10 (ng/mL) n (%)	11 (68.8%)	8 (42.1%)	0.787

AST - aspartate amino transferase; ALT - alanine amino transferase; TB – total bilirubin; PTr - prothrombin time ratio; AFP - alpha fetoprotein

significant (31.3% vs. 15.8%; P = 0.278). The overall mean tumor volume was 162.79 ± 35.5 mL (range: 0.6–1178 mL; median: 65). There were no significant differences between the two groups with regard to the overall tumor volume or number of lesions (P = 0.938 and P = 0.530, respectively). Tumors located in segment IV were more frequent in group B (36.9% vs. 6.3%; P = 0.032).

There were no differences between the groups for the type of liver resection (P = 0.968). The mean blood loss volume was lower in group A (459.37 ± 341.6 mL; range: 150 – 1500; median: 350 vs. 716.32 ± 648.16 mL; range: 250–3000; median: 500), but the difference was not statistically significant (P = 0.135). Similarly, the transfusion rate was similar in both groups (37.5% in group A vs. 36.8% in group B; P = 0.968). However, the operative time was slightly lower in group A (132.5 ± 61.5 min; range: 60–270; median: 120) than in group B (167.9 ± 46.3 min; range: 70–240; median: 170; P = 0.061). Pathological examination confirmed the R0 status of the resected margins in 33 cases (94.3%); in two cases, both of them for group B, pathological exam revealed a R1 resection. In other 2 cases, also from group B, even the resection was R0, the resection margins being less than 1 cm. Although both groups showed similar rates of intraoperative accidents and postoperative morbidity, the incidence of late postoperative morbidity (e.g., liver chronic failure, ascites, and postoperative incision hernias) was higher in group A (P = 0.016). There was one postoperative death in group B (overall postoperative death rate: 2.8%).

The local recurrence rate was 32.4% (n = 11), with development after a mean of 16.7 ± 2.6 months (range: 5–33; median: 13 months). Distant metastases in the lungs and bones were detected in three patients (8.6%) at one and three years after the operation, respectively.

The three-year survival rate was 60% (*Fig. 2 A*). The results were similar in both groups after one year (81.3% in group A and 84.2% in group B); however the three-year survival rate was lower in group A (43.7% vs. 73.7%). In terms of percentiles, 75% of the patients survived for 30 months, with a mean survival period of 62.9 ± 5.6 months, with no difference between the two groups (log rank, P = 0.343) (*Fig. 2 B*). There was a difference in follow-up time between the two groups, as shown in *Fig. 2 B*.

Discussion

Surgical liver resection is the main curative therapeutic procedure for HCC, with liver transplant and focal destruction using radiofrequency ablation also performed in selected cases (20-23). Rigorous preoperative planning, including the assessment of planned postoperative liver volume and function, as well as tumor staging, is mandatory to avoid postoperative complications and death (24-26). Thus, there is a tendency to perform atypical liver resection in cirrhotic patients to allow better postoperative hepatic function. However, in cases of non-anatomical resection, it is necessary to ensure R0 resection with negative margins to more than 1 cm from the tumor (27). In addition to liver failure, intraoperative and postoperative hemorrhage and postoperative biliary leakage remain the most important issues in increasing postoperative morbidity and mortality, especially in cirrhotic patients (17,28). Therefore, the "bloodless" resection technique using heat to coagulate the liver parenchyma was developed (17,21); in this study we used a radiofrequency generator energy source (18,19).

Different authors consider surgical resection assisted by RFAD a good choice for cirrhotic patients with HCC. However, the impact of this technique with regard to the

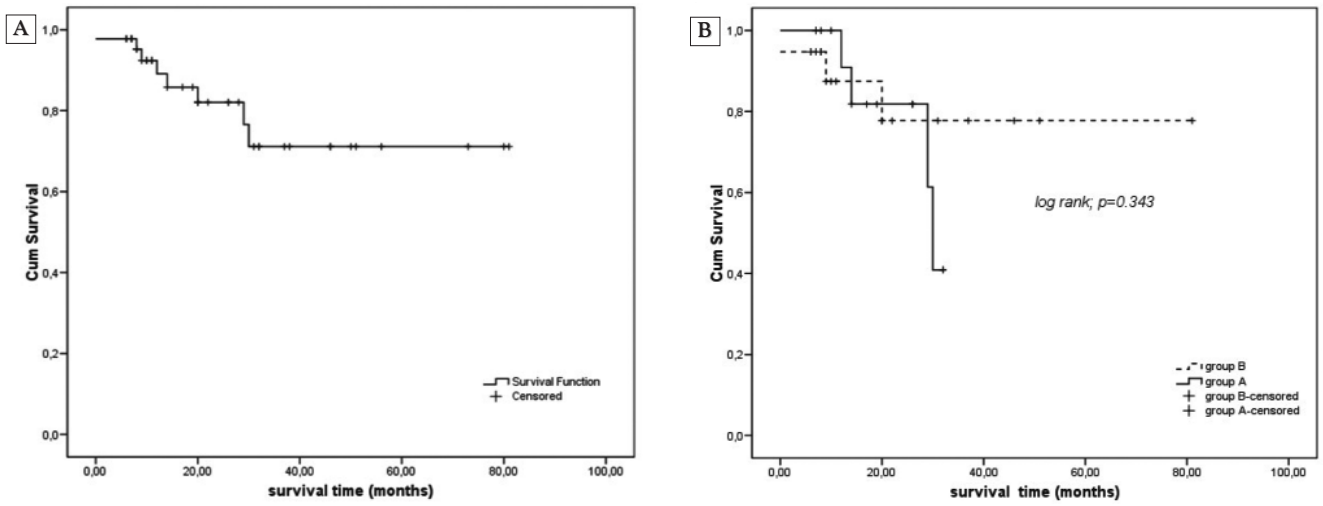


Figure 2. *(A) Overall survival time (Kaplan–Meier);* ***(B)*** *Survival time in the two groups (Kaplan–Meier; log rank test).*

remnant parenchyma has not been studied in depth (29,30). In the present study, we did not find any difference between the two groups with regard to postoperative liver function and follow-up for cirrhotic and non-cirrhotic patients. It is interesting to note that even though preoperative estimated risk assessments (i.e., MELD and ASA scores) were higher in group A, the postoperative results were similar in both groups as shown in *Tables 2* and *3*. These better outcomes may have been the result of the lower operative time and decreased intraoperative blood loss, as noted in group A, given that the two groups were homogenous in terms of liver resection type. However, there is a risk of injury to the main hilar biliary and vascular structures during the RFAD-assisted procedure (17). In our study, we avoided the use of RFAD-assisted liver resection for the central segments (especially segment IV).

The overall postoperative morbidity rates after liver resection for HCC reported in the literature are 16–36% in non-cirrhotic patients and 30–60% in cirrhotic patients, and the mortality rates range from 1% to 5% (20,28,31-37). In our group, overall morbidity was 40% and the mortality rate was 2.8%, with no significant difference between the two groups.

There were higher rates of late postoperative complications (including liver failure) in group A. This result could be explained by the higher percentage of cirrhosis patients included in this group. Thus, the MELD score, which was significantly higher in group A, is considered as an argument. Similar data regarding the link between preoperative and postoperative liver function in cirrhotic patients have been reported previously (38,39).

The overall recurrence rate was 32.4% and there was no significant difference between the two groups. However in group B we noted two R1 resection and two R0 resection but with resection margins less than 1 cm; in this way we consider the RFAD-assisted procedure more likely to comply with the gold standard guidelines for R0 liver resection: resection margins more than 1 cm from the tumor, "no touch" technique (24,40-42). We consider RFAD-assisted liver resection, as well

Table 3. *Operative and postoperative data*

	Group A (n = 16)	Group B (n = 19)	P
Multiple tumors	5 (31.3%)	3 (15.8%)	0.278
Minor liver resection	6 (37.5%)	7 (36.8%)	0.968
Major liver resection	10 (62.5%)	12 (63.2%)	0.968
Operative time (min)	132.5 ± 61.5	167.9 ± 46.3	0.061
Mean blood loss volume (mL)	459.37 ± 341.6	716.32 ± 648.16	0.135
Blood transfusion rate	6 (37.5%)	7 (36.8%)	0.968
Intraoperative accidents	5 (31.3%)	8 (42.1%)	0.508
Postoperative morbidity	6 (37.5%)	8 (42.1%)	0.782
Mean postoperative hospital stay (days)	13.6 ± 5.9	12.6 ± 6.9	0.764
Postoperative deaths	0	1 (5.3%)	0.352
Late postoperative morbidity	9 (56.3%)	3 (15.8%)	0.016
Recurrence	6 (37.5%)	5 (26.3%)	0.545
Metastasis	2 (12.5%)	1 (5.3%)	0.476

as other techniques that make use of heat to coagulate the liver parenchyma, to be a procedure that "seals" the tumor, as suggested in some previous reports (21,43,44).

The overall survival rates for liver resection with and without RFAD reported in the literature were 40% and 80%, respectively, after the first year and 40% in both groups after three years (45-47). Our results were similar. Specifically, we found over 80% survival in both groups after one year and 60% after three years; however, the survival rate was lower in group A than group B (43.7% vs. 73.7%, respectively). This difference is possibly explained by the higher percentage of cirrhotic patients in this group.

We must state that this study has several limitations i.e. small number of cases, observational study.

Conclusions

RFAD-assisted liver resection is a feasible and safe procedure for the treatment of HCC in cirrhotic and non-cirrhotic patients, and allows liver resection with low postoperative mortality and morbidity rates. Operative time and blood loss tended to be decreased as compared with conventional procedures. To avoid injury to the vascular and biliary hilar structures, we prefer to not use the RFAD-assisted technique for tumors located in the central segments, especially segment IV.

Conflict of interests

None to declare

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