ANTICANCER RESEARCH *41*: 5855-5861 (2021)
doi:10.21873/anticanres.15405

Far-advanced Colorectal Liver Metastases Successfully Managed With Modified ALPPS and Radiofrequency Ablation in Combination With Chemotherapy

YUKI ADACHI[1], KENSUKE YAMAMURA[2], SHINSEI YUMOTO[1], TAKAAKI HIGASHI[1], HIROYUKI ISHIODORI[1], SHINOBU HONDA[1], YOSHIHIRO HARA[1], KAZUKI MATSUMURA[1], ERI ODA[2], SHINICHI AKAHOSHI[2], HIDEAKI YUKI[3], HIDEAKI MIYAMOTO[4], KOICHI DOI[1] and TORU BEPPU[2]

[1]*Department of Surgery, Miyazaki Nobeoka Prefectural Hospital, Nobeoka, Japan;*
[2]*Department of Surgery, Yamaga City Medical Center, Yamaga, Japan;*
[3]*Department of Radiology, Yamaga City Medical Center, Yamaga, Japan;*
[4]*Department of Medical Oncology, Yamaga City Medical Center, Kumamoto, Japan*

Abstract. *Background: Large numbers of synchronous colorectal liver metastases are associated with poor prognosis. Case Report: A 47-year-old male patient with rectal cancer and unresectable colorectal liver metastases (over 15 cm in diameter and over 30 metastases) was treated with a multidisciplinary treatment including systemic chemotherapy with mFOLFOX6/panitumumab and surgical therapies (colostomy, modified associating liver partition and portal vein ligation for staged hepatectomy together with radiofrequency ablation). For solitary recurrent colorectal liver metastases, percutaneous radiofrequency ablation with chemoembolization and open radiofrequency ablation in combination with the same systemic chemotherapy was performed. Since the diagnosis 3 years ago, he has been leading a good quality of life, free of any tumor or treatment. Conclusion: For patients with far-advanced but liver-only colorectal liver metastases, surgical therapy, systemic chemotherapy, and interventional treatment can be important for achieving good prognosis.*

For patients with metastatic colorectal cancer, a large number of synchronous colorectal liver metastases (CRLM) is one of the most disadvantageous prognostic factor (1-3). Multidisciplinary treatment is recommended for initially unresectable CRLM and mainly consists of systemic chemotherapy and liver resection (3-7). Excellent long-term survival has been reported in patients who had initially unresectable but eventually resected CRLM; 5-year overall survival was between 33% and 55% (3-5). Radiofrequency ablation (RFA) in combination with liver resection after systemic chemotherapy has become an acceptable option for a large number of CRLM with little to no decrease in survival (8, 9). In contrast, sole use of RFA for resectable CRLM remains controversial (10, 11).

Preoperative chemotherapy could cause histological disorders of the liver, including steatosis, steatohepatitis, and sinusoidal obstruction (12-14). As a result, safely resectable liver volume is restricted. An associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was newly developed for patients with insufficient expected liver remnant even after insufficient portal embolization (PVE) or two-stage hepatectomy (TSH) (15-18). The liver-first approach has often been applied for the patients with more advanced synchronous CRLM compared with those undergoing a primary-first or simultaneous approach (19-21). Recent publication has noted that in patients with multiple bilateral CRLM, the liver-first approach is preferable compared with the other two approaches in terms of long-term survival (21).

We herein present a patient with super advanced multiple bilateral CRLM with rectal cancer who was successfully treated with surgical and nonsurgical approaches in combination with systemic chemotherapy.

Case Report

A 47-year-old male patient visited our hospital due to anal pain and had a notable medical history. Lower gastrointestinal endoscopy and fluoroscopy revealed an easy-bleeding subcircumferential type 3 lesion in the lower rectum. The

Correspondence to: Toru Beppu, MD, Ph.D., FACS, Department of Surgery, Yamaga City Medical Center, 511 Yamaga, Kumamoto 861-0593, Japan. Tel: +81 968442185, Fax: +81 968442420, e-mail: tbeppu@yamaga-mc.jp

Key Words: Liver partition, portal vein ligation, staged hepatectomy, colorectal liver metastases, multidisciplinary treatment, radiofrequency ablation, systemic chemotherapy.

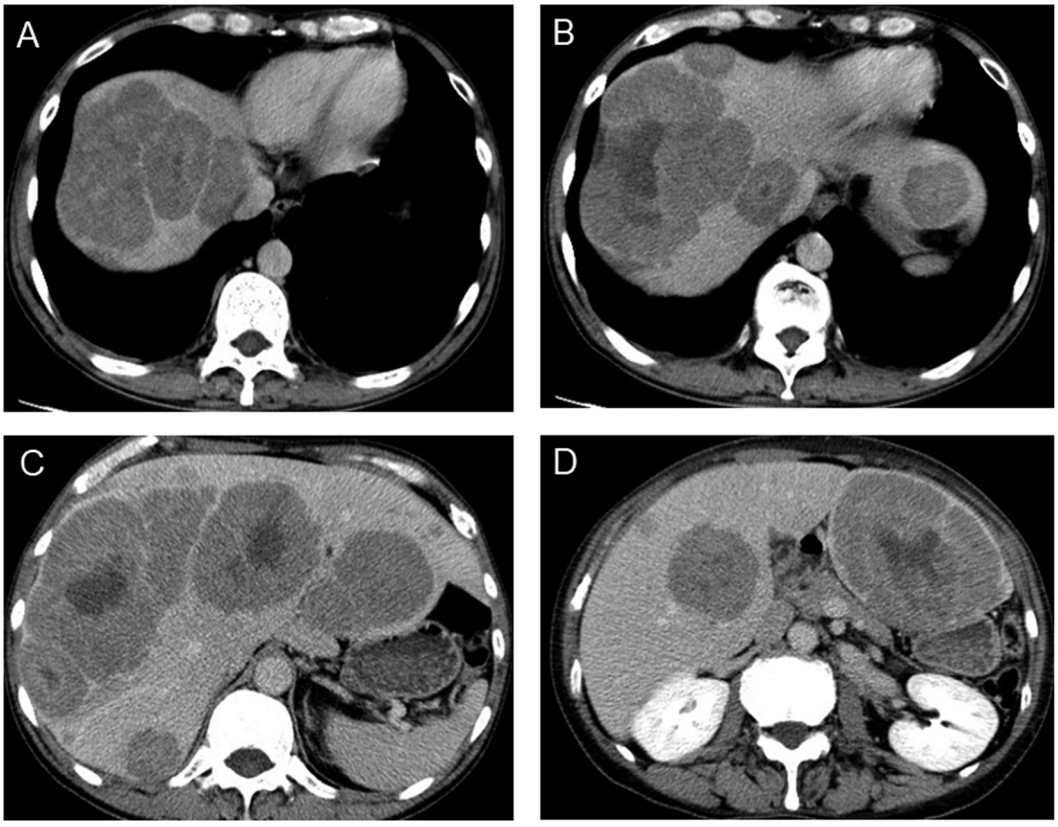

Figure 1. *Contrast-enhanced computed tomography prior to treatment. Cranial to caudal slice (A-D). Multiple bilateral liver metastases can be seen scattered in the whole liver.*

tumor biopsy revealed adenocarcinoma with wild type RAS and BRAF. Contrast-enhanced computed tomography (CT) showed some swollen regional lymph nodes and multiple liver metastatic lesions scattered in the bilateral liver (over 15 cm in diameter and over 30 metastases) (Figure 1). As for tumor markers, carcinoembryonic antigen (CEA) levels were elevated at 71.2 ng/ml (normal range ≤5 ng/ml), and serum levels of alpha-fetoprotein and carbohydrate antigen 19-9 were within normal limits. He was diagnosed with an advanced rectal cancer and liver-only unresectable liver metastases and was staged as cStage IVa [cT4N1M1a (H3 Grade A)] (22). First, a colostomy was constructed because of severe rectal stenosis. Systemic chemotherapy with mFOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) was started and panitumumab was added from the second cycle. After seven cycles of chemotherapy, the liver metastases shrank (target diameter: from 18.6 cm to 8.8 cm) and was judged as a partial response according to the Response Evaluation Criteria in Solid Tumors (Figure 2). Subsequently, the CEA levels retuned within the normal limit (1.1 ng/ml). The 15-minute indocyanine green retention rate was 15.8% (normal range ≤ 10%) and was slightly deteriorated by the previous chemotherapy. The liver resection rate of left trisectionectomy was 62.6%; therefore, hepatectomy after the left portal vein embolization (PVE) was selected. As the liver hypertrophy of the remnant liver after PVE was insufficient, two-stage hepatectomy was considered.

For the first surgery, a modified ALPPS procedure (23, 24) was performed, which consisted of 1) partial resection of two segment (S) 5 metastases and RFA for S6 and S6/7 metastases, 2) ligation of the left portal vein at the distal end of the left caudal portal vein, and 3) preceding dissection of the liver parenchyma between S4 and 5 and S5 and 8. One month later, the liver resection rate of the left liver plus S8 decreased to 46%, which led to conduction of the second surgery. An extended left hepatectomy was completed with dissection of the liver parenchyma between S7 and S8 and partial resection of ischemic area in S5 with preservation of the caudate lobe. Additionally, partial resection of the Spiegel lobe and RFA for S7 metastasis was performed. Thereafter, five cycles of mFOLFOX and panitumumab were administered, and Miles' operation for primary lesion was performed with a 6-month interval. The rectal cancer (Stage IIa, pN0) was curatively resected. Serum CEA levels returned

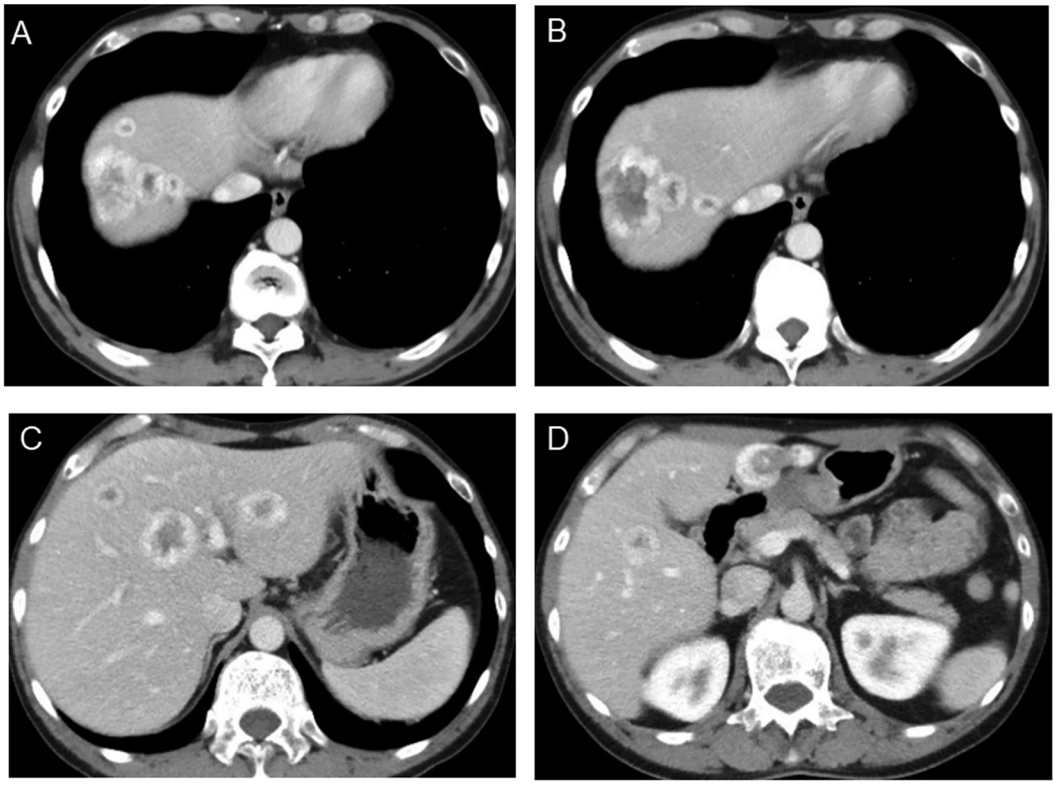

Figure 2. *Contrast-enhanced computed tomography before the first hepatectomy. Cranial to caudal slice (A-D). All metastatic tumors decreased in size with obvious calcification after induction of chemotherapy. No new obvious lesion was observed.*

to normal level but histopathological chemotherapeutic effect was classified as 3 by tumor regression grade (25).

Four months after the Miles operation, a new metastatic lesion (1.5 cm in diameter) was identified adjacent to the bifurcation of the right hepatic vein and V7 (Figure 3A, D). As the metastasis was tiny and difficult to resect, RFA was administered following chemotherapy (8). After four cycles of mFOLFOX and panitumumab, percutaneous RFA was performed under artificial pleural effusion and the tumor was diagnosed with complete necrosis by contrast-enhanced CT (Figure 3B, E). However, 4 months later, contrast-enhanced CT revealed a recurrent lesion at the previous therapeutic site, so a second percutaneous RFA was performed following transarterial chemoembolization using drug-eluting bead (DEB-TACE), which was followed by an outflow block of the S7 area that improved conservatively. There was no recurrence afterward, but a CT examination 6 months later showed a suspected recurrence at the same site. The recurrent lesion was located between the confluence of two hepatic veins, so it was quite difficult to be cured by percutaneous RFA. Thus, transdiaphragmatic RFA was performed with thoracotomy after four cycles of mFOLFOX and panitumumab. Approximately 6 months after the final surgery, contrast-enhanced CT showed complete necrosis of the target tumor (Figure 3C, F). The clinical course is demonstrated in Figure 4. He is disease-free with a good quality of life, and the overall survival time is 3 years from the initial therapy. Further detailed follow-up will be required.

Discussion

The present patient had rectal cancer with a far-advanced synchronous bilateral CRLM with a maximal size of 15 cm and over 30 metastases but no extrahepatic metastases or pathological lymph node metastasis. His Beppu score (1) was high at 14 points (synchronous, more than five metastases and >5 cm CRLM); therefore, the estimated median disease-free and overall survival was 8 months and 22 months, respectively. He underwent liver-first conversion hepatectomy using a modified ALPPS procedure in combination with RFA to be cured. Multidisciplinary treatment is indeed essential, as he received four surgeries, two percutaneous ablations, two interventional radiology, and multiple rounds of systemic chemotherapy. He presented

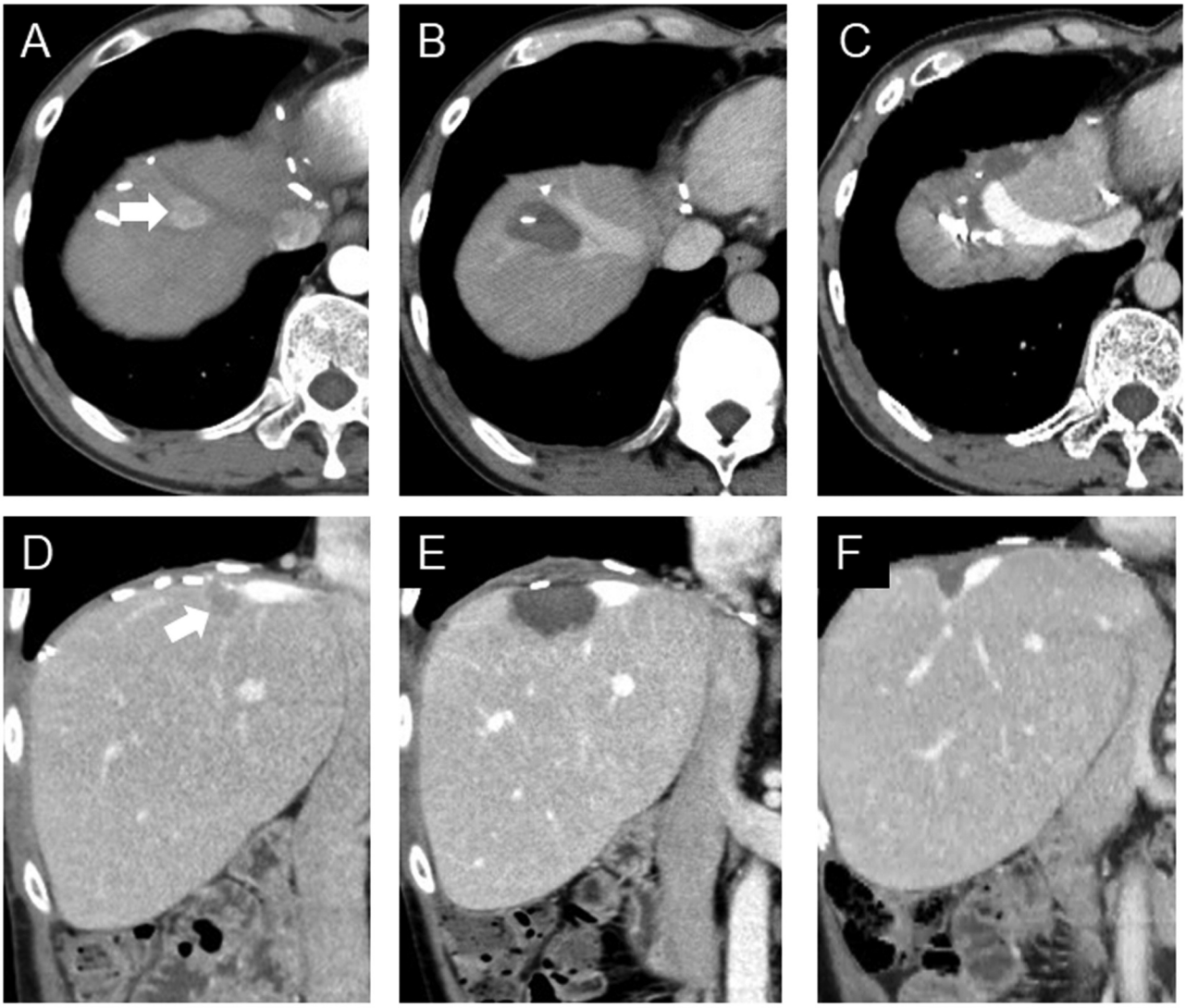

Figure 3. *Contrast-enhanced computed tomography (CT) before and after radiofrequency ablation. Axicial CT (A-C) and Coronal CT (D-F). Before ablation (A, D), 1 week after the first ablation (B, E), 3 months after open ablation (C, F). A viable lesion was found between the right hepatic vein and V7 at the time of initial recurrence (A, D). After the percutaneous radiofrequency ablation, the ablation margin was insufficient (B, E). Complete ablation was achieved after open radiofrequency ablation (C, F).*

with solitary liver metastasis early on; however, he is alive, tumor-free, treatment-free, and with good quality of life 3 years after diagnosis.

Conversion surgery is strongly recommended for patients with initially unresectable CRLM that became resectable after induction chemotherapy (3-6). The number of long-term survivors as well as patients with no tumors has been increasing (3, 5). Systemic chemotherapy with antiepithelial growth factor receptor antibody plus cytotoxic agents provides an excellent tumor regression effect for patients with RAS wild type left-sided metastatic colorectal cancer (26). Early tumor shrinkage and depth of response is additionally required to achieve conversion hepatectomy; these parameters were adequately obtained in our patient (27). mFOLFOX and panitumumab was administered for seven cycles before the first hepatectomy and five cycles between the second hepatectomy and Miles' operation. The other eight cycles were given for recurrent CRLM. If possible, no more than eight cycles of FOLFOX are recommended before a major hepatectomy, considering the therapeutic effect and possible adverse events (6, 28). Peripheral neuropathy is a limiting factor of oxaliplatin regimen (29); fortunately, the patient showed maximal grade 2 peripheral neuropathy despite of 20 cycles of the chemotherapy.

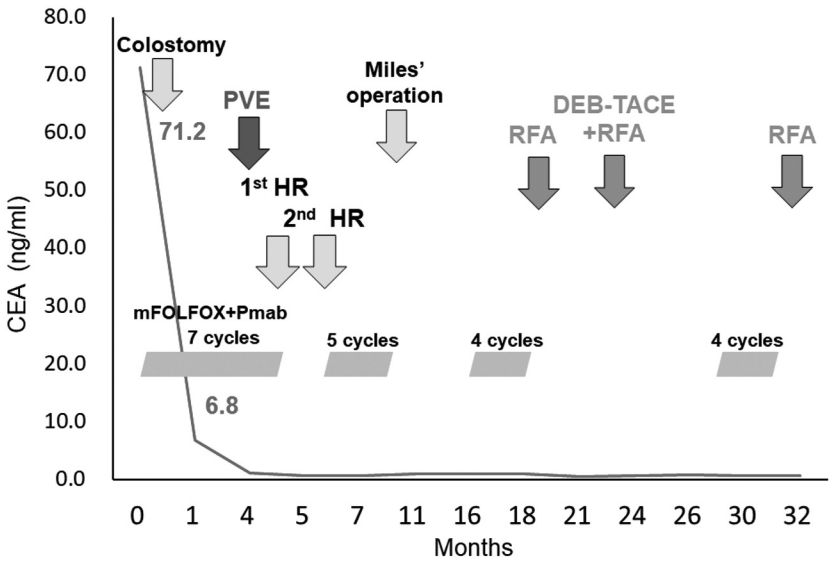

Figure 4. *Clinical course and changes in serum carcinoembryonic antigen levels. PVE, Portal vein embolization; RFA, radiofrequency ablation; DEB-TACE, transarterial chemoembolization using drug-eluting bead; HR, hepatic resection; mFOLFOX+Pmab, modified FOLFOX6 and panitumumab.*

Upfront RFA for resectable CRLM is not recommended by the international guidelines for liver metastases because of a relatively high recurrence rate at the therapeutic site and worse long-term survival compared to liver resection (10). If RFA is applied with liver resection for CRLM, a good response to chemotherapy is necessary (8, 30). Therefore, we applied RFA for the primary and recurrent CRLM in combination with systemic chemotherapy and/or DEB-TACE (31, 32). To complete the percutaneous RFA, enhanced ultrasound with Sonoazoid™ and/or fusion-ultrasound combined with CT or MRI images are beneficial (33). A randomized controlled trial (RCT) comparing the efficacy of RFA and liver resection for resectable CRLM is ongoing (34). The other RCT clearly demonstrated that RFA combined with systemic chemotherapy provided better progression-free survival *vs.* systemic chemotherapy alone (35). RFA is beneficial when combined with liver resection; however, the following criteria must be strictly met: metastases ≤2 cm, effective chemo/targeted therapy, and a distance of ≥5 mm from the first to second Glissonean capsule (8). Long-term survival is comparable between patients treated with liver resection alone and liver resection plus RFA using a propensity matching study (9).

Approaches of liver resection for synchronous CRLM include the primary-first, liver-first, and simultaneous approach. The liver-first approach has been applied mainly for advanced CRLM (20). Recently, a worldwide propensity-score matching analysis focused on the liver-first approach for synchronous CRLM from LiverMetSurvey (n=7,360) (21). Limited to patients with multiple bilateral metastases, the overall survival of the liver-first approach is marginally better (p=0.064) and significantly better (p=0.017) compared with the primary-first and simultaneous approach, respectively. The liver-first approach is recommended because no delay of liver resection is observed based on the postoperative complication of colorectal resection.

PVE followed by one-stage liver resection is the gold standard strategy for CRLM accompanying insufficient future remnant liver volume (35). For a salvage option, ALPPS is recommended (15). In our patient, insufficient hypertrophy was observed after the prior PVE; therefore, a modified ALPPS procedure was selected. Modified ALPPS without a large ischemic area can be achieved without serious complications (16). Recent RCTs have found that the resection rate for CRLM was significantly higher and median survival time was significantly longer in patients undergoing ALPPS than those with conventional two-stage hepatectomy (17).

Multidisciplinary treatment was successfully achieved between the two regional hospitals. For patients with advanced CRLM, appropriate surgical therapy, chemotherapy, and interventional treatment is essential, and liver-only metastases might be important.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

YA, KY, and TB identified the concept and wrote the draft of the article. All the authors treated the patient and collected data. All Authors have read and approved the final version of the article.

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Received September 6, 2021
Revised October 14, 2021
Accepted October 18, 2021