CANCER DIAGNOSIS & PROGNOSIS
2: 634-640 (2022) doi: 10.21873/cdp.10153

Efficacy and Safety of External-beam Radiation Therapy for Unresectable Primary or Local Recurrent Cholangiocarcinoma

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Abstract. *Background/Aim: Treatment options for unresectable cholangiocarcinoma are limited. The aim of the study was to evaluate the clinical outcomes of definitive external-beam radiation therapy (EBRT) for patients with unresectable cholangiocarcinoma. Patients and Methods: Patients with unresectable primary cholangiocarcinoma, or local recurrent cholangiocarcinoma after primary surgery, without distant metastasis who received definitive EBRT (≥45 Gy) between January 2006 and December 2020 at our Institution were analyzed retrospectively. EBRT was basically performed using conventional fractionation (1.8-2 Gy per fraction). Prophylactic nodal irradiation was not performed. Results: A total of 21 consecutive patients were analyzed: 7 primary and 14 recurrent cases. The median age was 70 (range=38–85) years at initiation of EBRT. A median dose of 54 (range=45-60) Gy comprising 1.8 (range=1.8-3) Gy per fraction was administered to the primary/recurrent local tumor site. The median follow-up period was 21.6 months. The 2-year overall survival, cause-specific survival, progression-free survival, and local recurrence-free rates were 35.7, 35.7, 16.1, and 32.7%, respectively. Long-term local control (>2 years after EBRT) was achieved in 19.0%. Grade 3 toxicities related to EBRT were observed in 4.8% (duodenum hemorrhage). No grade 4 or higher toxicities were observed. Conclusion: Definitive EBRT for unresectable cholangiocarcinoma was feasible and achieved long-term local control in a subset of patients. As the avoidance of local recurrence may lead to the benefits of prolonging biliary patency and subsequently alleviating the need for an invasive procedure for biliary drainage, EBRT could be one sustainable therapeutic option for patients with unresectable cholangiocarcinoma.*

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Key Words: Cholangiocarcinoma, unresectable, radiation therapy.

Cholangiocarcinoma is a form of refractory cancer (1). Although surgical resection is the only established curative treatment for cholangiocarcinoma, many patients present with locally advanced or unresectable disease at diagnosis. In addition, even if resected, a considerable number of patients develop clinical failure (CF) (2), and local recurrence (LR) is a major problem. LR often causes obstructive cholangitis, which necessitates invasive procedures such as biliary drainage or stenting and decreases the quality of life. Systemic chemotherapy has been a mainstay for such unresectable primary or recurrent cholangiocarcinoma, even for cases without distant metastasis (3).

External-beam radiation therapy (EBRT) is often used for various types of malignancies, with both curative and palliative intents. The low-invasiveness of EBRT facilitates its safe application for medically unfit patients, such as cases unsuitable for intensive chemotherapy or surgical resection

due to an advanced age or a poor general condition (4-6). However, the role of EBRT in the management of cholangiocarcinoma remains unclear due to the absence of high-level evidence. To our knowledge, reports on definitive EBRT for unresectable cholangiocarcinoma are limited (1).

Therefore, the aim of the current study was to evaluate clinical outcomes following definitive EBRT for unresectable cholangiocarcinoma in order to investigate its clinical significance.

Patients and Methods

This study followed the tenets of the Helsinki Declaration, with approval from the ethical review board of our institution (approval number: R1048-1).

Patients. We retrospectively reviewed our Institutional EBRT database and searched for eligible patients. The eligibility criteria for this study were as follows: 1) primary cholangiocarcinoma, or local recurrent cholangiocarcinoma after primary surgery, 2) diagnosed as unresectable disease, 3) no evidence of distant metastasis at EBRT (primary case) or both at initial diagnosis and at EBRT (recurrent case), and 4) treated with definitive EBRT (≥45 Gy) in our Institution between January 2006 and December 2020. Patients with ampullary cancer of the duodenum, with disease difficult to distinguish from pancreatic carcinoma, or with only lymph node metastasis, were excluded.

The initial evaluations basically consisted of enhanced computed tomography (CT), magnetic resonance imaging (MRI), pathological evaluation, and blood examination. Each case was generally discussed by the multidisciplinary hepato-biliary-pancreatic-oncologist tumor board, and clinical decisions regarding the treatment strategy were taken jointly. The judgement of operability in the current study was generally based on descriptions in the medical records. For cases whose operability could not be clearly determined based on their medical records, it was retrospectively re-evaluated by a single hepato-biliary-pancreatic surgeon (K.T.).

Treatment. For EBRT, a total dose higher than 50 Gy in conventional fractions (1.8-2 Gy per fraction) was basically prescribed for primary/recurrent local tumors and metastatic lymph nodes, using three-dimensional conformal radiation therapy (3D-CRT) or an intensity-modulated radiation therapy (IMRT) technique. Prophylactic nodal irradiation was generally not performed. However, there were some dose and field variations because the EBRT method was determined based on physicians' discretion, and not on pre-determined EBRT protocols. In addition, in some cases, the total dose was reduced to meet dose constraints for organs at risk, such as the duodenum or small bowel. In the current study, cases in which the total dose was reduced to lower than 45 Gy (such as cases treated with palliative intents) were excluded, as stated in the inclusion criteria.

Chemotherapy was basically performed concurrently or sequentially with the EBRT course, which generally consisted of S-1 or gemcitabine. However, the indication of chemotherapy was determined in consideration of each patient's condition and clinical course.

Follow-up and salvage treatment after failure. Follow-up examinations after EBRT included enhanced CT, MRI, endoscopic retrograde cholangiopancreatography (ERCP), or positron emission tomography (PET)/CT. The contents of salvage treatment for recurrent cases after definitive EBRT were based on physicians' discretion in consideration of each clinical course.

Statistical analysis. The endpoints of this study included overall survival (OS), cause specific survival (CSS), progression-free survival (PFS), LR-free rates, and rate of EBRT-related late toxicities. The time of occurrence of each event was calculated from the day of EBRT initiation. The Kaplan-Meier method was used to estimate OS, CSS, PFS, and LR-free rates. Patients who were lost to follow-up with best supportive care due to disease progression were categorized as "died from cholangiocarcinoma" on the day of the last visit or when clinical data were available. The diagnosis of CF after EBRT was based on the results of radiographic examinations (CT, MRI, PET/CT, or ultrasonography), ERCP, or pathological examinations. Patients who died due to disease progression without radiographic examinations, ERCP, or pathological examinations after EBRT were determined as occurrence of CF event at the last date of the EBRT course. PFS was defined as the time between the date of EBRT initiation and that of CF or death from any causes. LR was defined as CF at the irradiated site. Cases in which it was difficult to distinguish local recurrence from cholangitis were judged as LR. The LR-free duration was defined as the time between the date of EBRT initiation and that of LR, and death or lost to follow-up without an LR event was censored at the last date of radiographic examination or ERCP for calculation of the LR-free rate. As EBRT-related late toxicities, gastrointestinal disorders and radiation dermatitis (grade ≥3) were re-assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0).

All statistical analyses were carried out with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) (7).

Results

Patients. We identified 27 consecutive patients who met the inclusion criteria. Among them, 4 patients received EBRT for resectable tumors due to patient requests and 2 patients received EBRT as a preparation before liver transplantation. These 6 patients were excluded, and the remaining 21 patients were included in the study.

Among the 21 patients, 33.3% (n=7) had primary disease, and 66.7% (n=14) had locally recurrent disease after primary surgery. The median age was 70 (range=38-85) years at the initiation of EBRT. All but one patient were pathologically confirmed to have cholangiocarcinoma, while the remaining one patient without pathological confirmation was diagnosed based on clinical findings. The distributions of the primary tumor location at the initial diagnosis were: at the intrahepatic bile duct in 33.3% (n=7), at the extrahepatic bile duct in 52.4% (n=11), and at the border between the intrahepatic and extrahepatic bile duct in 14.3% (n=3). Among the 7 primary patients, 57.1% (n=4) had clinically T3 or higher stages, and 42.9% (n=3) had regional lymph

Table I. *Patient demographics and treatment characteristics.*

Sex	No. (%)
Male	16 (76.2%)
Female	5 (23.8%)
Age (years)	38-85 (median, 70)
Primary or recurrent	No. (%)
Primary	7 (33.3%)
Recurrent	14 (66.7%)
Diagnosis	No. (%)
Pathologically	20 (95.2%)
Clinically	1 (4.8%)
Tumor location	No. (%)
Intrahepatic	7 (33.3%)
Extrahepatic	11 (52.4%)
Border	3 (14.3%)
TNM stage of primary tumor (n=7)	
Clinical T stage	No. (%)
T2	3 (42.9%)
T3	1 (14.3%)
T4	3 (42.9%)
Clinical N stage	No. (%)
N0	4 (57.1%)
N1	3 (42.9%)
Clinical stage	No. (%)
II	3 (42.9%)
III	4 (57.1%)

Table II. *Patient treatment characteristics.*

Treatment modality	No. (%)
CRT	17 (81.0%)
Primary/Recurrent	5/12
Radiotherapy alone	4 (19.0%)
Primary/Recurrent	2 /2
Radiotherapy Total dose (median: 54 Gy)	No. (%)
60 Gy/30 fr	3 (14.3%)
57.6 Gy/32 fr	1 (4.8%)
56 Gy/28 fr	1 (4.8%)
54 Gy/30 fr	8 (38.1%)
50.4 Gy/28 fr	6 (28.6%)
45 Gy/18 fr	1 (4.8%)
15 Gy/5 fr plus 30 Gy/15 fr	1 (4.8%)
Radiation techniques	No. (%)
3D-CRT	19 (90.5%)
IMRT	2 (9.5%)
Chemotherapy (n=17)	No. (%)
Concurrent and Adjuvant	12 (70.6%)
GEM/S-1	7/5
Adjuvant only	5 (29.4%)
GEM and Cisplatin/GEM/S-1/UFT	2/1/1/1

CRT, Chemoradiotherapy; GEM, gemcitabine; UFT, tegafur-uracil.

node metastasis. Among the 14 recurrent patients, 78.6% (n=11) developed recurrence after the completion of adjuvant chemotherapy following primary surgery, and the remaining 21.4% (n=3) developed recurrence during adjuvant chemotherapy. The details of patient characteristics are summarized in Table I.

Treatment. All patients were treated with definitive EBRT, using 3D-CRT (90.5%, n=19) or IMRT (9.5%, n=2). A median dose of 54 (range=45-60) Gy comprising 1.8 (range=1.8-3) Gy per fraction (Gy/fr) was administered to the primary/recurrent local tumor site. Specifically, most patients (90.5%, n=19) were treated with conventional fractionated RT (1.8-2 Gy/fr). The details of EBRT are presented in Table II.

Among the 7 primary patients, 71.4% (n=5) received concurrent or adjuvant chemotherapy with EBRT, and the remaining 28.6% (n=2) received EBRT alone. Among the 11 patients who developed recurrence after completion of adjuvant chemotherapy following primary surgery, 81.8% (n=9) received concurrent or adjuvant chemotherapy with EBRT, and the remaining 18.2% (n=2) received EBRT alone. In the 3 recurrent patients who developed recurrence during adjuvant chemotherapy, chemotherapy was continued during EBRT in 2 and after EBRT in 1. In these 3 patients, contents of chemotherapy during or after EBRT were changed to different agents from those of adjuvant chemotherapy after primary surgery. In total, 81.0% (n=17) received CRT, whereas 19.0% (n=4) received EBRT alone. Chemotherapies mainly consisted of gemcitabine (GEM), S-1, or GEM plus cisplatin.

Endpoint evaluation: Oncological outcomes. The median follow-up period after initiation of EBRT was 21.6 (range=4.4-51.4) months. Nineteen patients died. Among them, 17 died from cholangiocarcinoma, and one patient was lost to follow-up while receiving best supportive care. These 18 patients were categorized as "died from cholangiocarcinoma". The median OS was 22.2 months, and OS rates were 71.4% (95% CI=47.2-86.0%) at 1 year and 35.7% (95% CI=16.1-55.9%) at 2 years (Figure 1a). The median CSS was 22.2 months, and CSS rates were 71.4% (95% CI=47.2-86.0%) at 1 year and 35.7% (95% CI=14.2-54.5%) at 2 years (Figure 1b).

Seventeen patients developed disease progression. The median PFS was 8.5 months, and PFS rates were 37.5% (95% CI=17.7-57.4%) at 1 year and 16.1% (95% CI=4.1-35.2%) at 2 years (Figure 2a). Fourteen patients developed LR. Among all patients, 19.0% (n=4) maintained local control over 2 years after EBRT. The median LR-free duration was 13.6 months, and LR-free rates were 53.6% (95% CI=29.5-72.7%) at 1-year and 32.7% (95% CI=12.0-55.5%) at 2 years (Figure 2b).

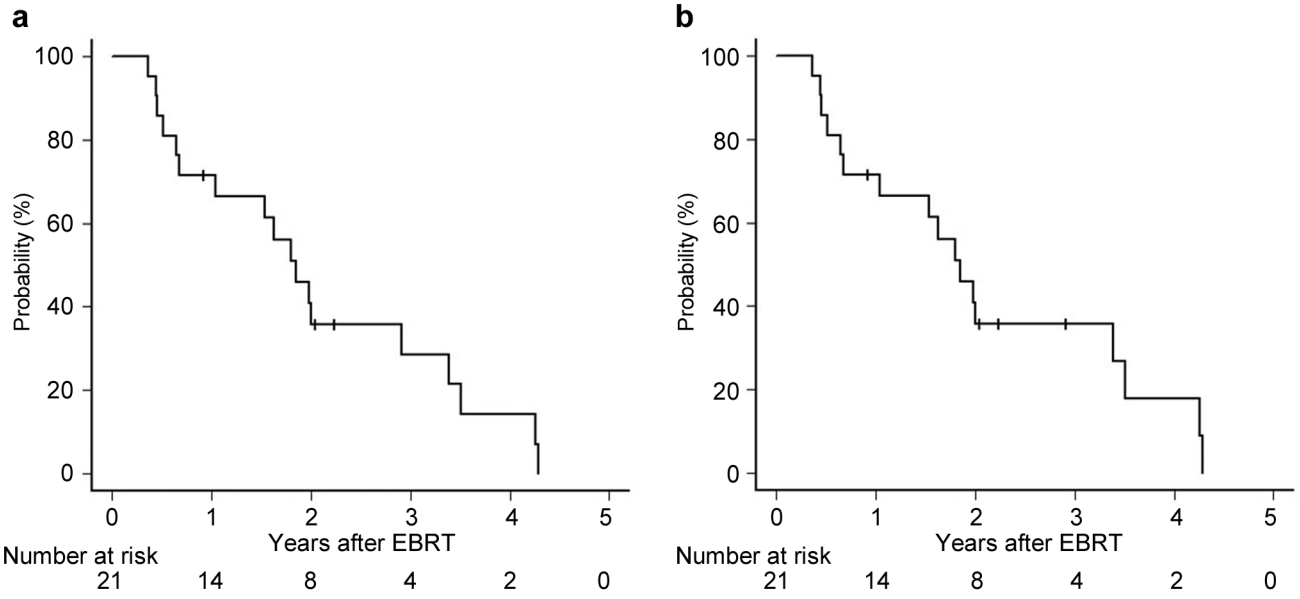

Figure 1. *Kaplan–Meier curves of overall survival (a), and cause-specific survival (b) of definitive external-beam radiation therapy (EBRT) for all patients. OS, Overall survival; CSS, cause-specific survival.*

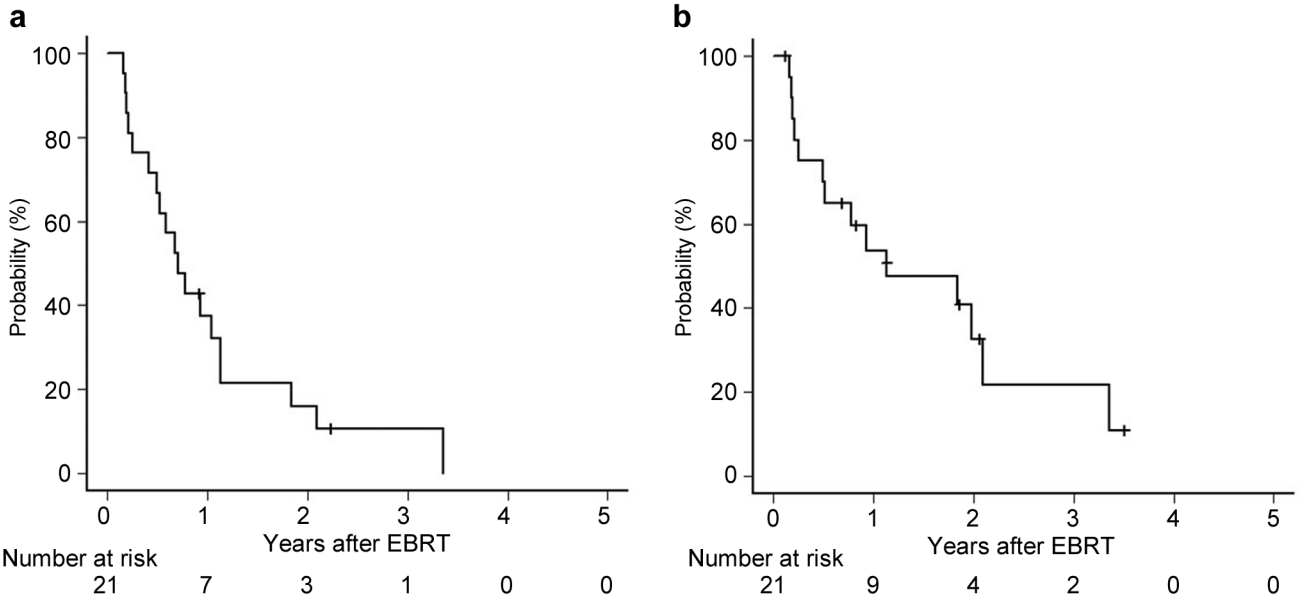

Figure 2. *Kaplan–Meier curves of progression-free survival (a), and local recurrence-free rates (b) of definitive external-beam radiation therapy (EBRT) for all patients. PFS, Progression-free survival; LR, local recurrence.*

Endpoint evaluation: Toxicities related to EBRT. One patient (4.8%) who received 60 Gy in 30 fractions, using 3D-CRT, developed grade 3 duodenal hemorrhage 2 months after EBRT completion. In this patient, duodenal hemorrhage was successfully controlled with endoscopic hemostasis. No grade 4 or higher EBRT-related toxicities were observed.

Discussion

In this study, we retrospectively evaluated clinical outcomes following definitive EBRT for unresectable cholangiocarcinoma without distant metastasis in the setting of primary disease or local recurrence after curative resection. Our treatment protocol

specified administration of the median cumulative dose of 54 Gy in conventional fractions to the primary/recurrent local tumor site using 3D-CRT or IMRT. Our treatment method was considered similar to the EBRT pattern most frequently adopted in Japanese clinical practice (8). As a result, the 2-year OS, CSS, PFS, and LR-free rates were 35.7, 35.7, 16.1, and 32.7%, respectively, and the median OS, CSS, PFS and LR-free times were 22.2, 22.2, 8.5, and 13.6 months, respectively. In addition, severe late toxicities (grade ≥3) related to EBRT were observed only in 4.8% (n=1) of the cohort. Although survival outcome rates were relatively low, definitive EBRT for primary or locally recurrent cholangiocarcinoma was considered feasible and effective at achieving long-term local control in a part of the patients.

The benefit of adding EBRT to chemotherapy for unresectable cholangiocarcinoma remains unclear. According to a phase II randomized trial, which compared the efficacy of chemoradiotherapy (EBRT with a dose of 50 Gy in 25 fractions plus chemotherapy using fluorouracil and cisplatin) *vs*. chemotherapy alone (gemcitabine plus oxaliplatin) for locally advanced biliary tract cancer, no significant differences were observed in either OS [median: 13.5 months in the chemoradiotherapy arm *vs*. 19.9 months in the chemotherapy arm, hazard ratio: 0.69 (95% CI=0.31-1.55)] or PFS [median: 5.8 months in the chemoradiotherapy arm *versus* 11.0 months in the chemotherapy arm, hazard ratio: 0.65 (95% CI=0.32-1.33)] (9). On the other hand, according to a population-based analysis of unresected extrahepatic cholangiocarcinoma, the receipt of chemoradiotherapy was associated with a decreased risk of death compared to the receipt of chemotherapy alone (HR=0.83, 95% CI=0.76-0.92, $p<0.001$), although this study included some cases treated with chemoradiotherapy in the setting of induction treatments for surgical resection (10). The reported median OS and PFS following definitive EBRT for unresectable cholangiocarcinoma ranged between 9.5-18.7 and 5.8-9.0 months, respectively (9-17). Although there were some differences regarding patients' background and OS and PFS rates in the current study, they were considered equivalent to those of previous radiotherapy series.

Rates of achieving the outcome of local control following definitive EBRT varied among previous reports, ranging between 25 and 80% at 2 years (11, 13-15, 18). This discrepancy of local control outcomes from previous reports can be considered to be due to differences in disease and treatment backgrounds, such as intrahepatic *versus* extrahepatic disease, or conventional EBRT *versus* dose-escalated radiotherapy using stereotactic body radiotherapy (SBRT) or brachytherapy. In the current study, intra- and extrahepatic diseases were both included, and all patients were treated with conventional EBRT. Although the rate of achieving local control as an outcome of the current study (LR-free rate: 32.7% at 2 years) was considered relatively low compared to those of previous reports, 19.0% (n=4) of the cases maintained a locally controlled status over 2 years after EBRT. These successful cases indicated the possibility that definitive EBRT can achieve long-term local control in a part of the patients with unresectable cholangiocarcinoma. Maintaining a local control status may have the benefit of avoiding biliary tract obstruction and subsequently sparing patients from highly invasive procedures such as endoscopic retrograde biliary drainage or stenting, and so patients' quality of life can be maintained (19). Therefore, there may be a merit of definitive EBRT in terms of achieving long-term local control. Recently, the favorable local control outcome of local dose escalation *via* SBRT was reported (20-22). According to a systematic review of SBRT for cholangiocarcinoma, the pooled local control rate was 83.4% at 1 year (20). In addition, a correlation between local control and the prescribed biological effective radiation dose (BED) was reported (22). According to a retrospective study of 64 patients (82 lesions) with intra- or extrahepatic cholangiocarcinoma treated with SBRT, the local control rate was significantly higher in patients who received maximum BED ($\alpha/\beta=10$) >91 Gy than those who received a lower dose (80 *vs*. 39% at 2 years, respectively, $p=0.009$). Further investigations are needed to determine the impact of local control on survival and the optimal RT method and dose administered to local sites.

Severe late toxicities related to definitive EBRT for cholangiocarcinoma have been reported relatively rarely in previous studies (9-15). According to a report of definitive EBRT for locally advanced or unresectable extra-hepatic carcinoma (15), the cumulative incidence of grade ≥3 late gastrointestinal complications related to EBRT was 17% at 2 years. In the current study, grade ≥3 late toxicities related to EBRT were observed only in 4.8% (n=1): grade 3 duodenum hemorrhage, which was finally resolved with endoscopic hemostasis (grade 0). Currently employed high-precision EBRT techniques, including IMRT or image-guided radiation therapy, would be helpful to achieve safer dose delivery.

This study had several limitations, including the retrospective nature of analysis of a small cohort. Our cohort consisted of a heterogeneous population, including both primary and recurrent cases. In addition, assessment of local control was mainly based on the findings of radiographical examinations or ERCP, and it was difficult to distinguish some lesions as local recurrence or cholangitis. As our cases in which it was difficult to distinguish LR from cholangitis were judged as LR, our LR-free rate might be lower than the true LR-free rate. Due to these limitations, the findings of the current study are not conclusive regarding the outcomes of LR-free status following definitive EBRT for unresectable cholangiocarcinoma, but merely hypothesis-generating.

Nevertheless, we trust that our results may be of use as real-world data of definitive EBRT for primary or local

recurrent unresectable cholangiocarcinoma because data from prospective trials are very limited.

Conclusion

In conclusion, definitive EBRT for primary or local recurrent cholangiocarcinoma was feasible and achieved long-term local control in part of the patients. Avoiding LR may have the merit of prolonging biliary patency and subsequently alleviating the need for an invasive procedure for biliary drainage, which leads to maintaining patients' quality of life. Therefore, definitive EBRT could be one of the therapeutic options, especially for patients whose treatment options are limited.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors' Contributions

Conceptualization, T.M. (Takashi Murakami), R.A., Y.M., H.H and T.M. (Takashi Mizowaki); Patient Treatment, R.A., Y.M., H.H., K.T., A.F., N.U., M.S., M.K., E.H., H.S., M.M and T.M. (Takashi Mizowaki); Study Methodology, T.M. (Takashi Murakami), R.A., Y.M., H.H., M.K. and T.M. (Takashi Mizowaki); Acquiring and interrupting data, T.M. (Takashi Murakami), R.A., H.H and K.T.; Writing the original manuscript, T.M. (Takashi Murakami) and R.A..; Reviewing and editing the original manuscript, Y.M., H.H., K.T., A.F., N.U., M.S., M.K., E.H., H.S., M.M and T.M. (Takashi Mizowaki). All Authors approved the final version of the manuscript.

Acknowledgements

We would like to thank EIGOCLINIC (https://eigoclinic.com/) for English language editing.

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Received June 28, 2022
Revised August 10, 2022
Accepted August 22, 2022