



Helical tomotherapy for asymptomatic chemotherapy-refractory or -unfit multiple (3 or more) metastases

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ABSTRACT

Background: Despite chemotherapy innovations, prognosis of patients with chemotherapy-refractory or -unfit multiple metastases (CRMM/CUMM) remains poor. In this prospective study, the efficacy and toxicity of helical tomotherapy for CRMM/CUMM were evaluated.

Materials and methods: Between 2014 and 2020, asymptomatic patients with CRMM/CUMM with ≥ 3 lesions and no prior radiotherapy of the targets were enrolled. Patients who had intolerable toxicities to chemotherapy and those who refused chemotherapy were included in the CRMM and CUMM groups, respectively. Prostate cancer patients and patients with metastases mainly localized in the liver, lung, or brain were excluded. By helical tomotherapy, up to 10 lesions per patient were irradiated in order of volume. The standard dose was 50–60 Gy in 25–30 fractions.

Results: Forty-five patients (median age, 63 years; 35 CRMM/10 CUMM) were enrolled. Primary tumors included lung, gynecological, and gastrointestinal cancers. The most frequently treated targets were lymph node metastases, followed by peritoneal/pleural disseminations and bone tumors. The 1-year survival rate was 51% (median, 12.5 months). In the 35 patients with CRMM, the median survival time was 12.5 months, and the median pre-radiation chemotherapy period was 8.8 months ($p > 0.05$). The 6-month target control rate was 78%. Acute adverse events (grade ≥ 2) occurred in 33 patients: hematologic toxicities in 23, dermatitis in 6, and others in 8. Late grade ≥ 2 toxicities occurred in 6 patients: pneumonitis in 4 and gastric hemorrhage in 2.

Conclusion: Tomotherapy for CRMM/CUMM resulted in median survival times > 1 year. This treatment should be investigated further in larger prospective studies.

Key words: multiple metastases; chemotherapy-refractory; chemotherapy-unfit; intensity-modulated radiotherapy; tomotherapy

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Introduction

Recently, the role of radiation therapy (RT) for the treatment of patients with oligometastases (≤ 3 metastases) has been increasing. Stereotactic RT (SRT) has been shown to be effective [1–4], but in patients with extensive metastases, systemic chemotherapy remains the gold standard of treatment. In such patients, palliative RT may be delivered to symptomatic sites; however, RT is not generally indicated for asymptomatic lesions, with the exception of brain and spinal metastases. Systemic chemotherapy including molecular targeted therapy has progressed remarkably in recent years. Favorable responses of multiple metastases to chemotherapy are often observed, contributing to increased survival. However, cure of multiple lesions is quite rarely observed. Even when a partial or complete response is achieved, regrowth of the tumors is inevitable. Furthermore, long-term adverse events are often intolerable, making the continuation of chemotherapy difficult. Due to these adverse effects, some patients cannot continue or refuse chemotherapy.

Since there are no other effective treatment for such patients, the survival time is usually expected to be no longer than 6 months. Although attending physicians usually recommend hospice care, many patients and their families wish to receive further intensive treatment. For such patients, we previously proposed a combination of dendritic cell (DC)-based vaccine therapy and intensity-modulated RT (IMRT) [5]. DCs are a specialized family of professional antigen-presenting cells that drive T-lymphocyte-mediated immune responses [6]. Even without immunotherapy, however, IMRT had significant local effects against chemotherapy-refractory cancers [7], and it was shown that tomotherapy could potentially treat multiple metastatic tumors [7, 8].

Thus, we started to use helical tomotherapy for patients with chemotherapy-refractory or -unfit multiple metastases (CRMM/CUMM). Our aim was to delay tumor progression and prolong survival times. Results of this treatment for multiple liver metastases were previously reported [7]. Following the initiation of the study for multiple liver metastases, we started this prospective study to evaluate the efficacy and toxicity of helical tomotherapy for multiple metastases other than those of the liver.

Combination with DC-based immunotherapy was not mandatory as it is not covered by medical insurance. The purpose of this study was to evaluate treatment outcomes for CRMM/CUMM.

Materials and methods

Study design and eligibility

This study was approved by the institutional review board of participating institutions (Nagoya City University Hospital No. 1304) and was conducted in compliance with the guidelines of the Helsinki Declaration. The primary endpoint was overall survival (OS). The secondary endpoints were local control (LC), progression-free survival (PFS), and toxicity. The inclusion criteria were:

- asymptomatic CUMM or CRMM with ≥ 3 metastatic lesions in organs other than the central nervous system;
- age ≥ 18 years;
- World Health Organization (WHO) performance status (PS) of 0–2;
- no prior RT treatment of the targets;
- written informed consent.

Presence of an active primary lesion was allowed. CRMM indicated chemotherapy-refractory status or intolerable toxicities and CUMM indicated the inability to undergo systemic chemotherapy because of patients' comorbidities, general conditions, and/or wishes.

The exclusion criteria were:

- presence of symptoms such as pain and bleeding, or compression of the spinal cord;
- prostate cancer as a primary lesion since life expectancies are generally ≥ 1 –2 years under supportive care;
- main disease conditions of multiple liver metastases since they were the subject of our previous study [7];
- multiple lung metastases requiring irradiation of multiple pulmonary sites, which is hazardous in terms of radiation pneumonitis;
- active infectious disease;
- severe psychological disorder;
- expected survival time < 2 months as estimated based on the prognosis using palliative care study predictor models [9].

Combined use with the DC-based immunotherapy was allowed as it did not shorten or markedly increase survival times in patients with highly ad-

vanced cancers. All RT was delivered simultaneously by tomotherapy, with up to 10 lesions irradiated in order of their volumes.

Assuming a 6-month overall survival rate of 50% for the treatment group compared with 20% for the best supportive care group [10], at least 43 patients were required based on a type-1 error of 5%, type-2 error of 20%, and a drop-out rate of 10%. Therefore, the sample size in this study was determined to be 45 patients [11]. Since the treatment was unfamiliar to many surgeons and medical oncologists, we assumed that 5-6 years would be necessary to accrue this number of patients, expecting an accrual of 8-10 patients per year.

Patients

Between April 2014 and June 2020, 45 eligible patients with CUMM or CRMM participated in this multi-institutional study. Characteristics of the patients and their treatments are shown in Table 1, which included 21 males and 24 females with a median age of 63 years (range, 32-96 years). Thirty-five patients were in a chemotherapy-refractory status and 10 patients were unfit for chemotherapy. Nine patients received the DC-based immunotherapy, and 14 patients had active primary lesions. The primary tumor types included 7 non-small cell lung cancers (16%), 5 endometrial cancers (12%), 5 cervical cancers (12%), 5 ovarian cancers (12%), 4 gastric cancers (9%), 4 pancreatic cancers (9%), and 15 others (35%). Of the 45 patients, 21 had 3-5 lesions, 10 had 6-9 lesions, and 14 had ≥ 10 lesions. The most frequently treated lesions were in the lymph node ($n = 161$), followed by peritoneal/pleural disseminations ($n = 36$), and bone tumors ($n = 17$).

Radiotherapy protocol

Our methods of tomotherapy are described in detail elsewhere [12, 13]. The BodyFIX system (Medical Intelligence, Schwabmuenchen, Germany) was used for patient immobilization and minimization of target respiratory movements. All patients were trained to breathe shallowly. Non-contrast and/or contrast-enhanced CT images were acquired with 2- to 2.5-mm slice thicknesses. Contouring was made on the non-contrast CT images fused with contrast-enhanced images, according to our previous study [14], using the Pinnacle (Philips Medical Systems, Best, The Netherlands) or RayStation (RaySearch Laboratories,

Table 1. Patient, tumor, and treatment characteristics ($n = 45$)

Age (years)	62
Median (range)	(32-96)
Sex [Male/Female]	21/24
WHO performance status [0/1/2]	34/10/1
Primary tumor	
Non-small cell lung ca./Endometrial ca./Cervical ca.	7/5/5
Ovarian ca./Stomach ca./Pancreatic ca./Others	5/4/4/15
Active primary tumor [Present/Absent]	14/31
Total number of tumors 3-5/6-9/ ≥ 10	21/10/14
Number of irradiated tumors 3/4/5-10	7/12/26
Target lesions	
Lymph node/Pleura and peritoneum/Bone	161/36/17
Primary lesion/Liver/Lung/Others	13/9/8/4
DC-based vaccine therapy [Used/Not used]	9/36
Duration of chemotherapy before tomotherapy [months]	
All patients	4.4
Median (range)	(0-96.3)
Chemotherapy-refractory patients ($n = 35$)	8.8
Median (range)	(0.5-96.3)
Total dose [Gy]	50
Median (range)	(24-60)
Dose per fraction [Gy]	2
Median (range)	(1.8-3)
Chemotherapy agents used before tomotherapy	
CBDCA/CDDP/PTX/NIVO/CPT-11/S-1/BEV/GEM	12/12/11/7/7/6/6/6
5-FU/DTX/DXR/L-OHP/EVL/AMR/ETOP/ERI/others	4/4/4/3/2/2/2/7

ca. — cancer; DC — dendritic cell; CBDCA — carboplatin; CDDP — cisplatin; PTX — paclitaxel; NIVO — nivolumab; CPT-11 — irinotecan; S-1 — tegafur + gimeracil + oteracil; BEV — bevacizumab; GEM — gemcitabine; 5-FU — 5-fluorouracil; DTX — docetaxel; DXR — doxorubicin; L-HOP — oxaliplatin; EVL — everolimus; AMR — amrubicin; ETOP — etoposide; ERI — eribulin

Stockholm, Sweden) treatment planning systems. The gross tumor volume (GTV) was the volume of all visible tumors to be treated, and the clinical target volume (CTV) was equal to the GTV or included 2- to 3-mm margins. The internal target volume (ITV) was defined as the summation of the inspiratory- and expiratory-phase CT images (if needed). The planning target volume (PTV) margin was 3 to 5 mm around the CTV or ITV. Delineated OARs were the liver, bilateral kidneys, pancreas, spleen, esophagus, stomach, duodenum, small intestines, colons, spinal cord, heart, and bilateral lungs.

Planning and treatments were carried out with the tomotherapy treatment planning station and TomoTherapy HDA system or Accuray Precision treatment planning system and Radixact system (Accuray, Inc, Sunnyvale, CA). Megavoltage CT for registration was performed before every treatment for all lesions, and the treatment position was adjusted for the lesion near the isocenter so as to adequately cover all lesions. When two or more treatment sessions were used, registration was performed for every session. The TomoHelical mode was exclusively employed. The dose was prescribed to 50% of the PTV, and the standard prescribed dose was 50–60 Gy in 25–30 fractions over 5 weeks; however, adjustment of the dose and fractionation schedule was permitted depending on patients' general condition, expected survival time, type, size, and site of tumors (range, 40–60 Gy in 1.8–3 Gy daily fractions). A 2.5-cm field width was used in the majority of patients. When the irradiation time exceeded 10 min, a 5.0-cm field width was used to shorten the treatment time. A pitch of 0.43 and a normal modulation factor of 2.0 were generally used. Inverse planning was performed with a variable number of iterations, with a range of about 30–100 during the optimization process per plan. The dynamic jaw mode was used to reduce the craniocaudal dose spread [12, 15]. In principle, lesions with a craniocaudal distance >15 cm from the neighboring lesion were treated in a separate session. For patient-specific quality assurance, the doses were evaluated with ArcCHECK (Sun Nuclear Corporation, Melbourne, FL, USA), MapCHECK3 (Sun Nuclear Corporation), and a dosimeter before treatment.

Radiation dose constraints for PTV and OARs

PTV constraints were: 1) $D_{2\%}$ (near maximum dose) $\leq 110\%$ and 2) $98\% < D_{50\%} < 102\%$. A goal of $D_{95\%}$ for the PTV was not set in order to decrease adverse events. The median PTV was 308 cm³ (42–2478 cm³). The following OAR constraints were strictly met in all cases:

- maximum dose < 65 Gy for the esophagus and rectum and < 55 Gy for the stomach, small bowel, and spinal cord;
- $V_{20Gy} < 30\%$ for the bilateral lungs;
- mean dose < 30 Gy for the liver and < 15 Gy for the bilateral kidney.

The constraints for other organs were equal to the tolerance dose of normal tissue in 3-dimensional conformal radiation therapy (3DCRT) [16].

DC-based vaccine therapy and other treatments

DC-based vaccine therapy was allowed according to the wishes of patients. The patients were evaluated for their eligibility for enrollment and the availability of cancer antigens at the immunotherapy clinic (Seren Clinic Nagoya, Nagoya, Japan). The methods for the preparation of the DC-based vaccine were previously reported [5, 17]. The DC-based vaccine was administered intradermally every other week for at least 7 times. Treatment at recurrence was allowed at the discretion of attending physicians.

Follow-up evaluation and statistical analysis

Pre- and post-treatment evaluation included physical examination, blood tests including tumor markers, and non-contrast and/or contrast-enhanced CT and/or MRI. Progressive disease of any irradiated tumor according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was regarded as LC failure. Growth of any lesion including tumors in unirradiated regions was regarded as progression. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events version 5.0.

OS, LC, and PFS rates were calculated from the start of RT using the Kaplan-Meier method. Differences in the curves were analyzed by the log-rank test. Differences between survival times and pre-tomotherapy durations of chemotherapy were compared using the paired t-test. All statistical analyses were carried out using an open-source software, R Version 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria). $p < 0.05$ was considered to indicate a significant difference.

Results

Treatment plan and PS changes

Figure 1 shows a dose distribution in a patient with bone and lymph node metastases and peritoneal disseminations from uterine cervical cancer. The vertebral lesion and pelvic lesions were treated separately. During and soon after treatment, PS was

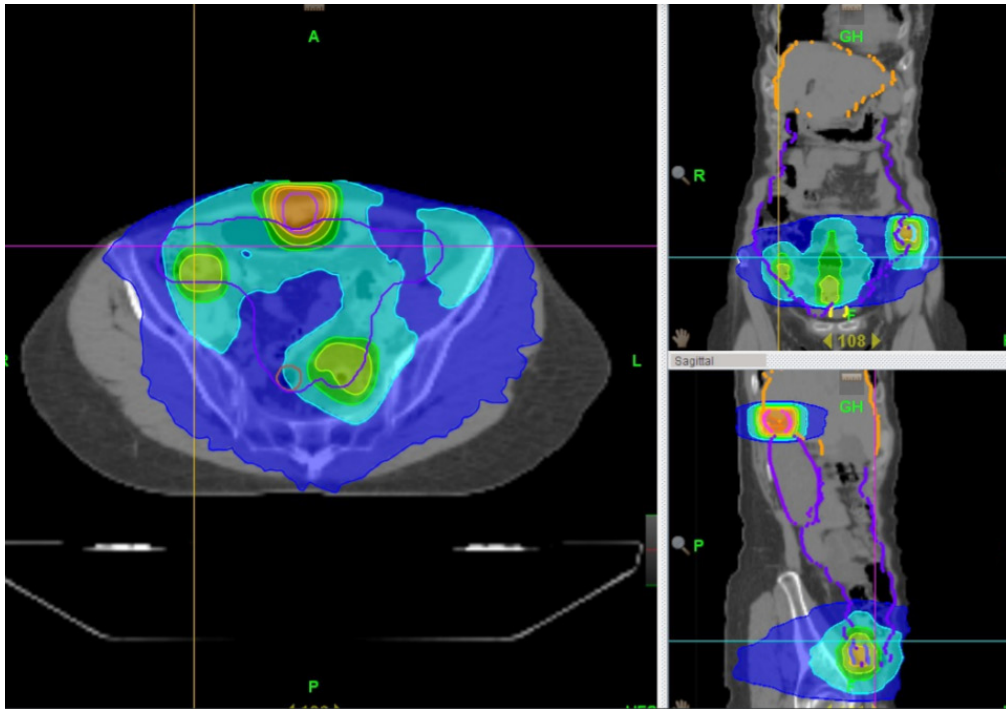


Figure 1. Dose distribution for bone and lymph node metastases and peritoneal disseminations in a patient with uterine cervical cancer

maintained in 41 of the 45 (91%) patients but PS became worse in 4 patients (9%).

Overall survival

Thirty-eight of the 45 patients completed the planned treatment, while treatment was terminated at 24–36 Gy in 7 patients due to worsening of general conditions, disease progression, or acute toxicity. For the other patients, median RT doses and fraction numbers (and their ranges) were 54 (42.5–60) Gy in 25 (15–30) fractions. For all 45 patients, the median follow-up period was 13.5 months (range, 0.1–49.7 months). The median survival time (MST) was 12.5 months, the 6-month OS rate was 75%, and the 1-year OS was 51% (Fig. 2). Excluding 3 patients who had breast or renal cell cancers, the MST was 9.8 months and the 1-year OS was 47%. For the 35 patients with CRMM, the MST and 1-year OS were 12.5 months and 51%, respectively (Fig. 2). In these patients, the period of systemic chemotherapy was 0.5–96.3 months (median, 8.8 months; $p = 0.68$ compared to OS times). Excluding 6 patients who underwent only 1 course of chemotherapy due to toxicity, the median period of systemic chemotherapy was 11.6 months (range, 2.4–96.3), and the MST was 13.6 months for the

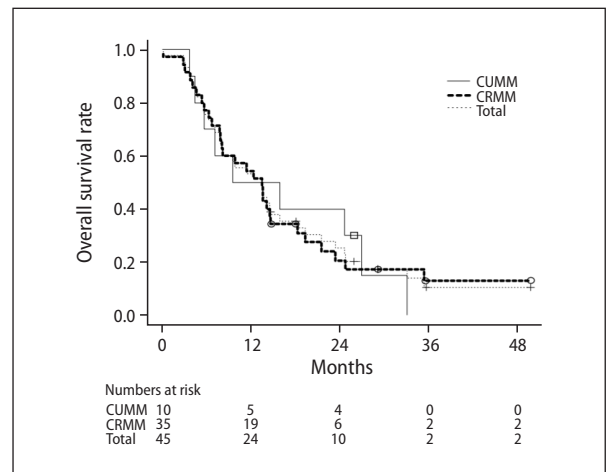


Figure 2. Overall survival curves for all chemotherapy-refractory (CRMM) and chemotherapy-unfit (CUMM) multiple metastases patients

29 patients ($p = 0.51$). For the 10 patients with CUMM, the MST and 1-year OS were 9.5 months and 44%, respectively.

Table 2 shows OS data according to potential prognostic factors. Patients receiving higher RT doses (> 45 Gy) had better OS ($p = 0.01$) and PFS than those receiving ≤ 45 Gy ($p < 0.01$). Other factors were not associated with prognosis. The MST

Table 2. Univariate analysis

Potential prognostic factor	n	MST [months]	p	HR (95% CI)
Age (years) [$< 65/\geq 65$]	24/21	12.5/13.5	0.50	0.80 (0.42–1.5)
Sex [Male/Female]	21/24	13.6/10.6	0.45	1.28 (0.66–2.46)
Duration of chemotherapy (months)				
$< 5/\geq 5$	23/22	9.5/13.6	0.98	0.99 (0.52–1.88)
CUMM/CRMM	10/35	12.7/13.5	0.98	1.01 (0.47–2.15)
DC-based vaccine therapy [Used/Not used]	9/36	11.4/13.6	0.66	1.20 (0.60–2.39)
Active primary tumor [Present/Absent]	14/31	7.55/13.6	0.60	0.83 (0.42–1.66)
Number of tumors [$< 6/\geq 6$]	21/24	18.2/12.5	0.08	1.79 (0.92–3.48)
Number of irradiated tumors [$< 5/\geq 5$]	19/26	18.2/12.5	0.30	1.41 (0.73–2.71)
Unirradiated tumor [Present/Absent]	23/22	9.5/14.4	0.37	0.75 (0.39–1.42)
PTV (cm ³) [$< 300/\geq 300$]	21/24	8.6/13.6	0.38	0.75 (0.40–1.43)
Radiation dose (Gy) [$\leq 45/> 45$]	13/32	4.6/14.6	0.01	0.39 (0.19–0.81)

CUMM — chemotherapy—unfit multiple metastases; CRMM — chemotherapy—refractory multiple metastases; DC — dendritic cell; PTV — planning target volume; MST — median survival time; HR — hazard ratio; CI — confidence interval

and 1-year OS for the patients who underwent DC-based vaccine therapy were 9.8 months and 41%, respectively, compared with 13.5 months and 51% ($p = 0.66$) for patients who did not receive the treatment.

Local control and progression-free survival

Figure 3 shows LC and PFS curves after tomotherapy. The median LC period was 9.1 months, the 6-month LC rate was 78%, and the 1-year LC rate was 38%. The median PFS time was 2.6 months, the 6-month PFS rate was 26%, and the 1-year PFS rate was 8%. Decreases ($\geq 30\%$) in tumor markers were observed in 17 (63%) of the

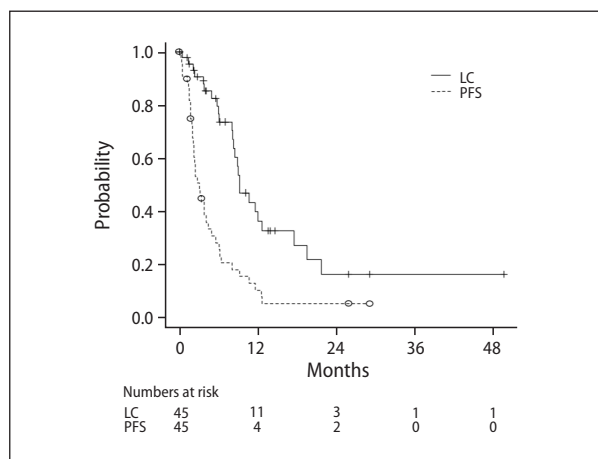


Figure 3. Progression-free survival (PFS) and local control (LC) curves for all patients

27 evaluable patients with pretreatment tumor marker elevation.

Adverse events

Acute toxicity (\geq grade 2) occurred in 33 patients: hematologic toxicities in 23 patients, dermatitis in 6, nausea in 3, and others in 5. The most common hematologic toxicity was transient lymphocytopenia, which occurred in 23 patients. Grade 3 acute toxicity occurred in 15 patients: lymphocytopenia in 14, leukopenia in 2, and thrombocytopenia in 1. Grade 4 acute toxicity occurred in 4 patients, all of whom had lymphocytopenia. Late toxicity (\geq grade 2) occurred in 6 patients: grade 2 pneumonitis in 3, grade 2 gastric hemorrhage in 1, grade 3 gastric hemorrhage in 1, and grade 5 pneumonitis in 1. A 60-year-old female patient with non-small cell lung cancer developed grade 5 pneumonitis after receiving systemic chemotherapy for 17.9 months. Her status became chemotherapy-refractory, and the active primary tumor and 4 separate mediastinal lymph nodes were irradiated with 50 Gy in 25 fractions. The V_{20Gy} of bilateral lungs was 15%. After irradiation, pneumonitis occurred at 5.8 months, and she died at 8 months.

Retreatment for recurrence

For recurrence after tomotherapy, 22 received RT, 7 received chemotherapy, and 2 received intra-arterial infusion therapy for new metastases outside of the irradiated volume. Three patients

received repeat tomotherapy for recurrence in the irradiated volume.

Discussion

Generally, RT has not been used in the treatment of asymptomatic multiple metastases. According to Japanese guidelines, SRT or particle therapy is not indicated for patients with multiple ($n > 3$) metastases. Also, patients with 3 metastases are rarely treated with SRT because of the greater workload. Plans for a randomized study of SRT for 4–10 metastatic tumors have been published, but no results are currently available [18]. On the other hand, recent developments in RT technology have enabled simultaneous treatment of multiple metastases by tomotherapy. This study demonstrated the feasibility and safety of treating 3–10 tumors with doses up to 50–60 Gy in 25–30 fractions. Therefore, this method has the potential to become a new treatment for multiple metastases.

In the present study, MST was 12.5 months and 1-year survival of 51% for patients with CRMM/CUMM. These results compare favorably with previous reports on the treatment of multiple metastases; for example, the median OS was 9 months in patients with PS of 0–2 after at least 2 lines of palliative chemotherapy in a previous study [19]. Another study showed a median OS of 197 days for ECOG PS 0 patients, 104 days for PS 1 patients, and 55 days for PS 2 patients with advanced cancer, most of whom had metastases after various treatments [20]. However, since various tumor types and metastatic tumor sites were included, our results must be interpreted with caution. In patients with CRMM, the OS time tended to be longer than the pre-tomotherapy duration of chemotherapy. Therefore, we believe that controlling the major parts of multiple metastases by RT is useful in reducing the tumor loads of patients, and that tomotherapy for CRMM and CUMM is effective in prolonging OS in a considerable proportion of patients.

The median LC period for irradiated tumors and PFS time were 9.1 and 2.6 months, respectively. Since all the tumors were progressing at the start of tomotherapy, these results indicate a modest efficacy of the treatment in terms of LC and PFS. A dose of 50–60 Gy in 25–30 fractions may be insufficient to obtain long-term control of all tumors, but local

tumor progression was delayed in most patients. The low PFS rates may be attributed to the fact that not all visible tumors were necessarily irradiated, and unirradiated tumors progressed at relatively early periods. In addition, patients with multiple metastases can easily develop metastases outside of the treatment volume. Nevertheless, reducing the overall tumor burden may be effective in prolonging OS.

A concern for the treatment of CRMM was the radioresistance of tumors acquired from preceding chemotherapy. After tumors are treated by chemotherapy (especially DNA-damaging agents), cross resistance to radiation has been reported [21–23]. Most of the chemotherapy regimens used before tomotherapy in this study included DNA-damaging agents, so it was a concern that the effects of radiation may not be sufficient. Previous studies have indicated that acquisition of cross resistance depends on the cell line and is related to an increase in glutathione levels [22, 23]. Nevertheless, we obtained LC of > 6 months in most irradiated tumors. Therefore, it appears worthwhile to attempt RT for chemotherapy-refractory tumors. Combining IMRT with chemotherapy as a first-line treatment of multiple metastases may be a topic of future investigations.

Hematological toxicities were frequently observed, probably because of the reduced bone marrow reserve due to preceding chemotherapy. In view of the high incidence of hematological toxicities, it may be better to contour the bone marrow as an OAR in future studies. One patient died as a result of toxicity, despite stringent dose constraints; V_{20Gy} of the bilateral lungs was only 15%, which was not excessively higher than in other studies. This finding suggests that the minimization of toxicity should be considered when delivering tomotherapy for CRMM/CUMM, especially in cases where the lungs are to be irradiated. Further minimization of regions to low-dose exposure may be important in order not to cause a decline in patient quality of life. A disadvantage of the TomoHelical mode is that the regions receiving low-dose radiation are generally broad compared with 3DCRT. In recent years, the TomoDirect mode has been gaining attention, the technical efficacies of which are being ascertained [24, 25]. Depending on the location of metastases, using the TomoDirect mode could be suitable for reducing low-dose exposure outside the PTV, which could prevent a decrease in host immunity.

The TomoDirect mode has been shown to be viable for multiple metastases in a relatively short treatment time [26]. Lastly, although we evaluated PS changes by treatment, assessment of the quality of life before and after treatment would have been desirable, since all patients were treated with palliative intent; this should be considered in future studies.

Conclusion

This study demonstrated that helical tomotherapy for CRMM/CUMM is a potentially feasible and effective treatment with acceptable adverse events. Further clinical studies are warranted in order to evaluate the overall benefit of this treatment.

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Conflict of interest

None declared.

Funding

None declared.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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