# Role of high-dose salvage radiotherapy for oligometastases of the localised abdominal/pelvic lymph nodes: A retrospective study

**Makoto Ito** ( itou.makoto.292@mail.aichi-med-u.ac.jp )
Aichi Cancer Center Hospital, Aichi Medical University Hospital https://orcid.org/0000-0001-7733-1594
**Takeshi Kodaira**
Aichi Cancer Center Hospital
**Yutaro Koide**
Aichi Cancer Center Hospital
**Takahito Okuda**
Toyota Memorial Hospital
**Shinichiro Mizumatsu**
Aoyama Hospital
**Yukihiko Oshima**
Aichi Medical University Hospital
**Arisa Takeuchi**
Aichi Medical University Hospital
**Toshie Mori**
Aichi Medical University Hospital
**Souichirou Abe**
Aichi Cancer Center Hospital, Aichi Medical University Hospital
**Ayumi Asai**
Aichi Medical University Hospital
**Kojiro Suzuki**
Aichi Medical University Hospital

**Research article**

**Keywords:** Oligometastasis; Oligo-recurrence; Radiotherapy; Stereotactic body radiotherapy (SBRT); Lymph node

**Posted Date:** October 5th, 2019

**DOI:** https://doi.org/10.21203/rs.2.15725/v1

**Version of Record:** A version of this preprint was published at BMC Cancer on June 9th, 2020. See the published version at https://doi.org/10.1186/s12885-020-07033-7.

# Abstract

Background: Abdominal/pelvic lymph node (LN) oligometastasis is a pattern of failure that is observed occasionally. Although radiotherapy may be useful for salvage therapy, the optimal prescription dose has not yet been clarified. This study assessed the efficacy of high-dose radiotherapy. Methods: Between 2008 and 2018, the medical records of 113 patients with 1–5 abdominal/pelvic LN oligometastases treated with definitive radiotherapy at 4 institutes were retrospectively analysed. The exclusion criteria were non-epithelial tumours, uncontrolled primary lesions, palliative intent, and re-irradiation. The prescription dose was evaluated by using the equivalent dose in 2 Gy fractions (EQD2); patients with EQD2 ≥60 Gy were the high-dose group. Kaplan-Meier analysis was used to evaluate the endpoints of overall survival (OS), local control (LC), and progression-free survival (PFS). Univariate log-rank and multivariate Cox proportional hazards model analyses were performed to clarify predictive factors for each endpoint. Toxicity rates were compared between the high-dose and low-dose groups. Results: The primary tumour sites included the colorectum (n = 28), uterine cervix (n = 27), endometrium (n = 15), and ovaries (n = 10). The 2-year OS, LC, and PFS rates were 63.1%, 59.7%, and 19.4%, respectively. On multivariate analyses, solitary oligometastasis, high-dose radiotherapy, and long disease-free interval were associated with significantly favourable OS (hazard ratio [HR]: 0.48, p = 0.02), LC (HR: 0.93, p < 0.001), and PFS (HR: 0.59, p = 0.01), respectively. Although high-dose radiotherapy did not significantly improve the 2-year OS of the entire cohort (74.8% vs. 52.7% in the high-dose vs. low-dose group; p = 0.08), it showed a significant difference on subgroup analysis for solitary oligometastasis (88.8% vs. 56.3%; p = 0.009). Late grade ≥3 toxicity included ileus in 7 cases (6%) and gastrointestinal bleeding in 4 (4%). There was no significant association between the irradiation dose and toxicity incidence. Conclusions: Salvage radiotherapy was feasible for oligometastasis of the abdominal/pelvic LNs. For solitary oligometastasis, the high-dose group showed favourable results considering LC and OS.


# Background

The standard treatment for recurrent cancer is systemic chemotherapy; however, local therapy is often used to treat a small number of recurrent tumours. In 1995, oligometastases were defined as metastatic disease confined to a limited number of sites that were amenable to potentially curable local therapy such as surgery or radiotherapy [1].

Abdominal/pelvic lymph node (LN) oligometastasis is a pattern of failure that is observed occasionally, and it is usually unresectable [2, 3]. Although radiotherapy may be the treatment choice for salvage therapy, treatment is very difficult because abdominal/pelvic LNs move randomly owing to the effect of breathing and being located close to the gastrointestinal tract. Therefore, only a few studies have evaluated the use of radiotherapy for abdominal/pelvic LN oligometastasis, and the efficiency and safety have not been established [4, 5]. In particular, the optimal prescription dose for radiotherapy has not yet been clarified.

Along with the increasing use of high-precision irradiation technology, reports regarding the use of high-dose radiotherapy for oligometastasis are also increasing [6, 7]. Recently, the SABR-COMET trial, a randomised phase 2 open-label trial, compared radiotherapy and standard of care palliative treatment for oligometastasis [8]. According to the trial, stereotactic ablative radiotherapy (SABR) was associated with improved overall survival (OS). The median OS was 28 months in the control group versus 41 months in the SABR group (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.30–1.10; p = 0.090). However, treatment-related death was observed in 4.5% of patients; therefore, researchers concluded that high-dose radiotherapy should be adapted for those who would show a survival benefit. In addition, as various irradiation regions were included in the trial, further study is required to evaluate the balance between the risks and benefits of localised irradiation. Moreover, it is important to clarify the role of high-dose radiotherapy especially in locations where radiotherapy is difficult to perform, such as abdominal/pelvic LNs.

Therefore, in this study, we retrospectively reviewed the data of patients with oligometastases in the abdominal/pelvic LNs and investigated the optimal method of salvage radiotherapy. Moreover, we assessed the survival benefit of high-dose radiotherapy.

# Methods

Ethics approval and study design

The institutional review board of Aichi Medical University Hospital, Japan, approved this retrospective observational study (application number 2018-H211). This study was also examined and approved by Aichi Cancer Center Hospital, Toyota Memorial Hospital, and Aoyama Hospital, Japan. The study was conducted in accordance with the tenets of the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all patients.

Patients

Between January 2008 and April 2018, the medical records of patients treated with radiation to their abdominal/pelvic LN with a definitive intent were retrospectively reviewed from 4 institutes. In this study, patients aged 20 to 85 years who developed localised abdominal/pelvic oligometastases in 1–5 LNs after initial treatment were included. The exclusion criteria were as follows: patients with non-epithelial tumours, those with uncontrolled primary lesions, patients treated with palliative intent, those with a short follow-up (<3 months), and those who received re-irradiation. Finally, a total of 113 patients were included.

As initial treatment, 101 patients underwent surgery while the remaining 12 patients received radiotherapy. Before undergoing salvage radiotherapy, all the patients underwent whole-body computed tomography (CT) and/or positron emission tomography-CT (PET-CT) to confirm that there were no oligometastases other than those in the abdominal/pelvic LNs. Owing to the presence of

oligometastases after initial treatment, 91 patients underwent chemotherapy and 33 underwent concurrent chemotherapy and salvage radiotherapy.

## Radiotherapy

A linear accelerator or CyberKnife (CK) was used for salvage radiotherapy. Patients were immobilised in the supine position, and a CT scan with a 1–5-mm slice thickness was obtained for treatment planning. For high-precision radiotherapy, such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), an external vacuum-type body mould and/or a thermoplastic body mask were used for precise fixation. To avoid large displacement of the gastrointestinal tract during daily treatment, planning CT was performed with the patient in a fasting state, especially when the target was near the stomach. The clinical target volume (CTV) was defined as the gross tumour volume with a 0–0.5-cm margin considering microscopic disease and the anatomical structure. The planning target volume (PTV) was defined as the CTV with a 0.3–1.0-cm margin, considering the internal motion and the setting error in each institution. Moreover, the PTV margin was suitably adjusted to protect organs at risk (OARs). While using linear accelerators, the prophylactic CTV was contoured as the nodal area that included the regional LNs close to the gross tumour. The prophylactic PTV was defined as the prophylactic CTV with a 0.5-cm margin. The main OARs were evaluated by using the equivalent dose in 2 Gy fractions (EQD2) at $\alpha/\beta = 3$, including the stomach, small bowel, large bowel, kidneys, and spinal cord. For 3-dimensional conformal radiotherapy (3DCRT), dose constraints were defined as follows: the maximum doses to the stomach and small bowel, large bowel, and spinal cord were 52 Gy, 62 Gy, and 50 Gy, respectively. In contrast, dose constraints for high-precision radiotherapy were as follows: the stomach and small bowel volumes received 54 Gy (V54) for <3 $cm^3$, the large bowel received V64 for <3 $cm^3$, the kidneys received V50 of <33%, and the maximum dose to the spinal cord was <52 Gy.

### *Linear accelerator*

Both the target volume and normal organ structures were contoured using treatment planning systems (either XiO, Electa, CMS, St Louis, MO, USA or Eclipse, Varian Medical System, Palo Alto, CA, USA). All the patients were treated with 10 MV photons, using the 3DCRT or IMRT technique. Patients treated with 3DCRT (n = 47) were prescribed 39.6–70 Gy in 15–37 fractions to the PTV isocenter; the median dose per fraction was 2 Gy (range, 1.8–3 Gy) and the median EQD2 was 50 Gy. In contrast, patients treated with IMRT (n = 22) received 45–70 Gy in 15–35 fractions to cover the PTV with a 95% dose; the median dose per fraction was 2 Gy (range, 1.8–3.5 Gy) and the median EQD2 was 60 Gy. The prophylactic PTV received almost 70–80% of the PTV dose in both 3DCRT and IMRT.

### *CyberKnife*

CK G4 and M6 (Accuray Inc., Sunnyvale CA, USA) and B were used for SBRT. In addition to using the IRIS variable collimator, the InCise multileaf collimator was used and contributed to reduction in the treatment time for CK-M6. Generally, the tumour was followed-up by using the fiducial-less tracking capability of CK under free breathing. Using a 6-MV photon beam, all treatment plans were generated using the Multiplan

treatment planning software (Accuray Inc., Sunnyvale, CA, USA). The dose was prescribed for covering the PTV, ranging from 21 to 60 Gy, and it was fractionated 2 to 30 times with a 60% to 90% isodose line; the median dose per fraction was 6 Gy (range, 4–13.5 Gy) and the median EQD2 was 63.5 Gy.

Data collection and statistical analyses

As the fractionation schedules and dose evaluation method were not standardised, the dose-volume histograms of all the cases were confirmed. Then, the prescription dose of all the cases was re-evaluated by using the EQD2 (D50%). The median EQD2 for all the patients was 59.7 Gy (range, 40.3–101.4 Gy); using the median value as the cut-off, the high-dose group was defined as patients with EQD2 ≥ 60 Gy and the low-dose group was defined as those with EQD2 < 60 Gy.

According to the Response Evaluation Criteria in Solid Tumors, the initial tumour response was evaluated based on CT scans [9]. The first follow-up visit was scheduled within 1–4.5 months (median, 2.2 months) from the end of treatment. The disease-free interval (DFI) was defined as the time since the last treatment to salvage radiotherapy. OS was measured from the start date of salvage radiotherapy to the date of the last follow-up or death from any cause. Local control (LC) was defined as progression in the target LN as evaluated on CT or PET-CT images. Progression-free survival (PFS) was calculated from the start date of salvage radiotherapy until the date of disease progression or death from any cause. The OS, LC, and PFS rates were estimated using the Kaplan-Meier method [10]. Log-rank tests were used to compare the estimates of subgroups on univariate analysis. The Cox proportional hazards model was used for multivariate analysis. P-values < 0.05 were statistically significant. Factors that showed a difference with $p < 0.1$ on univariate analysis were entered into the multivariate analysis. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 5.0), and grade ≥ 3 events were counted. All statistical analyses were performed with EZR version 1.33 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), based on the R and R commander [11].

# Results

Patient characteristics

The median follow-up period for all the included 113 patients was 17.8 months (range, 3.7–109.8 months). At the time of analysis, 46 patients had died. The median follow-up time for the remaining surviving patients was 23.7 months (range, 4.0–109.8 months). The patient characteristics are listed in Table 1. Regarding the primary site, the number of cases of colorectal and ovarian cancer was high in the high-dose group, while the number of cases of uterine cervix and endometrium cancer was high in the low-dose group. There were no patients with prostate cancer. Significantly more patients were treated with SBRT and IMRT in the high-dose group. Prophylactic nodal irradiation and concurrent chemotherapy were often performed with 3DCRT. The median EQD2 to the PTV in the high-dose group, the low-dose group, and all patients was 66.6 Gy (range, 60.4–101.4 Gy), 50 Gy (range, 40.3–59.8 Gy), and 59.7 Gy (range, 40.3–101.4 Gy), respectively.

## Treatment outcomes

The 2-year OS, LC, and PFS rates were 63.1% (95% CI: 52.1–72.2%), 59.7% (95% CI: 48.8–69.0%), and 19.4% (95% CI: 12.2–27.8%), respectively. A total of 67 patients (59.3%) were alive at the time of analysis: 36 were alive without disease and 31 were alive with disease. Only 3 patients died of other causes: pneumonia (n = 2) and owing to the adverse effects of a steroid pulse for myelitis (n = 1). Regarding the initial response in the entire group (n = 113), 23 patients showed a complete response (CR), 66 showed a partial response (PR), 19 had stable disease, and 5 had progressive disease. There was no significant difference in the CR/PR rate between the high-dose and low-dose groups (80.0% vs. 77.6%, p = 0.82).

The results of univariate analysis for the OS, LC, and PFS rates are shown in Table 2. Neither the primary site nor the pathological type significantly contributed to any endpoint. A longer DFI (≥ 8.5 months) was associated with significantly better 2-year OS (72.5% vs. 53.4%, p = 0.04) and LC (24.9% vs. 13.5%, p = 0.01). The number of LNs was a prognostic factor, and solitary oligometastasis showed favourable OS (73.3% vs. 51.3%, p = 0.01) and LC (70.4% vs. 47.8%, p = 0.01) compared with multiple metastasis. In contrast, the size of the LNs did not show apparent correlation with any parameters. Although the high-dose group had significantly better LC than the low-dose group (74.9% vs. 45.2%, p < 0.001), there was no significant difference in OS between the groups.

On multivariate analyses, solitary oligometastasis, high-dose radiotherapy, and long DFI were associated with significantly favourable OS (HR: 0.48, 95% CI: 0.27–0.87, p = 0.02), LC (HR: 0.93, 95% CI: 0.90–0.96, p < 0.001), and PFS (HR: 0.59, 95% CI: 0.39–0.90, p = 0.01), respectively (Table 3).

## Subgroup analysis for solitary oligometastasis

High-dose radiotherapy did not significantly improve the 2-year OS on analysis of the entire cohort. However, on subgroup analysis, solitary oligometastasis, compared with multiple oligometastases, was a significantly favourable factor for 2-year OS (88.8% vs. 56.3%, p = 0.009, Fig. 1a) but not for 2-year LC (83.2% vs. 54.2%, p = 0.01, Fig. 1b). The characteristics of patients with only solitary oligometastasis are shown in Table 4. There was no significant bias in the important background factors that tended to contribute to OS on univariate analysis.

## Toxicities

There was no significant difference in the incidence of grade ≥3 toxicities between the high-dose and low-dose groups. Among acute toxicities, grade 3 diarrhoea, stomach-ache, and loss of appetite were observed in 3 (3%), 1 (1%), and 1 patient (1%), respectively. No grade ≥ 4 toxicity was observed.

Among late toxicities, grade 3 ileus developed in 7 patients (6%), with 4 (7%) in the high-dose group and 3 (5%) in the low-dose group. Of those 7 patients, 6 (86%) had received prophylactic nodal irradiation and 2 (29%) had received re-irradiation. After being diagnosed with ileus, 3 of the 7 patients (43%) underwent elective bowel resection or synectenterotomy. Grade ≥3 gastrointestinal bleeding was observed in 4 patients (4%). Of the 4 patients, 2 showed grade 3 gastrointestinal bleeding and both had received re-

irradiation, while the remaining 2 patients had grade 4 and grade 5 gastrointestinal bleeding, respectively, with 1 patient each in the high-dose and low-dose groups. Although both these patients were identified as having PR as the initial response, disease progression was again observed during follow-up. Chemotherapy or re-irradiation could not be administered again, and best supportive care was performed. Accordingly, the cause of serious gastrointestinal bleeding for these 2 patients was clinically interpreted to be tumour progression instead of treatment-related.

Re-irradiation was performed for a total of 6 patients after salvage radiotherapy: 2 patients in the high-dose group and the remaining 4 in the low-dose group. As described above, 4 of the 6 patients (67%) presented with grade 3 late toxicity after re-irradiation, with 2 in the high-dose group and the remaining 2 in the low-dose group.

# Discussion

In the current retrospective study of 113 patients with abdominal/pelvic LNs recurrent cancer and oligometastasis from 4 institutions, the 2-year OS, LC, and PFS rates were 63.1%, 59.7%, and 19.4%, respectively. Among grade ≥3 late toxicities, ileus was observed in 7 patients (6%) and gastrointestinal bleeding in 4 (4%). The efficacy and safety were similar to those observed in previous studies [4, 5, 12-14].

In the current study, the high-dose group (n = 55) had significantly improved 2-year LC rates (74.9% in the high-dose group vs. 45.2% in the low-dose group; $p < 0.001$); however, improvement in 2-year OS did not reach statistical difference (74.8% in the high-dose group vs. 52.7% in the low-dose group; $p = 0.08$). A reason for this might be that our cohort included patients with a poor prognosis, which is a bias accompanying the retrospective nature of the study. One of the important prognostic factors is the condition of the primary lesion. Niibe et al. defined the concept of oligo-recurrence as the state in which patients with cancer have ≤5 metastatic or recurrent lesions with a controlled primary lesion; they showed better prognosis than metastatic cases with active primary lesions [15]. Accordingly, in the current study, the inclusion of only patients with oligometastases was insufficient for analysis. The effect of the tumour burden was observed in ≤5 LNs, and the number of oligometastases seems to be a very important prognostic factor. Nakamura et al. performed a retrospective study of 76 patients with oligo-recurrent lesions in the lungs and liver treated with SBRT. In their study, a single metastatic lesion was a significant factor of good PFS ($p = 0.008$) and a favourable OS ($p = 0.053$) [16]. Similarly, in the current study, the presence of solitary oligometastasis was associated with significantly favourable OS (HR 0.48, 95% CI 0.27–0.87; $p = 0.02$). Furthermore, on subgroup analysis of solitary oligometastasis, high-dose radiotherapy significantly improved LC ($p = 0.01$) and OS ($p = 0.009$). Thus, there is scope for improvement in the OS of patients with these favourable prognoses by improving LC using high-dose radiotherapy.

The 2-year PFS was very poor (19.4%) regardless of the administration of prophylactic nodal irradiation. Although chemotherapy may contribute to tumour control, the precise advantage could not be determined because of the effect of bias in our study. Moreover, regarding the effectiveness of previous or adjuvant

chemotherapy, there is no consensus till date [14, 16, 17]. Further individual analysis is required to clarify the efficacy of chemotherapy according to the primary disease. The DFI may be a good indicator of disease recurrence. Gandhidasan et al. reported 132 patients treated with SABR for oligometastasis [6]. In their analysis, a long DFI was significantly associated with favourable recovery from widespread disease (HR: 0.91, 95% CI: 0.82–1.01, p = 0.041). Similarly, in the current study, a long DFI was associated with significantly favourable PFS (HR: 0.59, 95% CI: 0.39–0.90, p = 0.01). Therefore, careful follow-up will be required especially in patients with a short DFI.

High-dose radiotherapy was as safe as low-dose radiotherapy, without any significant increase in the incidence of adverse events. However, re-irradiation is a high-risk treatment. Of 6 patients who received re-irradiation, 4 patients (67%) presented with grade ≥3 late toxicity. As the incidence of adverse events was high, we cannot recommend re-irradiation to the abdominal/pelvic LNs. In addition, prophylactic irradiation may be associated with the risk of ileus and its use should be considered carefully; however, as surgery is also associated with the risk of ileus, the use of prophylactic irradiation is not a major issue per se. Moreover, in the current study, no treatment-related deaths were observed. However, in the SABR-COMET trial, the incidence of adverse events of grade ≥2 increased by 20%, and 4.5% of patients in the SABR group experienced treatment-related death [8]. Accordingly, we should determine the survival benefit of using salvage radiotherapy considering the risk of adverse events.

The current study was limited by its retrospective nature and multi-institution analysis. Although our cohort did not include patients with prostate cancer, which could have led to bias, we included patients with multiple cancer types. Thus, we cannot ignore the histology-specific differences in tumour biology. Furthermore, the treatment protocol was not constant, and the number of patients and the follow-up period were insufficient. Accordingly, future trials should evaluate the treatment efficacy in a cohort of patients with the same tumour histology and using the same initial treatment protocol. Moreover, another limitation was the mechanical diversity. Although all the plans were reappraised by using EQD2, linear accelerators and the CK system have fundamentally different characteristics [18]. Thus, the optimal irradiation dose should be evaluated using any one of the devices according to a single protocol.

# Conclusions

Salvage radiotherapy was a feasible and safe approach for oligometastasis of the abdominal/pelvic LNs, especially in patients treated with high-dose radiotherapy (EQD2 ≥ 60 Gy), as we observed excellent LC. For OS, the number of LNs was the most important factor, and solitary oligometastasis is an indicator of good prognosis. In patients with solitary oligometastasis, high-dose radiotherapy may play an important role in improving LC and OS. Accordingly, considering these promising results, a prospective study in a more homogeneous patient population is required to clarify the survival benefits of salvage high-dose radiotherapy.

# Abbreviations

3DCRT: 3-dimensional conformal radiotherapy

CI: confidence interval

CK: CyberKnife

CR: complete response

CT: computed tomography

CTV: clinical target volume

DFI: disease-free interval

EQD2: equivalent dose in 2 Gy fractions

HR: hazard ratio

IMRT: intensity-modulated radiotherapy

LC: local control

LN: lymph node

OARs: organs at risk

OS: overall survival

PET-CT: positron emission tomography-computed tomography

PFS: progression-free survival

PR: partial response

PTV: planning target volume

SABR: stereotactic ablative radiotherapy

SBRT: stereotactic body radiotherapy

# Declarations

### Ethics approval and consent to participate

All procedures involving human participants were in accordance with the ethical standards of the institutional research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Consent for publication

All patients gave written informed consent.

### Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.


### Funding

This work was partially supported by the 24th General Assembly of the Japanese Association of Medical Sciences (grant number 150-2019-3-05).


### Authors' contributions

MI conceived the study, performed all analyses, and drafted the manuscript, supported by TK, TO, and SM. YK, YO, AT, TM, SA, AA, and KS were involved in the study design and contributed significantly to the editing of the manuscript. All authors read and approved the final manuscript.


### Acknowledgements

A part of the study results was presented at the 61st Annual Meeting of American Society of Radiation Oncology (Chicago, 2019).

We would like to thank Editage (www.editage.com) for English language editing.


## References


1. Hellman S, Weichselbaum RR: **Oligometastases.** *J Clin Oncol* 1995, **13:**8-10.

2. Lee J, Yoon HI, Rha SY, Hyung WJ, Lee YC, Lim JS, Kim HS, Koom WS: **Integration of radiotherapy and chemotherapy for abdominal lymph node recurrence in gastric cancer.** *Clin Transl Oncol* 2017, **19:**1268-1275.
3. Ito M, Kodaira T, Tachibana H, Tomita N, Makita C, Koide Y, Kato D, Abe T, Muro K, Tajika M, et al: **Clinical results of definitive chemoradiotherapy for cervical esophageal cancer: Comparison of failure pattern and toxicities between intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy.** *Head Neck* 2017, **39:**2406-2415.
4. Jereczek-Fossa BA, Piperno G, Ronchi S, Catalano G, Fodor C, Cambria R, Fossati Ing P, Gherardi F, Alterio D, Zerini D, et al: **Linac-based stereotactic body radiotherapy for oligometastatic patients with single abdominal lymph node recurrent cancer.** *Am J Clin Oncol* 2014, **37:**227-233.
5. Franzese C, Cozzi L, Franceschini D, D'Agostino G, Comito T, De Rose F, Navarria P, Mancosu P, Tomatis S, Fogliata A, Scorsetti M: **Role of Stereotactic Body Radiation Therapy with Volumetric-Modulated Arcs and High-Intensity Photon Beams for the Treatment of Abdomino-Pelvic Lymph-Node Metastases.** *Cancer Invest* 2016, **34:**348-354.
6. Gandhidasan S, Ball D, Kron T, Bressel M, Shaw M, Chu J, Chander S, Wheeler G, Plumridge N, Chesson B, et al: **Single Fraction Stereotactic Ablative Body Radiotherapy for Oligometastasis: Outcomes from 132 Consecutive Patients.** *Clin Oncol (R Coll Radiol)* 2018, **30:**178-184.
7. Fumagalli I, Bibault JE, Dewas S, Kramar A, Mirabel X, Prevost B, Lacornerie T, Jerraya H, Lartigau E: **A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases.** *Radiat Oncol* 2012, **7:**164.
8. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, Mulroy L, Lock M, Rodrigues GB, Yaremko BP, et al: **Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial.** *Lancet* 2019, **393:**2051-2058.
9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, et al: **New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).** *Eur J Cancer* 2009, **45:**228-247.
10. Kaplan EL MP: **Nonparametric estimation from incomplete observations.** *J Am Stat Assoc* 1958, **53:**457-481.
11. Kanda Y: **Investigation of the freely available easy-to-use software 'EZR' for medical statistics.** *Bone Marrow Transplant* 2013, **48:**452-458.
12. Bignardi M, Navarria P, Mancosu P, Cozzi L, Fogliata A, Tozzi A, Castiglioni S, Carnaghi C, Tronconi MC, Santoro A, Scorsetti M: **Clinical outcome of hypofractionated stereotactic radiotherapy for abdominal lymph node metastases.** *Int J Radiat Oncol Biol Phys* 2011, **81:**831-838.
13. Corvo R, Lamanna G, Vagge S, Belgioia L, Bosetti D, Aloi D, Timon G, Bacigalupo A: **Once-weekly stereotactic radiotherapy for patients with oligometastases: compliance and preliminary efficacy.** *Tumori* 2013, **99:**159-163.

14. Alongi F, Fogliata A, Clerici E, Navarria P, Tozzi A, Comito T, Ascolese AM, Clivio A, Lobefalo F, Reggiori G, et al: **Volumetric modulated arc therapy with flattening filter free beams for isolated abdominal/pelvic lymph nodes: report of dosimetric and early clinical results in oligometastatic patients.** *Radiat Oncol* 2012, **7:**204.
15. Niibe Y, Chang JY: **Novel insights of oligometastases and oligo-recurrence and review of the literature.** *Pulm Med* 2012, **2012:**261096.
16. Nakamura M, Hashimoto N, Mayahara H, Uezono H, Harada A, Nishikawa R, Matsuo Y, Kawaguchi H, Nishimura H: **Additional chemotherapy improved local control and overall survival after stereotactic body radiation therapy for patients with oligo-recurrence.** *Radiat Oncol* 2018, **13:**75.
17. Klement RJ, Guckenberger M, Alheid H, Allgauer M, Becker G, Blanck O, Boda-Heggemann J, Brunner T, Duma M, Gerum S, et al: **Stereotactic body radiotherapy for oligo-metastatic liver disease - Influence of pre-treatment chemotherapy and histology on local tumor control.** *Radiother Oncol* 2017, **123:**227-233.
18. Ito M, Kawamura T, Mori Y, Mori T, Takeuchi A, Oshima Y, Nakamura K, Aoyama T, Kaneda N, Ishiguchi T, Mizumatsu S: **Dose distributions of high-precision radiotherapy treatment: A comparison between the CyberKnife and TrueBeam systems.** *International Journal of Radiation Research* 2018, **16:**395-402.

# Tables

Table 1. Patient characteristics.

| Characteristic | | High dose group (n = 55) | Low dose group（n = 58） | All cases (n = 113) |
|---|---|---|---|---|
| Age (years) | Median | 67 | 62.5 | 65 |
| | Range | 49-83 | 36-83 | 36-83 |
| Gender | Male | 24 | 21 | 45 |
| | Female | 31 | 37 | 68 |
| Performance status | 0 | 35 | 33 | 68 |
| | 1 | 18 | 24 | 42 |
| | 2 | 2 | 1 | 3 |
| Primary site | Colorectum | 20 | 8 | 28 |
| | Uterine cervix | 9 | 18 | 27 |
| | Endometrium | 5 | 10 | 15 |
| | Ovary | 8 | 2 | 10 |
| | Urothelial | 4 | 4 | 8 |
| | Others | 9 | 16 | 25 |
| Histopathology | Adenocarcinoma | 41 | 31 | 72 |
| | Squamous cell carcinoma | 10 | 23 | 33 |
| | Others | 4 | 4 | 8 |
| Initial category | T-category 1:2:3:4 | 13:20:18:4 | 18:13:19:8 | 31:33:37:12 |
| | N-category positive | 32 | 32 | 64 |
| Duration from initial diagnosis (months) | Median | 25.4 | 22.4 | 24.1 |
| | Range | 2.9-102.4 | 1.9-100.4 | 1.9-102.4 |
| DFI (months) | Median | 8.7 | 8.3 | 8.5 |
| | Range | 0.6-64.4 | 0.5-86.6 | 0.5-86.6 |
| Radiation therapy method | 3DCRT | 12 | 35 | 47 |
| | SBRT&IMRT | 43 | 23 | 66 |
| LN site | Para-aortic | 29 | 43 | 72 |
| | Iliac | 8 | 10 | 18 |
| | Presacral | 9 | 3 | 12 |
| | Obturator | 9 | 2 | 11 |
| Extra-regional LN for primary site | no | 37 | 28 | 65 |
| | yes | 18 | 30 | 48 |
| Number of lymph node | 1 | 33 | 28 | 61 |
| | 2-5 | 22 | 30 | 52 |
| LN size (cm) | Median | 2 | 2 | 2 |
| | Range | 1-5.5 | 1-5 | 1-5.5 |
| Prophylactic nodal irradiation | no | 40 | 29 | 69 |
| | yes | 15 | 29 | 44 |
| Concurrent chemotherapy | no | 43 | 37 | 80 |

| | | | | |
|---|---|---|---|---|
| | yes | 12 | 21 | 33 |
| EQD2 (Gy) | Median | 66.6 | 50 | 59.7 |
| | Range | 60.4-101.4 | 40.3-59.8 | 40.3-101.4 |
| Follow-up time of entire group (months) | Median | 20.2 | 15.9 | 17.8 |
| | Range | 5.8-84.7 | 3.7-109.8 | 3.7-109.8 |
| Follow-up time in surviving patients (months) | Median | 23 | 24.2 | 23.7 |
| | Range | 7.6-84.7 | 4.0-109.8 | 4.0-109.8 |

n, number of patients; LN, lymph node; DFI, disease-free interval; 3DCRT, 3-dimentional conformal radiation therapy; SBRT, Stereotactic Body Radiation Therapy; IMRT, intensity-modulated radiation therapy; EQD2, equivalent dose in 2 Gy fraction.

Table 2. Univariate analysis of prognostic factors of each endpoint.

| Factor | | 2y-OS | | 2y-LC | | 2y-PFS | |
|---|---|---|---|---|---|---|---|
| | | % | *P* | % | *P* | % | *P* |
| Age (years) | < 66 (n = 57) | 56.6 | 0.21 | 50.8 | 0.04 | 16.2 | 0.150 |
| | ≥ 66 (n = 56) | 71.3 | | 69.2 | | 22.5 | |
| Gender | Male (n = 45) | 55.1 | 0.11 | 59.1 | 0.42 | 21.1 | 0.97 |
| | Female (n = 68) | 68.2 | | 60.3 | | 17.8 | |
| Performance status | 0 (n = 68) | 69.2 | 0.49 | 61.6 | 0.97 | 19.1 | 0.93 |
| | 1-2 (n = 45) | 54.5 | | 56.7 | | 19.9 | |
| Primary site | Colorectum | 73.5 | 0.49 | 64.1 | 0.79 | 21.9 | 0.96 |
| | Uterine cervix | 88.4 | | 60.7 | | 25.8 | |
| | Endometrium | 54.4 | | 59.3 | | 23.3 | |
| Pathological type | Adenocarcinoma | 66.1 | 0.86 | 59.7 | 0.37 | 19.4 | 0.76 |
| | Squamous cell carcinoma | 67.2 | | 60.4 | | 23.5 | |
| Initial T-category | T1-2 (n = 64) | 68.7 | 0.07 | 64.2 | 0.61 | 22.9 | 0.69 |
| | T3-4 (n = 49) | 56.0 | | 54.7 | | 16.2 | |
| Initial N-category | N negative (n = 49) | 66.6 | 0.09 | 64.2 | 0.72 | 23.8 | 0.61 |
| | N positive (n = 64) | 60.2 | | 56.1 | | 16.6 | |
| Duration from initial diagnosis (months) | < 24.1 (n = 57) | 60.9 | 0.94 | 63.8 | 0.43 | 20.7 | 0.59 |
| | ≥ 24.1 (n = 56) | 63.9 | | 54.9 | | 18.0 | |
| DFI (months) | < 8.5 (n = 57) | 53.4 | 0.04 | 52.4 | 0.30 | 13.5 | 0.01 |
| | ≥ 8.5 (n = 56) | 72.5 | | 66.0 | | 24.9 | |
| Radiation therapy method | 3DCRT (n = 47) | 56.1 | 0.49 | 50.9 | 0.01 | 26.0 | 0.82 |
| | IMRT&SBRT (n = 66) | 67.9 | | 64.9 | | 14.5 | |
| Extra-regional LN for primary site | no (n = 65) | 65.5 | 0.07 | 60.6 | 0.92 | 21.9 | 0.45 |
| | yes (n = 48) | 59.7 | | 57.7 | | 15.3 | |
| Number of LN | 1 (n = 61) | 73.3 | 0.01 | 70.4 | 0.01 | 25.1 | 0.08 |
| | 2-5 (n = 52) | 51.3 | | 47.8 | | 12.9 | |
| LN size (cm) | < 2 (n = 62) | 71.6 | 0.17 | 66.0 | 0.06 | 18.1 | 0.68 |
| | ≥ 2 (n = 51) | 52.0 | | 52.4 | | 20.7 | |
| Prophylactic nodal irradiation | no (n = 69) | 63.7 | 0.69 | 63.3 | 0.41 | 15.8 | 0.80 |
| | yes (n = 44) | 61.4 | | 54.9 | | 28.2 | |
| Concurrent chemotherapy | no (n = 80) | 63.5 | 0.92 | 58.8 | 0.69 | 11.0 | 0.20 |
| | yes (n = 33) | 59.5 | | 60.8 | | 36.1 | |
| EQD2 (Gy) | < 60 (n = 58) | 52.7 | 0.08 | 45.2 | <0.001 | 21.1 | 0.87 |
| | ≥ 60 (n = 55) | 74.8 | | 74.9 | | 17.5 | |

n, number of patients; OS, overall survival rate; LC, local control rate;
PFS, progression-free survival rate; DFI, disease-free interval; 3DCRT, 3-dimentional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, Stereotactic Body Radiation Therapy; LN, lymph node; EQD2, equivalent dose in 2 Gy fraction.

Table 3. Multivariate analysis of each endpoint.

| Factor | | OS | | | LC | | | PFS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Age (years) | < 66 vs ≥ 66 | | | | 0.99 | (0.97-1.02) | 0.69 | | | |
| Initial T-category | T1-2 vs T3-4 | 1.57 | (0.86-2.83) | 0.14 | | | | | | |
| Initial N-category | N negative vs N positive | 1.33 | (0.69-2.53) | 0.39 | | | | | | |
| DFI (months) | < 8.5 vs ≥ 8.5 | 0.99 | (0.99-1.01) | 0.11 | | | | 0.59 | (0.39-0.90) | 0.01 |
| Radiation therapy method | 3DCRT vs IMRT&SBRT | | | | 0.95 | (0.46-1.97) | 0.89 | | | |
| Extra-regional LN for primary site | no vs yes | 0.87 | (0.45-1.67) | 0.67 | | | | | | |
| Number of LN | 1 vs 2-5 | 0.48 | (0.27-0.87) | 0.02 | 0.56 | (0.30-1.03) | 0.06 | 0.71 | (0.47-1.08) | 0.11 |
| LN size (cm) | < 2 vs ≥ 2 | | | | 1.52 | (0.83-2.80) | 0.18 | | | |
| EQD2 (Gy) | < 60 vs ≥ 60 | 0.97 | (0.95-1.01) | 0.09 | 0.93 | (0.90-0.96) | <0.001 | | | |

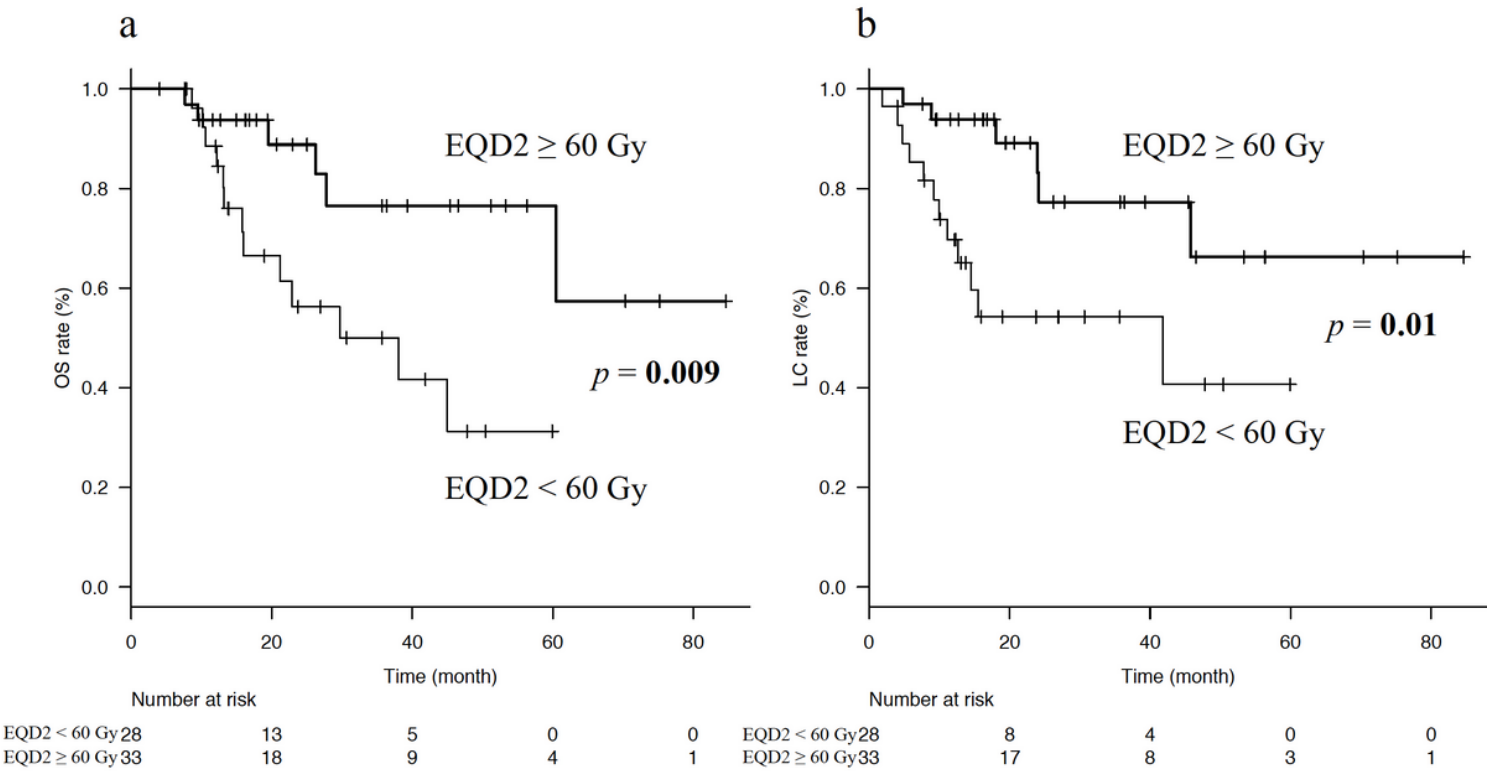
HR,hazard ratio; CI, confidence interval; OS, overall survival rate; LC, local control rate;
PFS, progression-free survival rate; DFI, disease-free interval; 3DCRT, 3-dimentional conformal radiation therapy;
IMRT, intensity-modulated radiation therapy; SBRT, Stereotactic Body Radiation Therapy; LN, lymph node;
EQD2, equivalent dose in 2 Gy fraction.

Table 4.The extract of patient characteristics in a solitary oligometastasis group.

| Characteristic | | High dose group (n = 33) | Low dose group (n = 28) |
|---|---|---|---|
| Initial category | T-category 1:2:3:4 | 11:10:11:1 | 6:8:11:3 |
| | N-category positive | 17 | 13 |
| DFI (months) | Median | 8.7 | 9.5 |
| | Range | 0.6-64.4 | 0.5-86.6 |
| Extra-regional LN for primary site | yes | 11 | 12 |
| Follow-up time in surviving patients (months) | Median | 22.7 | 23.8 |
| | Range | 7.6-84.7 | 4.0-60.0 |

n, number of patients; DFI, disease-free interval; LN, lymph node.

# Figures




## Figure 1

Kaplan-Meier curves in the solitary oligometastasis groups. Kaplan-Meier curves for OS (a) and LC (b) in the solitary oligometastasis groups divided by EQD2. OS, overall survival; LC, local control; EQD2, equivalent dose in 2 Gy fractions