Efficacy, toxicities, and prognostic factors of stereotactic body radiotherapy for unresectable liver metastases

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A B S T R A C T

Introduction: This study aims to determine the outcomes of stereotactic body radiotherapy (SBRT) for liver metastases in patients not eligible for surgery.

Methods: This study included 31 consecutive patients with unresectable liver metastases who received SBRT between January 2012 and December 2017; 22 patients had primary colorectal cancer and nine patients had primary non-colorectal cancer. Treatments ranged from 24 Gy to 48 Gy in 3 to 6 fractions over 1 to 2 weeks. Survival, response rates, toxicities, clinical characteristics, and dosimetric parameters were evaluated. Multivariate analysis was performed to identify significant prognostic factors for survival.

Results: Among these 31 patients, 65% had received at least one prior regimen of systemic therapy for metastatic disease, whereas 29% had received chemotherapy for disease progression or immediately after SBRT. The median follow-up interval was 18.9 months; actuarial in-field local control rates at 1, 2, and 3 years after SBRT were 94%, 55%, and 42%, respectively. The median survival duration was 32.9 months; 1-year, 2-year, and 3-year actuarial survival rates were 89.6%, 57.1%, and 46.2%, respectively. The median time to progression was 10.9 months. Stereotactic body radiotherapy was well-tolerated, with grade 1 toxicities of fatigue (19%) and nausea (10%). Patients who received post-SBRT chemotherapy had significant longer overall survival (P=0.039 for all patients and P=0.001 for patients with primary colorectal cancer).

Conclusion: Stereotactic body radiotherapy can be safely administered to patients with unresectable liver metastases, and it may delay the need for chemotherapy. This treatment should be considered for selected patients with unresectable liver metastases.

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New knowledge added by this study

- Stereotactic body radiotherapy (SBRT) for unresectable liver metastases was effective and well-tolerated. It may delay the need for chemotherapy while prolonging progression-free survival.
- The receipt of post-SBRT chemotherapy is a significant prognostic factor for survival.

Implications for clinical practice or policy

- Stereotactic body radiotherapy can be regarded as an alternative to surgery for patients with liver metastases, particularly patients with unresectable tumours.
- We recommend offering SBRT to patients with unresectable liver metastases if they have good performance status (ie, Eastern Cooperative Oncology Group 0-1), liver tumours ≤6 cm in diameter, three or fewer liver tumours, normal liver volume >700 cm^3, adequate organ function, and adequate liver function (Child-Pugh class A).

Introduction

The liver is a common site of metastases, which most frequently originate from primary colorectal cancer via portal circulation. Surgical resection is the standard treatment for medically and technically operable liver metastases, particularly from primary colorectal cancer. However, most patients are not eligible for surgery because of co-morbidities or unfavourable tumour factors. Most patients receive systemic therapy as initial treatment for liver metastases, but such treatment rarely leads to permanent elimination of the metastases; some

立體定向體部放射治療不可切除肝轉移的療效、毒性和預後因素

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引言：本研究旨在確定立體定向體部放射治療對不符合手術條件的肝轉移患者的療效。

方法：本研究納入了2012年1月至2017年12月期間接受立體定向體部放射治療的31例無法切除的肝轉移患者；22名患者患有原發性結直腸癌，9名患者患有原發性非結直腸癌。治療劑量為24 Gy至48 Gy，在一至兩週內分為3至6次。我們評估了生存期、反應率、毒性、臨床特徵和劑量學參數，並進行了多變量分析以確定生存的重要預後因素。

結果：在這些患者中，65%曾接受過至少一種針對轉移性疾病的全身治療方案，而29%曾因疾病進展或在SBRT後立即接受過化療。中位隨訪時間間隔為18.9個月；立體定向體部放射治療後1、2和3年的精算領域內局部控制率分別為94%、55%和42%。中位生存期為32.9個月；1年、2年和3年精算生存率分別為89.6%、57.1%和46.2%。中位進展時間為10.9個月。立體定向放療耐受性良好，1級毒性為疲勞（19%）和噁心（10%）。接受立體定向體部放射治療後化療的患者總生存期顯著延長（所有患者P=0.039，原發性結直腸癌患者P=0.001）。

結論：對於無法切除的肝轉移患者，可以安全地進行立體定向放療，並可能延遲化療的需要。這種治療應考慮用於經選擇的肝轉移不可切除的患者。

form of local ablative intervention is required. For patients with unresectable limited liver metastases, numerous local therapeutic approaches are available, such as radiofrequency ablation, transcatheter arterial chemoembolisation, cryotherapy, and high-intensity focal ultrasound. However, all of these approaches exhibit a degree of invasiveness and are currently limited by tumour size (usually <3 cm), distance from critical structures, and distance from critical vasculature.[1]

In the past, radiotherapy has had a limited role in the management of liver metastases because of concerns regarding radiation-induced liver disease.[2,3] Because the liver is subject to the parallel architecture principles of radiobiology, the risk of radiation-induced liver disease is generally proportional to the mean dose of radiation delivered to normal liver tissue. Therefore, small hepatic lesions can be safely treated with high doses of radiation via stereotactic body radiotherapy (SBRT). Advances in tumour imaging, radiotherapy planning and delivery, and motion management have facilitated the delivery of highly precise and four-dimensional SBRT. This non-invasive method can be used to deliver ablative treatments on an outpatient basis, thereby decreasing morbidity and cost.[4]

Ablative techniques offer a minimally invasive treatment option for selected patients with oligometastatic liver disease.[5] There is increasing evidence to support the use of SBRT.[6] To our knowledge, there is limited published information regarding the role of SBRT in the treatment of unresectable liver metastases in Hong Kong. In this study, we investigated the efficacy, toxicities, and prognostic factors of SBRT in patients with unresectable liver metastases.

Methods

Patient eligibility

Data regarding consecutive patients with unresectable liver metastases who received SBRT between January 2012 and December 2017 were retrospectively retrieved from the treatment database of the Department of Clinical Oncology at Tuen Mun Hospital. All patients with liver metastases were evaluated in multidisciplinary team meetings involving radiation oncologists and hepatobiliary surgeons. Eligibility was determined using the following criteria: (1) histologically confirmed malignancy (hepatic lesion biopsy not required); (2) biphasic computed tomography (CT) scan or positron emission tomography–CT of the liver within 4 weeks of radiation planning demonstrating liver tumours ≤6 cm in diameter, presence of three or fewer liver tumours, and normal liver volume >700 cm^3; (3) discussion of the case in a multidisciplinary team meeting that included an opinion regarding the lack of qualification for radiofrequency ablation, along with a determination of non-resectability by a qualified hepatic surgeon; (4) patient refusal of surgical treatment; (5) Eastern Cooperative Oncology Group performance status 0 or 1; (6) adequate organ function (absolute neutrophil count ≥1.5×10^9/L; platelet count ≥75×10^9/L; creatinine level ≤1.5×upper limit of normal), liver function test results (aspartate aminotransferase and alanine aminotransferase levels ≤1.5×normal level), and Child-Pugh score of ≤6 (class A); (7) controlled extrahepatic disease and life expectancy >6 months; (8) no chemotherapy concurrent with radiotherapy (previous chemotherapy was not an exclusion criterion); and (9) previous treatment with radiofrequency ablation was not an exclusion criterion if recurrence had been confirmed.

Radiotherapy treatment

During four-dimensional CT scans, patients were positioned supine on an evacuated foam bag (Klarity Medical, China) with both arms abducted. The extent of tumour motion during respiration was used to determine whether treatment would be administered with free breathing plus abdominal compression or active breathing control. The gross tumour volume (GTV) was determined using contrast CT and co-registered with positron emission tomography–

CT. For patients who required optimal abdominal compression to mitigate organ motion, planning was conducted using the mid-ventilation–based planning target volume (PTV) approach, and the GTV was determined using intravenous contrast CT. The clinical target volume was 0 mm outside of the GTV within the liver (ie, equal to GTV); it included the position of the tumour in all phases of respiration. The PTV was defined by adding an isotropic margin of 3 to 5 mm from the clinical target volume or 7 to 10 mm in the cranial-caudal axis and 4 to 6 mm in the anterior-posterior and lateral axes. Pretreatment four-dimensional cone-beam CT was performed prior to each treatment for all patients to adjust for setup uncertainties. Tumour localisation was conducted using the diaphragm or whole liver as a surrogate for the tumour. A two-step four-dimensional registration approach was used to align the diaphragm/liver surrogate to its time-weighted mean position. The SBRT dose, ranging from 8 to 16 Gy × 3 fractions to 5 to 7.5 Gy × 6 fractions, was individualised according to the following normal tissue constraints: (1) maximum spinal cord dose <15 Gy; (2) ≥700 cm^3 of liver should receive <15 Gy, and D5% <30 Gy; (3) maximum stomach point dose of 25 Gy; and (4) maximum duodenum point dose of 25 Gy.

Evaluation

Patients were evaluated weekly during SBRT, immediately after completion of treatment, at 6 weeks after treatment, every 3 months for the first 2 years, and every 4 months thereafter. Physical examinations and blood tests were performed at each follow-up visit. Triphasic CT of the liver was conducted at 3 months after SBRT and then every 6 months until disease progression. Tumour response was assessed using modified response evaluation criteria for solid tumours.

The primary endpoint of the study was local control; secondary endpoints were overall survival and toxicity. Local control was defined as the absence of progressive disease within the PTV. The appearance of new lesions outside of the PTV was regarded as intrahepatic out-field failure. Overall survival was calculated from the start of SBRT until the end of follow-up or death.

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Toxicities were defined as adverse events that occurred <3 months after SBRT. Newly developed toxicities or toxicities that progressed to one grade above baseline were regarded as adverse events. Grade 5 liver failure related to SBRT was defined as death from liver failure in the presence of acute grade 3 liver toxicities during <6 months without intrahepatic progression.

Statistical analysis

Data were analysed using SPSS software (Windows version 23.0; IBM Corp, Armonk [NY], United States). Fisher's exact test and independent *t* tests were used for univariate analysis of patient, disease, and treatment factors associated with liver toxicity. Binary logistic regression analysis was used for

TABLE 1. Patient characteristics

Characteristic	
Sex	
Male	19 (61.3%)
Female	12 (38.7%)
Age, y (median [range])	66 (48-81)
No. of liver metastases	
1	19 (61.3%)
2-3	12 (38.7%)
Primary cancer	
Colorectal	22 (71.0%)
NPC	4 (12.9%)
Breast	2 (6.5%)
Lung	2 (6.5%)
Cervical	1 (3.2%)
Timing of liver metastases	
Synchronous	21 (67.7%)
Metachronous	10 (32.3%)
RAS status for primary colorectal cancer (n=22)	
Wild type	11 (50.0%)
Mutated	9 (40.9%)
Unknown	2 (9.1%)
Systemic treatment before SBRT	
Yes	20 (64.5%)
No	11 (35.5%)
Systemic treatment after SBRT	
Yes	9 (29.0%)
No	22 (71.0%)
Stable extrahepatic metastases	
Present	9 (29.0%)
Absent	22 (71.0%)
Prior local liver treatment	
Yes (surgery)	10 (32.3%)
No	21 (67.7%)
Lesion diameter, mm	
≤30	22 (71.0%)
>30	9 (29.0%)

Abbreviations: NPC = nasopharyngeal carcinoma; RAS = rat sarcoma virus; SBRT = stereotactic body radiotherapy

* Data are shown as No. (%), unless otherwise specified

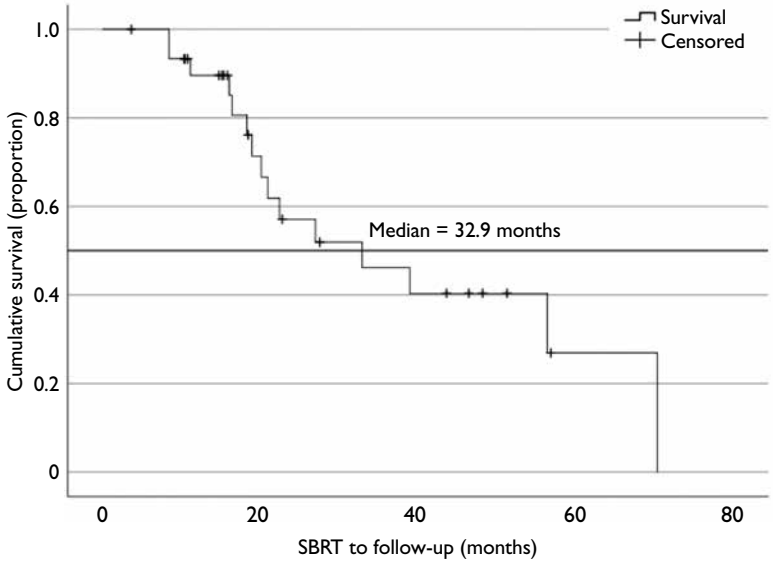

FIG 1. Overall survival of the whole group after stereotactic body radiotherapy (SBRT)

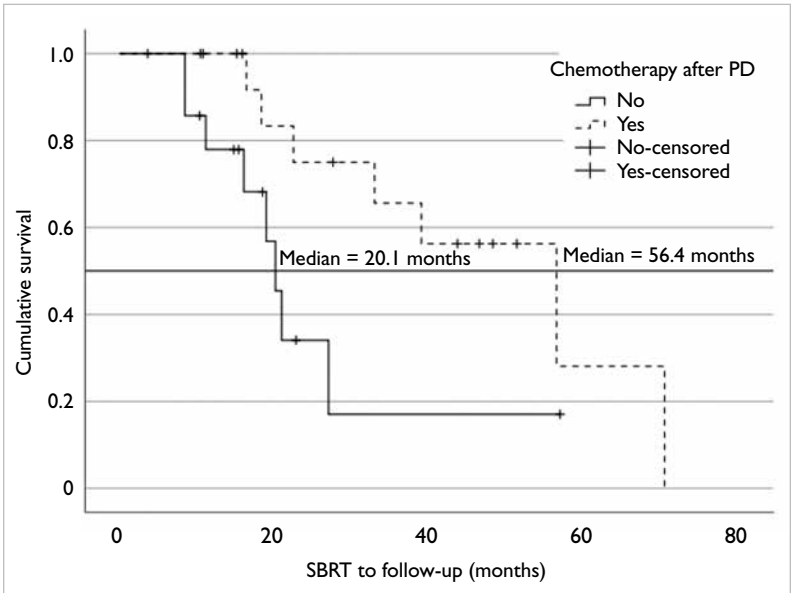

FIG 2. Overall survival of patients who received chemotherapy after stereotactic body radiotherapy (SBRT) for disease progression (PD) versus those who did not

univariate analysis of dose-volumetric parameters associated with liver toxicity. Kaplan–Meier test was used for univariate analysis of overall survival, with a significance threshold of P<0.25; it was used for multivariate analysis of overall survival, with a significance threshold of P<0.05. Cox regression was used for further evaluation of variables which were significant in univariate analysis of overall survival.[7,8]

Results

Patients and treatment

During the study period, 31 consecutive patients with unresectable liver metastases underwent SBRT at our institution. Their characteristics are shown in Table 1. Colorectal cancer was the most common primary cancer. A total of 64.5% of patients received systemic treatment before SBRT; 71% of liver lesions were ≤ 30 mm. All patients received a fixed course of 3 or 6 fractions with total prescribed dose ranges of 24-48 Gy. The mean GTV was 26.9 cm^3 (range, 1.5-137) and mean PTV was 91.8 cm^3 (range, 21.7-269). The mean biological equivalent dose (BED10) to GTV was 79.8 Gy (range, 43.2-124.8). The median BED10 to GTV was 76.8 Gy. Surgical resection or radiofrequency ablation were performed in 32% of patients before SBRT. Targeted or non-targeted systemic chemotherapy was administered to 65% and 29% of patients before and after SBRT, respectively.

Toxicities

Stereotactic body radiotherapy was well-tolerated. There were no grade 2-4 toxicities. Most patients were asymptomatic (grade 0) during radiotherapy; 19% of patients had grade 1 fatigue, 10% of patients had grade 1 nausea, and 3% of patients had skin reaction. No patients exhibited a change in Child-Pugh class after SBRT, and no significant prognostic factors for liver toxicities were identified.

Local control, survival, and prognostic factors

The median follow-up interval was 18.9 months. The 1-year, 2-year, and 3-year local control rates were 94% (29/31), 55% (17/31) and 42% (13/31), respectively. Only two patients (9% of all patients) with primary colorectal cancer had in-field recurrence at 1 year after SBRT. Sixteen patients in all treatment groups had out-field recurrence at 1 year after SBRT. The median time to progression was 10.9 months.

The median survival duration in all treatment groups was 32.9 months. The 1-year, 2-year, and 3-year survival rates were 89.6%, 57.1%, and 46.2%, respectively. The only significant prognostic factor for overall survival was receipt of post-SBRT chemotherapy for disease progression (P=0.039). Figures 1 and 2 show the survival curves and prognostic factors for all treatment groups. Previous local treatment, rat sarcoma virus status of colorectal cancer, number of liver metastases, extrahepatic metastases, BED to the liver, extrahepatic metastasis status, number of chemotherapy lines before or after SBRT, and carcinoembryonic antigen level after SBRT were not significant prognostic factors for overall survival. Table 2 summarises the factors that affected overall survival.

TABLE 2. Prognostic factors affecting overall survival

Variable	Hazard ratio	Univariable (95% CI)		P value	Multivariable adjusted hazard ratio (95% CI)	P value
Sex	0.977	0.3	3.19	0.97		
Age*	1.049	0.991	1.11	0.096	1.018 (0.950-1.091)	0.611
Chemotherapy before SBRT	0.573	0.19	1.73	0.324		
Chemotherapy after SBRT*	0.37	0.083	1.658	0.194	0.505 (0.102-2.488)	0.401
Timing of liver metastases	1.307	0.409	4.177	0.651		
Metastatic site	0.78	0.27	2.257	0.647		
Chemotherapy after PD*	0.327	0.108	0.991	0.048	0.327 (0.108-0.991)	0.039
No. of metastases	0.913	0.314	2.65	0.867		
Size of metastases	0.733	0.253	2.119	0.566		
Median BED10 to GTV	1.011	0.266	3.844	0.987		
Previous treatment	0.902	0.276	2.947	0.864		

Abbreviations: BED10 = biological equivalent dose; CI = confidence interval; GTV = gross tumour volume; PD = progressive disease; SBRT = stereotactic body radiation therapy

* Variables analysed in the multivariable analysis

The median survival duration in the colorectal cancer subgroup was 32.9 months. The only significant prognostic factor for overall survival was receipt of post-SBRT chemotherapy for disease progression (P=0.001). No other significant prognostic factors for overall survival were identified. Figures 3 and 4 show the survival curves and prognostic factors for the colorectal cancer subgroup.

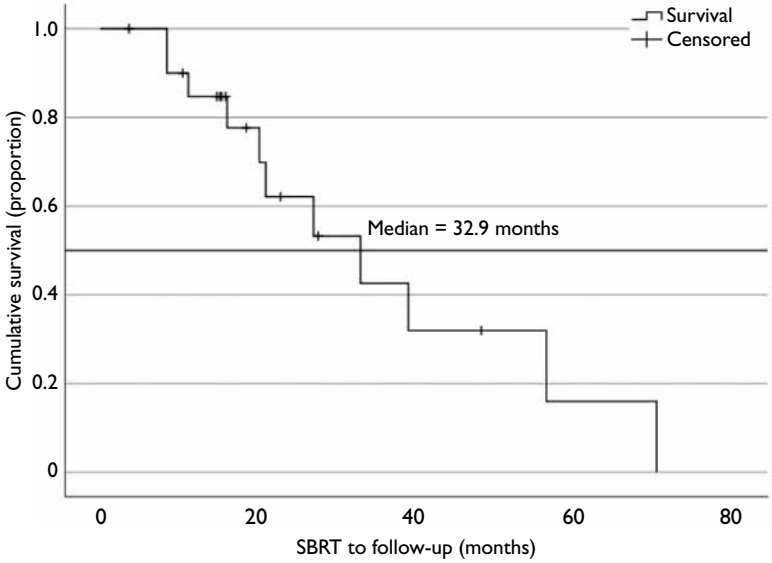

FIG 3. Overall survival of colorectal cancer patients after stereotactic body radiotherapy (SBRT)

Discussion

Although surgical resection is the standard treatment for liver metastases, many patients are not eligible for such treatment. Multiple retrospective and prospective studies have demonstrated SBRT is a promising, safe, and non-invasive alternative to surgery for unresectable liver metastases.[9,10] To our knowledge, there is limited published information regarding the use of SBRT to treat liver metastases in Hong Kong. In the present study, we retrospectively collected data regarding consecutive patients who received SBRT for unresectable liver metastases after multidisciplinary team evaluation; we assessed outcomes in terms of safety, local control, and survival. Among the 31 patients treated with SBRT, the 1-year and 2-year local control rates were 93% and 55%, respectively. The median survival duration was 32.9 months; the 1-year and 2-year survival rates were 89.6% and 57.1%, respectively. In the colorectal cancer subgroup, the 1-year and 2-year survival rates were 84.7% and 62.1%, respectively.

Multiple retrospective and prospective studies have been performed regarding SBRT for liver metastases from colorectal cancers (Table 3).[11-14] In the present study, local control rates and survival rates were comparable with findings in previous reports. Notably, McPartlin et al[11] conducted a prospective study using SBRT doses of 22-62 Gy in 6 fractions. The present study, with SBRT doses of 24-48 Gy in 3-6 fractions, demonstrated better 1-year local control (93% vs 50%) and 2-year survival (62.1% vs 26%) than the study by McPartlin et al.[11]

Three other SBRT trials[12-14] (45-75 Gy in 3 fractions) all demonstrated better local control rates than the findings in the present study (Table 3). These results indicate that a higher local control rate

is associated with a higher radiation dose. Compared with the present study, Scorsetti et al[12] and Joo et al[14] showed higher 2-year survival rates (65% and 75%, respectively vs 62.1% in the present study), whereas Hoyer et al[13] revealed a considerably lower 2-year survival rate (38%). These discrepant findings may be related to radiation dose—Scorsetti et al[12] and Joo et al[14] reported higher BED than that achieved by Hoyer et al[13] and the present study. Among patients with primary colorectal tumours, the survival rate in the present study was comparable with rates in the previous studies.[11-14] However, overall survival is dependent on many factors other than local control of irradiated liver metastases. Compared with earlier studies, overall survival is expected to be better in more recent studies because of stage migration, improvements in diagnostic techniques, and enhanced systemic treatment. Importantly, although the present study showed that post-SBRT chemotherapy was a prognostic factor for longer survival, selection bias may have been involved in the decision to administer chemotherapy to patients with better performance status.

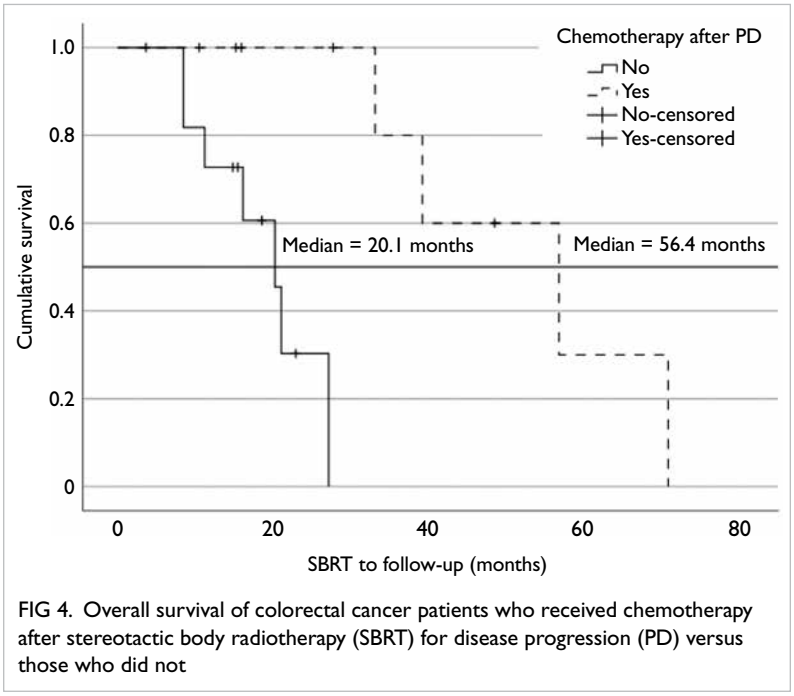

FIG 4. Overall survival of colorectal cancer patients who received chemotherapy after stereotactic body radiotherapy (SBRT) for disease progression (PD) versus those who did not

In the present study, the incidence of toxicities was low, and there were no grade 2-4 toxicities. Among patients who received SBRT, only grade 1 toxicities were reported (fatigue, nausea, and skin reaction); these findings indicate that SBRT was well-tolerated.

Based on our results, we recommend that patients with unresectable liver metastases are evaluated in multidisciplinary team meetings; patients should be offered SBRT if they have good performance status (ie, Eastern Cooperative Oncology Group 0-1), liver tumours ≤6 cm in diameter, three or fewer liver tumours, normal liver volume >700 cm^3, adequate organ function,

TABLE 3. Summary of literature regarding stereotactic body radiotherapy for liver metastases from colorectal cancers

Primary author	Choi et al (the present study)	McPartlin et al[11] (2017)	Scorsetti et al[12] (2015)	Hoyer et al[13] (2006)	Joo et al[14] (2017)
Study design	R	P	P	P	R
No. of patients	22*	60	42	44	70
Tumour volume, cm^3	1.5-137	31-765	1.8-134.3	1-8.8	
Primary cancer	CRC	CRC	CRC	CRC	CRC
Radiotherapy dose	27-48 Gy (3-6 Fr)	22-62 Gy (6 Fr) [phase 1 study] 33-57 Gy (6 Fr) [phase 2 study]			
33-57 Gy (6 Fr)	75 Gy (3 Fr)	45 Gy (3 Fr)	45-60 Gy (3-4 Fr)		
≥G3 toxicities	0	0	0	1 liver failure	
2 severe late gastrointestinal toxicities	0				
1-Year LC	93%	50%	95%	Not available	93%
2-Year LC	55%	32%	91%	79%	73%
Median survival, mo	32.9	14.9	29	Not available	20.5
1-Year survival	84.7%	63%	Not available	67%	Not available
2-Year survival	62.1%	26%	65%	38%	75%

Abbreviations: CRC = colorectal cancer; Fr = fraction; LC = local control; P = prospective; R = retrospective

* Only includes patients in colorectal cancer subgroup

and adequate liver function (Child-Pugh class A). Considering its minimal invasiveness and toxicity, as well as its potential for improving progression-free survival, SBRT should be regarded as an alternative to surgical resection of liver metastases to those patients who refuse surgical treatment.

There were some limitations in the present study. First, the BED to the tumour was low (median BED10 >100 Gy was administered to 35.5% of patients), and the mean GTV was high (26.9 cm^3). The local control rate may have been influenced by the lower total radiation dose administered and larger tumour volume. Second, this was a retrospective study, and the sample size was small. Thus, a randomised controlled trial with a large number of patients is needed to determine whether SBRT can prolong overall survival in patients with liver metastases.

Conclusion

Stereotactic body radiotherapy can be safely administered to patients with unresectable liver metastases, and it may delay the need for chemotherapy. Considering its minimal invasiveness and toxicity, this treatment should be offered to selected patients with unresectable liver metastases; such an approach may improve progression-free survival. A phase III randomised study is needed to confirm these results.

Author contributions

All authors contributed to the concept or design of the study, acquisition of data, analysis or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors declare no conflict of interest.

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Ethics approval

Ethics approval document was issued by New Territories West Cluster Research Ethics Committee of Hospital Authority, Hong Kong (Ref No.: NTWC/REC/20035). Informed consent was obtained from patients for stereotactic body radiotherapy.

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