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Review

The evolving role of radiation therapy as treatment for liver metastases

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ABSTRACT

Liver metastases occur commonly in many solid malignancies. With advances in systemic therapies and increased life expectancy, the role of using local therapies in oligo-metastases is rapidly increasing. Stereotactic body radiotherapy (SBRT) is an emerging precision therapy that is being used more frequently in the treatment for unresectable liver metastases. This review focuses on the role of SBRT for liver metastases, principles of treatment, clinical outcomes, toxicity, and optimal patient selection.

1. Introduction

Liver metastases occur commonly in many solid malignancies,[1] are the most distant metastases in colorectal cancer. More than 1.9 million new colorectal cancer cases and 935,000 deaths occurred in 2020.[2] About 30-50% of patients with colorectal cancer develop liver metastasis.[3] Oligo-metastatic disease, first described in 1995,[4] is defined by the presence of limited metastases, with most guidelines and clinical trials defining it as metastatic disease of up to 5 lesions at no more than 3 sites.[5] With more effective systemic therapies, increased life expectancy in metastatic disease, and advances in technology, there has been an increasing role for the use of local therapies in oligo-metastases. According to guidelines published by American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO), surgical resection is considered the first line treatment of patients with limited liver metastases.[6] In a phase II clinical trial, *Ruer et al.* randomized 119 patients with colorectal liver metastases to radiofrequency ablation (RFA) plus systemic therapy *vs.* systemic therapy alone. Overall survival was higher at the RFA plus systemic therapy group.[7] As local liver metastasis therapies become more accessible, the role of non-surgical local liver directed treatment modalities increases. These include: trans-arterial chemoembolization (TACE), trans-arterial radio-embolization (TARE), stereotactic body radiotherapy (SBRT), thermal ablation (microwave or radiofrequency ablation), and hepatic artery chemotherapy infusion. In colorectal cancer with liver metastases, surgical metastasectomy and systemic treatment have been shown to significantly improve survival outcomes.[8] However, only about 25%-30% of patients are amenable to resection.[9] The rationale of adding SBRT to treatment regimens of patients with oligo-metastatic disease include improving quality of life with less invasive therapy, compared to other modalities, making it even suitable for patients with comorbidities. Different strategies can be utilized to deliver high dose ablative radiotherapies, including external beam radiation therapy (EBRT), SBRT, proton radiotherapy, and carbon ion radiotherapy.[10]

Local ablative therapies such as SBRT or RFA or microwave ablation (MWA) have been successfully used by many centers to patients with liver metastasis who are not suitable for surgical resection.[11] *Dawson et al.* reported their early experience in treating patients with liver metastasis in the 1990s at the University of Michigan. In their phase I trial, 43 patients (27 unresectable liver cancer patients and 16 colorectal liver metastases patients) were treated with high doses of hyperfractionated conformal radiotherapy to a total dose of 90 Gy in 1.5 Gy twice daily.[12] This was delivered safely using an individualized dose prescription approach. The reported response rate was 68% in 25 assessable patients. Patients who were treated with higher doses of more than 70 Gy had better survival. This was longer than expected survival in patients with colorectal liver metastasis. Since that time, SBRT has become more widely available in most modern radiation therapy delivery machines. This has increased the interest in using radiation to

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treatment of oligo-metastases using conformal treatment delivery with motion management such as active breath control, thus allowing a high dose conformal radiotherapy to be delivered in fewer fractions (1 to 5 fractions).[13] SBRT is delivered as an outpatient treatment requiring relatively shorter treatment time in comparison to other modalities. It is considered as a non-invasive type of treatment delivery and regarded as highly tolerable by patients if delivered with safety considerations. Delivering SBRT for colorectal liver metastasis needs to consider the step of simulation CT. The motions of the liver should be taken into account. Different strategies to account for and resolve liver respiratory motions for SBRT have been used, including abdominal compression, respiratory gating, four-dimensional computed tomography (4DCT),[14] implantation of fiducial markers for tumor tracking, and taking breath-hold methods.[15] Contrast-enhanced computed tomography (CT) has been used to identify tumors and normal tissues,[16] however, the variation of the Hounsfield unit value due to contrast media may lead to minor dose calculation uncertainties in radiotherapy.[17, 18] The conventional linac-integrated X-ray systems have the following disadvantages, including poor tumor visibility, and potential surrogacy errors.[18] In order to accurately delineate target structures and organs at risk, magnetic resonance imaging (MRI) and CT fusion are used together. The planning process starts with simulation using CT and MRI scans. Then the planning team creates a high-dose, highly conformal radiotherapy plan in which steep dose gradients are usually created near the tumor edge to limit the dose delivered to surrounding organs at risk.[19]

Organ motion management has been used as a way to decrease the high dose to organs at risk while better targeting the tumor. There are many commercially approved systems to assist in tracking organ and tumor target motions. These systems include electronic portal imaging device (EPID), fluoroscopy with fiducial markers, Calypso 4-D localization system, cone-beam computer tomography (CBCT), and stereoscopic X-ray gimbal.[20] Magnetic resonance imaging guided linear accelerators (MRLs) have been increasingly used recently in treatment delivery.[21] There are benefits of using MRLs, including the implementation of an adaptive radiotherapy allowing the treating team to change treatment volume based on daily patients' anatomy changes. This allows for more personalized radiotherapy that would facilitate even further safe implementation of SBRT.

2. Rationales and mechanisms of SBRT

The most common mechanism of radiotherapy cell damage is by causing non-repairable, double standard DNA breaks, which preferentially affects cancer cells compared to normal tissues. Another mechanism is by delivering a high dose of radiation that results in ablation of cancer cells. It is thought that the former is the main cell pathway in conventional radiotherapies while the latter occurs more at SBRT. A high dose per fraction has several effects at the molecular level, including initiation of various signal transduction pathways, modulating target cell phenotypes,[22] and initiating immune response, where there is a pro-inflammatory environment (activation of tumor-specific T cells, or increasing immune modulator molecules) that is triggered with radiotherapy allowing immunotherapies to be more effective.[23]

3. Clinical outcomes of SBRT

There has been evolving evidence about the use of SBRT in the management of liver oligo-metastases in the last two decades. Results of some prospective studies are summarized in Table 1,[24-32] and some retrospective studies in Table 2.[33-40] A recent meta-analysis indicated that the two-year local control (LC) rate was significantly higher in the SBRT group compared to that of the radiofrequency ablation group (83.6% *vs.* 60.0%, $P < 0.001$).[41] A systematic review published in 2018 reported that 1- and 2-year overall survival (OS) rates were 67.18% and 56.5%, respectively. Median progression-free survival (PFS) was 11.5 months and median OS was 31.5 months. Higher SBRT dose was associated with better LC and OS. Mild moderate and severe liver toxicities were 30.7% and 8.7%, respectively.[11]

Herfarth et al. reported 55 liver metastases that were treated with single fraction SBRT at a dose range of 14 to 26 Gy. The reported local control rate was 67% at 18 months with no reported grade 3-5 toxicities.[42] *Schefter et al.* evaluated 18 patients treated with SBRT of 36 to 60Gy in 3 fractions in a multicenter phase I trial. No dose-limiting toxicity was observed.[43] At Princess Margaret Hospital (PMH), *Dawson et al.* also conducted a phase I trial using SBRT with a six-fraction regimen in treating patients with unresectable liver metastasis who were unsuitable for systemic therapy.[27] This study included 68 patients in the early 2000s. The median tumor volume was 75 cc. The median dose was 42 Gy in 6 fractions. The LC rate at one-year was 71% and the median OS was 17 months. There were no reported grade 3-5 liver toxicities. Low toxicity profile sustained on their follow-up study of 2014 that included more than 200 patients with liver metastases. PMH continues to treat patients with liver metastases with 5 or 6 fraction SBRT using the same strategy safely. It is of note that a small percentage of patients treated on the previously mentioned studies did not receive systemic therapy, and survived cancer free for about 5 to 15 years following SBRT; one of the longest-term survivors had five metastatic lesions from colorectal cancer with no evidence of disease at the last follow-up.[44] Many other trials have reported promising outcomes with use of SBRT. For example, a report from the Colorado group reported the feasibility and safety of 60 Gy in 3 fractions at a population of 47 patients.[26] The 2-year LC was high at 90 to 100 % in lesions with sizes less than 3 cm. The median survival was 25 months. The latter is considered one of the first reports to show different survival outcomes for different primary tumor sites. The reported favorable tumor types included breast, colorectal, renal, carcinoid, gastrointestinal stromal tumor, and sarcoma. Favorable tumor types correlated with longer survival with a median of 32 months compared to those with unfavorable tumor types that had a median survival of 12 months.

More recent studies have been looking at single fraction liver SBRT. A report from UT Southwestern Texas included 33 patients with 39 metastases located at peripheral liver who received a dose of 35-40 Gy in one fraction.[31] LC was reported to be 96.6% at 4 years. Two and four-year OS rates were 82% and 50%, respectively. No grade 3-5 toxicities were reported. The dose constraints used in the study are summarized in Table 3.[31] This high dose SBRT must be delivered with highly conformal techniques. Risk of unpredictable toxicities, including biliary toxicity, should be taken into consideration. Using highly accurate and precise radiotherapy delivery techniques, single fraction SBRT can be used for the treatment of small liver metastases (less than 5 cm).

A recent study from the Netherlands reported outcomes of 550 patients with 668 metastases of the liver. The majority of the study population had colorectal cancer (80%) and 9 % had lung cancer primaries. Variable dose fractionations were used, including 3 fractions of 18-20 Gy, 5 fractions of 11-12 Gy, 8 fractions of 7.5 Gy, and 12 fractions of 5 Gy. Grade 3-5 toxicity was 3.9%. There was one grade 5 biliary stenosis toxicity, which occurred one year after treatment, suggesting that even with fractionated SBRT, it is important to carefully review doses to critical structures, such as the biliary system and portal region.[45] The reported median OS was 2.5 years and the LC rate at 3 years was 68%. This is consistent with other reports that showed colorectal metastases are more challenging to control in the long term. Colorectal liver metastases had worse overall LC compared to the metastases of other primary malignancies. There was no significant correlation between dose fractionation and response, although patients treated with 8 fractions of 7.5 Gy had less long-term LC. Other reports of colorectal metastases include a study from Italy of 270 patients with 437 colorectal metastases treated with high dose SBRT. The reported tumor LC was 75 %. The time to SBRT impacted the LC. In this group of patients with unresectable metastases, the one-year OS was 85 % and at 5 years was 22%. Factors that impacted OS, include site of treated metastases (lung vs. non-lung), systemic therapy used prior to SBRT,

Table 1
Summary of some selected prospective stereotactic body radiotherapy series.

Study	Design	Case and lesions	Dose (Gy) /fractions	Follow-up	Local control	Overall survival	PFS	Toxicity
Hoyer M 2006	Phase II	64 patients 141 lesions	45/3	4.3 (0.2-6.3) years	1-year: 86%	1-year: 67% 5-year: 13%	Median: 6.5 Mo 2-year: 19%	Grade 2: 48%
Kavanagh B 2006	Phase I-II	21 patients	60/3	19 (6-29) Mo	Median: 18 Mo 1-year: 93%	NA	NA	Grade 3: 1
Rusthoven K 2009	Phase I/II	47 patients 63 lesions	36-60/3	16 (6-54) Mo	1-year: 95% 2-year: 92%	Median: 20.5 Mo 2-year: 30%	NA	Grade 3: 2%
Lee M 2009	Phase I	68 patients	54-60/6	10.8 Mo	1-year: 71%	Median: 17.6 Mo 1-year: 63%	NA	Grade 3: 10%
Rule W 2011	Phase I	27 patients 37 lesions	30-60/5	20 (4-53) Mo	1-year: 72%	Median: 37 Mo 2-year: 57.6%	NA	Grade 3: 1
Scorsetti M 2012	Phase II	61 patients 76 lesions	75/3	6.1 years	1-year: 95%	Median: 27.6 Mo 1-year: 85% 5-year: 18%	Median: 12 Mo	No grade 3
Hong T 2017	Phase II	89 patients 143 lesions	40 GyE/5	30.1 (14.7-53.8) Mo	1-year: 71.9% 3-year: 61.2%	1-year: 66.3% 2-year: 35.9% 3-year: 20.8%	NA	No Grade ≥ 3
Folkert M 2021	Phase I	33 patients 39 lesions	35-40/1	25.9 Mo	4-year: 96.6%	2-year: 82%	NA	No Grade ≥ 3

Abbreviations: Mo, months; NA, not available; PFS, progression-free survival.

Table 2
Summary of some selected retrospective stereotactic body radiotherapy series.

Study	Design	Case and lesions	Dose (Gy) /fractions	Follow-up	Local control	Overall survival	PFS	Toxicity
Chang D 2011	Retrospective	65 patients 102 lesions	22-60/1-6	1.2 (0.3-5.2) years	1-year: 67% 2-year: 55%	1-year: 72% 2-year: 38%	NA	Grade 2 GI: 17% Grade 3 liver disease: 3%
Cazic D 2020	Retrospective	16 patients	60/8	12 Mo	1- year: 62.5%	1-year: 87.5%	Median: 11 Mo	No Grade 3
Nicosia L 2020	Retrospective	61 patients 97 lesions	NA	24 Mo	NA	Median: 23 Mo 1-year: 68.6% 2-year: 42.7%	Median: 7 Mo	NA
de la Pena C 2020	Retrospective	24 patients 32 lesions	NA	22 (1-65) Mo	1-year: 82% 2-year: 76.2%	Median: 35 Mo 1-year: 85.83% 2 -year: 68%	NA	No grade 3 No radiation-induced liver disease
Coffman A 2021	Retrospective	46 patients 81 lesions	36-60/3	15 (1-54) Mo	1-year: 92.5%	NA	NA	Grade 1: 37% Grade 2: 6.5%
Py J.F. 2021	Retrospective	67 patients 99 lesions	37.5-54/3-5	47 (28-59) Mo	1-year: 86.6% 2-year: 72.4%	Median: 53Mo 1-year: 95.5% 5-year: 43.5%	2-year: 54%	Grade ≥ 3: 3%
Yu J 2021	Retrospective	44 patients 62 lesions	36-60/3-5	31.8 (3.2-122.9) Mo	NA	1-year: 91%	NA	0
Stera S 2021	Retrospective	135 patients 227 lesions	NA	12.5 (0.5-84.3) Mo	1-year: 90% 5-year: 68.7%	1-year: 67% 2-year: 37%	NA	NA
Voglhuber T 2021	Retrospective	115 patients 150 lesions	35/5	11.4 Mo	Median: 35.1 Mo 1-year: 82% 2-year: 77%	Median: 20.4 Mo 1-year: 72% 2-year: 45%	Median: 4.3 Mo 1-year: 20% 2-year: 10%	Grade 3: 8.7%

Abbreviations: GI, Gastrointestinal; Mo, months; NA, not available; PFS, progression-free survival.

control of other treated metastases, and larger clinical target volume.[46] Moreover, for liver metastases, outcomes were significantly better for lesions treated with a biologic effective dose (BED) of more than 100 Gy_{10} (3-year LC 93%) compared to a BED of ≤100 Gy_{10} (3-year LC 65%, $P < 0.001$).[47]

4. Patient selection of SBRT for liver metastases

Several factors need to be considered to ensure safety, including presence of enough reserve of non-irradiated liver (more than 1000cc), good liver function, and tumor location being far from luminal gastrointestinal (GI) tissues (>10 mm ideally), so that ablative doses of SBRT can be delivered while avoiding potential toxicity. Better outcomes are noted in patients with limited extrahepatic disease, smaller size lesions (<3 cm *vs.* >3 cm), limited number of hepatic lesions (< 3 *vs.* >3 lesions) and when high doses are delivered. Patients should be appropriately selected taking patient comorbidities, tumor type and planning factors into consideration. As to assess extent of disease at liver, a Primovist MRI is considered more sensitive compared to other imaging sequences. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) may be useful in the assessment of extrahepatic cancer.

Table 3
Normal tissue dose constraints on and per protocol according to previous studies

Structure	Maximum point dose constraint*	Volume constraint
Uninvolved liver	14 Gy	700 ml receives < 9.1 Gy
Spinal cord		< 0.35 ml exceeds 10 Gy < 1.2 ml exceeds 7 Gy
Stomach	12.4 Gy	< 10 ml exceeds 11.2 Gy
Duodenum	12.4 Gy	< 5 ml exceeds 11.2 Gy
Jejunum/Ileum	15.4 Gy	< 5 ml exceeds 11.9 Gy
Colon	18.4 Gy	< 20 ml exceeds 14.3 Gy
Skin	26 Gy	< 10 ml exceeds 23 Gy

* Point dose volume = 0.035 ml

5. Molecular biomarkers for SBRT planning

Treatment of liver metastasis should consider the biology nature of the primary tumors. Molecular biomarkers should be considered when planning SBRT for oligo-metastatic diseases. This includes but not limited to the lung and colorectal cancers. Patients with an immune genotype of *NRAS, CDK12*, and *EBF1* mutations have lower local recurrence rates compared to those with wild type who have lower survival rates.[48] *Krishan et al.* reported results of 85 patients with 109 metastatic lesions treated with SBRT. Patients with *KRAS* mutation had lower OS compared to those patients with *KRAS* wild type. The median OS in patients with combined *KRAS* and *TP53* mutation was 14 months, and for patients with either *KRAS* or *TP53* mutation, the median survival was 38 months. Moreover, patients with *TP53* mutation had a higher rate of local recurrence compared to patients with *TP53* wild type.[49]

The importance of mutations in the treatment of liver metastases with SBRT has also been shown by a group from Harvard,[30] as *KRAS* and *TP53* mutations correlated with LC more than primary tumor type. The results demonstrated superior LC for lesions without *KRAS* mutation (1-year LC of 73% *vs.* 42% with *KRAS* mutation), and better LC for those without *KRAS* and *TP53* mutations (1-year LC of 69% *vs.* 20% with mutant *KRAS* and *TP53*). This is consistent with results from other groups, including a study from a UK group[50] that showed patients with wild type *KRAS* had a superior PFS compared to those with *KRAS* mutation. Moreover, OS was reported to be better in patients who have *KRAS*-wild type compared to the *KRAS*-mutant type.

In the future, radiotherapy sensitivity signatures (*KRAS* wild, oligophenotype, immune molecular subtype) may help in treating patients who are likely to benefit more from SBRT treatment.

6. SBRT versus RFA

There are few studies comparing SBRT to RFA in patients with liver metastases. A recent retrospective study by *Yu et al.*[38] reported analysis of 222 patients with 330 liver lesions of metastatic colorectal cancer who were treated with SBRT or RFA. The median follow-up was 30.5 months. The median tumor size was significantly larger in the SBRT group than in the RFA group (2.3 cm *vs.* 1.5 cm; $P < 0.001$). By adjusting with inverse probability of treatment weighing adjusted analysis, the two groups showed no significant difference in 1-year and 3-year recurrence-free survival, OS, and freedom from local progression. SBRT showed higher freedom from local progression compared with the RFA group ($P < 0.001$) in treated tumor sizes of more than 2 cm. In 2017, a study from *Jackson et al.*[51] evaluated 161 patients with liver metastases. Most of those patients had limited disease (< 5 cm) or stable extra hepatic disease. There were 69 patients with 112 lesions treated with RFA and 92 patients with 170 lesions were treated with SBRT. The two approaches were similar with regards to local control in treated lesions of less than 2 cm in diameter. SBRT improved LC in lesions that were larger than 2 cm compared to those treated with RFA. In particular, 1- and 2-year LC rates were 96% and 88.2% in patients treated with SBRT and 74.7% and 60.6% for those treated with RFA, respectively, though such differences were not statistically significant. In a recent meta-analysis[41] that included three studies comparing the efficacy of SBRT and RFA for treatment of liver metastases, the reported 2-year LC rate was higher in the SBRT group compared to that of the RFA group (83.6% *vs.* 60.0%, $P < 0.001$), and OS was not significantly different between the two approaches.

7. Limitations of SBRT

Treatment with SBRT does come with some limitations. SBRT has less chance of sustained ablation for larger tumors (> 6 cm). In tumors that are less sensitive to radiotherapy (i.e. colorectal cancer with *KRAS* and/or *TP53* mutations), higher doses are needed for better LC. One should pay attention to dose limiting factors including surrounding luminal structures so that SBRT may be delivered safely. Systemic therapies may need to be held prior to, during and after SBRT.

8. Conclusions

In conclusion, there is an expanding role of SBRT for treatment of liver metastases. Indications include non-surgical candidates with large lesions (3 to 6 cm), and patients who are not suitable for or refractory to RFA (i.e. in central dome, or adjacent to large vessels). It is also an excellent treatment for metastases near portal structures, but one needs to be considerate of the organs at risk, and avoid hot spots on the biliary track. Single fraction SBRT should not be recommended for lesions around the porta-hepatis. As there is a degree of clinical equipoise about some topics of SBRT related to liver metastases (i.e. maximum number of treated metastases, dose fractionation), more prospective, and ideally randomized clinical trials are encouraged.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Author contributions

G.L., K.A. and L.D. designed and drafted the manuscript. G.L., Q.S., C.C. and L.D. edited the manuscript. All of the authors read and approved the final manuscript.

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