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Stereotactic radiotherapy for liver oligometastases

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ABSTRACT

The liver is the first metastatic site in 15–25% of colorectal cancer patients and one of the first metastatic sites for lung and breast cancer patients.

A computed tomography (CT) scan with contrast medium is a standard procedure for assessing liver lesions but magnetic resonance imaging (MRI) characterizes small lesions better thanks to its high soft-tissue contrast. Positron emission tomography with computed tomography (PET-CT) plays a complementary role in the diagnosis of liver metastases. Triphasic (arterial, venous and time-delayed) acquisition of contrast-medium CT images is the first step in treatment planning. Since the liver exhibits a relatively wide mobility due to respiratory movements and bowel filling, appropriate techniques are needed for target identification and motion management. Contouring requires precise recognition of target lesion edges. Information from contrast MRI and/or PET-CT is crucial as they best visualize metastatic disease in the parenchyma. Even though different fractionation schedules were reported, doses and fractionation schedules for liver stereotactic radiotherapy (SRT) have not yet been established. The best local control rates were obtained with BED_{10} values over 100 Gy. Local control rates from most retrospective studies, which were limited by short follow-ups and included different primary tumors with intrinsic heterogeneity, ranged from 60% to 90% at 1 and 2 years. The most common SRT-related toxicities are increases in liver enzymes, hyperbilirubinemia and hypoalbuminemia. Overall, late toxicity is mild even in long-term follow-ups.

Key words: stereotactic radiotherapy; radiosurgery; oligometastasis; liver metastases; organ motion; hypofractionation; bed; local control; toxicity

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Introduction

The liver is the first metastatic site in 15–25% of colorectal cancer patients [1, 2]. As demonstrated by autopsy findings metastases are localized only in the parenchyma in 40% of cases [3] and occur synchronously with the primary tumor in 10–20% of cases [4]. A population study of 3655 patients with colorectal cancer reported a higher incidence of liver metastases in patients under 55 years old

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(19.8%), who were males (15.9%) and affected by colon cancer (14.8%). The cumulative incidences at 1, 2 and 3 years were 4.3%, 12%, and 16.5%, respectively [5]. The liver is also one of the first metastatic sites for lung and breast cancer. In a study on 912 patients with breast cancer, Hoe et al. [6] showed a 5.2% risk of developing liver metastases. Liver metastases are less common for tumors of the bladder, esophagus, head and neck, pancreas, and for rare cancers, such as neuroendocrinal tumors and ovarian adenocarcinomas [3].

Metastatic disease characteristics impacted upon overall survival (OS). Metastases from colorectal cancer, surgical resection for a single metastasis under 5 cm in diameter, metastases arising at least one year after the primary tumor was diagnosed, low CEA levels and negative surgical margins, were associated with a 5-year OS above 60% *vs* 14% when such features were absent [7, 8]. Data are less promising for patients with metastases from breast tumors, neuroendocrine tumors or cancer of origins other than colorectal. At five years, median survival after radical resection for metastases from breast cancer ranged from 18% to 61%, probably due to metastatic spread to other sites and different responses to the associated systemic therapies. However, a recent analysis of the National Cancer Database reported that, compared to no metastasectomy, hepatic metastasectomy was independently associated with a 37% reduction in the risk of death [hazard ratio (HR): 0.63; confidence interval (CI): 0.44–0.91; p = 0.01] in selected sub-groups of patients [9].

Until recently, irradiation of liver metastases, especially with ablative doses, was limited by the high radiosensitivity of healthy liver tissue, the proximity of organs at risk (OARs), such as the stomach, duodenum and right kidney and, consequently, the risk of unacceptable toxicity. Technological developments have increased the chances of moving from merely palliative to ablative intent. Stereotactic radiotherapy (SRT) reduces the dose to healthy liver tissue and OARs, thus helping to prevent severe toxicities like radiation-induced liver disease (RILD) [10, 11].

A recent article [12] showed the metastatic cascade was established either initially by the primary tumor (linear progression model) or, subsequently, by metastases (parallel progression model). In the former instance, genomic analyses revealed the primary tumor and metastases were very similar while in the latter, major genetic differences were observed in the primary tumor and metastases, with earlier occurrence of metastases which evolved independently of the primary lesion. In both progression models, a metastatic "cascade" may be generated in a relatively short time from a progenitor metastasis. This model highlights different phases and might explain how SRT on progenitor lesions (oligometastases) prevents the onset of a polymetastatic wave, thus extending survival.

This review aims at highlighting the role of SRT for liver oligometastases, focusing on candidate selection, treatment planning and delivery, response assessment and outcomes.

Initial staging and candidate selection for SRT

Accurate assessment of metastatic liver disease is crucial for decision making [4, 13]. Conventional ultrasound is the first investigation because it is non-invasive and reproducible. Sensitivity in its identification of liver metastases ranges from 53% to 84%, dropping to 20% when metastases are < 1 cm in diameter [14]. Diagnostic accuracy is increased with echo-color-doppler, which detects and characterizes blood flow, together with harmonic imaging [15] which improves the signal-to-noise ratio, reduces image artifacts, increases contrast resolution and allows real-time full dynamic contrast enhancement of focal liver lesions. Since abnormal blood flow in the hepatic/venous portal artery is associated with tumor angiogenesis [16], its evaluation might be helpful for small lesions that cannot be visualized on standard examinations. A computed tomography (CT) scan with contrast medium is standard procedure for assessing liver lesions because of its speed and reduced susceptibility to motion artifacts. In most cases, the venous phase easily identifies liver metastases while the arterial phase detects hypervascularized tumors such as neuroendocrine carcinoma, melanoma and clear cell renal carcinoma [17]. Thanks to its high soft-tissue contrast, magnetic resonance imaging (MRI) characterizes small lesions better than CT, especially in a steatotic liver, and better differentiates small cysts from solid lesions [18]. Data on MRI sensitivity and specificity are, however, often discordant and influenced by the type of contrast medium [19]. The fluorodeoxyglucose-positron emission tomography (FDG-PET) scan was associ-

ated with wide ranges of sensitivity (54–100%) and specificity (58–100%) [20] which may depend on primary tumor histology, metastasis location and size. Since MRI and CT scans remain the standard of care because of wide availability and low cost, PET-CT, although able to identify extrahepatic metastases [21], plays a complementary role in the diagnosis of liver metastases.

In the decision making process for SRT the number of metastatic lesions (less than 3 are suggested) and their size (preferably each lesion should be lower than 6 cm, and combined lower than 15 cm) should be taken into account together with liver function as it may be impaired due to pre-existing conditions, such as hyperbilirubinemia over 3 or Child-Pugh 2 or 3 cirrhosis [22], thus reducing healthy tissue tolerance. Furthermore, sufficient hepatic reserve parameters were required: ideally total liver volume more than 1000 mL, with at least 700 mL spared from doses more than 15 Gy [23]. As age under 60 years, good performance status, no co-morbidities and favorable primary tumor histology (e.g., colorectal and breast tumors) were associate with good outcomes after ablative therapy, these clinical and pathological factors must also be considered when candidates for SRT are selected [10, 11, 24, 25].

Contouring, doses, fractionation and delivery

Appropriate imaging techniques are needed for target identification and precise recognition of target lesion/s edges. Information from contrast MRI and/or PET-CT is crucial as they best visualize the real extent of metastatic disease in the hepatic parenchyma [26, 27]. Triphasic (arterial, venous and time-delayed) acquisition of contrast-medium CT images, is the first step in treatment planning as liver metastases may display different behavior patterns during contrast perfusion at different image acquisition stages. Since the liver exhibits a relatively wide mobility due to respiratory movements and bowel filling, motion management, preferably with a four-dimensional computed tomography (4D-CT), is required for high-dose ablation of focal lesions. Respiratory movements may also be managed by abdominal compression during the planning CT and treatment delivery. During contouring the internal target volume (ITV) should include the tumor volume to be treated as well as its, albeit small, respiratory ranges. More recent methods use breath-hold techniques or target tracking systems that recognize internal fiducials and their respiratory displacements [28]. Once the oligometastatic lesion/s is/are contoured, margins should be defined on the basis of the methodology of contouring, respiratory management and set-up reproducibility [29]. Besides, the entire liver, OARs also need to be contoured. These include the right and left kidneys, the duodenum, the bowel, the esophagus, the heart and the spinal cord.

Even though different fractionation schedules were reported [30], doses and fractionation schedules for liver SRT have not yet been established. The best local control (LC) rates were obtained with BED_{10} values over 100 Gy [31, 32]. Joo et al. [33] demonstrated that BED values between 132 and 180 improved outcomes (89% at 3 years). Chang et al. [34] proposed a dose higher than, or equal to, 48 Gy in 3 fractions, respecting constraints of the OARs. For lesions < 3 cm in diameter, a total dose of 60 Gy in 3 fractions was recommended [35]. For lesions > 3 cm in diameter Scorsetti et al. [36] escalated the dose up to 75 Gy in 3 fractions. Single fraction SRT was evaluated in a phase I dose escalation trial: 35 Gy and 40 Gy were delivered to lesions ranging from 0.5 to 5.0 cm (median size 2 cm). Constraint of the OARs were respected, e.g. at least 700 cc of normal liver had to receive < 9.1 Gy [37].

In the liver, treatment failure was most observed outside the irradiation field. After treating 500 liver and lung metastatic lesions in 388 patients with SRT, Klement et al. observed that no prior chemotherapy was associated with higher LC rates. They predicted that 90% tumor control probability (TCP) at 2 years could be achieved with BED of 187 Gy_{10} with no prior chemotherapy but that 300 Gy_{10} would be needed in case of prior chemotherapy [38].

Primary tumor histology should be considered when deciding the prescription dose. Ahmed et al. [39] developed a multigene expression model of tumor radiosensitivity, showing it correlated with tumor radioresistance. It was higher in colorectal metastases than in, for example, anal squamous cell cancer, breast and lung adenocarcinoma. Similarly, Klement et al. [40] showed that breast cancer metastases responded better to SRT than colorectal liver metastases (a 2-year TCP of 90% with BED_{max} of 157 Gy, *vs* BED_{max} of 257 Gy).

Dose prescriptions varied. The dose was usually prescribed to a peripheral reference isodose or to the isocenter [41–43]. The isodose prescription signified a higher dose to the isocentre. For example, a dose prescription of 36–37.5 Gy in 3 fractions to the peripheral reference isodose of 67% means that more than 50 Gy reach the isocenter. The treatment plan must consequently be optimized so that, even in isocenter prescriptions, the prescription dose covers at least 90% of the PTV. Coverage of under 80% is not acceptable.

More agreement exists on OAR dose limits according to different fractionations. Data from the report of American Association of Physicists in Medicine Task Group 101 (AAPM101) [44] can be used as references.

Liver SRT is generally delivered using traditional linear accelerators that are equipped to deliver such advanced treatments and have image-guided radiation therapy (IGRT) systems. Fiducial markers are useful as target surrogates for precise daily repositioning of the patient and assessing target position on-line [45, 46], due to the poor resolution of portal images and cone beam CT (CB-CT) compared with diagnostics. Specifically dedicated therapy units, such as Cyberknife, may also be used. More recently, liver metastasis SRT has been delivered by MRI-guided adaptive radiotherapy which allows for real-time MRI imaging (before and continuously during the treatment). Its use confers clear advantages, such as improved soft tissue target and OARs delineation, finer tracking which requires smaller margins, and minimization or elimination of external surrogates, such as patient surface anatomy, without imaging dose to the patient [47–49].

Response assessment and outcome

Following SRT, monitoring the response to the treatment is crucial. Some Authors suggested that patients treated with SRT should undergo imaging follow up at 3, 6 and 12 months after treatment [50, 51].

Although experience with SRT for liver metastases has been reported for several years, the majority of studies were retrospective, limited by short follow-ups and included different primary tumors with intrinsic heterogeneity. Consequently, outcomes are hard to compare [52, 53]. Tables 1 and 2 summarize the results of the major studies on SRT for liver metastases. In one long-term experience Scorsetti et al. demonstrated that the 5-year LC rate was 78% [54]. After single fraction SRT, 4-year actuarial LC was 96.6% [37]. Menichelli et al. showed the LC rate correlated with lesion size, BED_{10} value, and primary histology [55].

The use of advanced motion management for liver metastases improved LC, as demonstrated by

Table 1. Results from retrospective studies on stereotactic radiotherapy (SRT) for liver metastases

Study	N pts	N lesions	Histology	Total dose/n fractions	Follow-up, median [months]	Local control (%)	Overall survival (%)	Toxicity (%)
Chang et al. (2011) [34]	65	102	Colon-rectum	22–60 Gy/1–6	14.4	1-yr — 62%	1-yr — 72%	G ≥ 2: 3%
Menichelli et al. (2012) [55]	100	173	Colon-rectum, breast, lung	Median dose 35 Gy	15	1-yr —78% 2-yr — 62%	Nr	No G ≥ 3
Wulf et al. (2006) [56]	44	51	Colon, breast, ovary	30–37.5 Gy/3; 26 Gy/1	24	1-yr — 92% 2-yr — 66%	1-yr —72% 2-yr —32%	No G ≥ 2
Lanciano et al. (2012) [57]	30	41	Colon-rectum, breast, other	36–60 Gy/3; 50 Gy/5	22	1-yr — 92% 2-yr — 56%	1-yr —73% 2-yr —31%	No G ≥ 3
Katz et al. (2007) [65]	69	174	Colon-rectum, breast, pancreas, lung, other	30–55 Gy/5–15	14.5	20 months — 57%	6 months — 46% 1-yr — 24%	No G ≥ 3
Vautravers-Dewas et al. (2011) [66]	42	62	nr	40 Gy/4; 45 Gy/3	14.3	2-yr — 86%	2-yr — 48%	Nr
Habermehl et al. (2013) [67]	138	138	Colon-rectum, breast, pancreas, other	10 Gy/1	21.7	1-yr — 69% 18 months — 59%	1-yr — 70% 18 months — 59%	Nr

Table 2. Results from prospective trials on stereotactic radiotherapy (SRT) for liver metastases

Study	Phase	N pts	N lesions	Histology	Total dose/n fractions	Follow-up, median [months]	Local control (%)	Overall survival (%)	Toxicity (%)
Rusthoven et al. (2009 [35]	I/II	47	63	Colon-rectum, lung, esophagus, hepatocellular carcinoma, other	36–60/3	16	1-yr — 95% 2-yr — 92%	2-yr — 62%	G ≥ 3: 2%
Scorsetti et al. (2013) [36]	II	61	76	Colon-rectum, breast, other	75 Gy/3	12	1-yr — 64%	1-yr — 83% 18 months — 65%	G3: 2%
Folkert et al. (2020) [37]	I	33	39	Colon-rectum, kidney, other	35 Gy/1 40 Gy/1	25.9	4-yr (entire cohort) — 96.6%	2-yr — 82.0% 4-yr — 49.7%	G ≥ 3: 0%
Mendez-Romero et al. (2006) [42]	I/II	27	34	Colon-rectum, hepatocellular carcinoma, other	30–37.5 Gy/3	12.9	1-yr — 100% 2-yr — 86%	1-yr — 85% 2-yr — 62%	G3: 4%
Hoyer et al. (2006) [62]	II	64	44	Colon-rectum	45 Gy/3	51.6	2-yr — 79%	2-yr — 38%	G ≥ 3: 4%
Lee et al. (2009) [64]	I	68	140	Colon-rectum, breast, other	27.7–60 Gy/6	10.8	1-yr — 71%	Median 18 months	No toxicity
Rule et al. (2011) [68]	I	27	37	Colon-rectum, other	30 Gy/3, 50 Gy/5; 60 Gy/5	20	2-yr — 56% (30 Gy), 89% (50 Gy), 100% (60 Gy)	Nr	G ≥ 3: 2%

Andratschke et al. in 623 metastases (HR: 0.46, 95% CI: 0.29–0.72; p ≤ 0.001) [41].

The impact of SRT on OS appears unclear. Even though LC rates remained stable for years after treatment, survival rates were high in the first two years (30-70%) but then tended to drop [56, 57]. It is worth noting that out-field liver progression, i.e. the onset of new metastases, occurred in 45% of cases [58]. Metastatic progression in the liver or other organs was related to the number of lesions (patients with ≤ 3 metastases had a lower risk of subsequent metastatic spread), lesion size (which should be ≤ 5–6 cm in maximum diameter to achieve better outcome), type of primary tumor, histological grading. Furthermore, systemic treatments during or after SRT [41] that are aimed at controlling micrometastases may improve outcome [10, 24]. Randomized trials are needed to define patient selection better and to integrate SRT with other loco-regional treatments and systemic therapies [59].

Toxicity

RILD, with ascites, hepatosplenomegaly and increased alkaline phosphatase, has never been reported as an adverse event following SRT for liver metastases although it was associated with radiotherapy for hepatocellular carcinoma in cirrhotic patients [60]. The most common SRT-related toxicities include increases in liver enzymes [45], hyperbilirubinemia, and hypoalbuminemia [61]. Liver failure with the death of the patient was reported once [62]. Toxicity after SRT is linked to high doses to the OARs, particularly the right colic flexure and the gastro-duodenal tract due to their proximity. Indeed, in 3 patients receiving a total dose to the bowel that was higher than or equal to 30 Gy in 3 fractions, duodenal ulceration was reported in 2 and colon perforation in 1 [29]. When the target lesion is located in liver segments IV and V i.e., near the gastrointestinal tract, or when previous metastases have been resected, it may be advisable to reduce the total prescribed dose or to increase the number of fractions [63]. The ribs are another OAR. Lee et al. [64] diagnosed rib fractures at 6 and 23 months after SRT in 2 patients who had received maximum rib doses of 51.8 Gy and 66.2 Gy at 0.5 cm^3, respectively. Overall, the pattern of late toxicity remains mild even in long-term follow-ups. In fact, as one study reported, only 1 patient experienced late G3 toxicity at 6 months with severe chest wall pain while 2 patients complained of G2 moderate chest wall pain at 5 and 7 months, respectively [36].

Conclusions and practical remarks

SRT is a valid option for the treatment of oligometastatic liver disease, with very promising results in terms of LC (1-, and 2-year rates from 66–100%, and 56–100%, respectively). Contouring for liver SRT should be based on contrast MRI and/or PET-CT; triphasic CT scan is the first step in the planning procedures. 4D-CT is required to evaluate tumor motion.

Doses and fractionation for liver SRT have not yet been defined and should be tailored for each patient; although they are currently based on lesion size, location, and radiosensitivity of primary tumour, schedules with BED_{10} values over 100 Gy are commonly suggested. High dose SRT was effective, safe and well-tolerated.

Conflicts of interest

The authors have no conflict of interest to declare.

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References

1. Sheth KR, Clary BM. Management of hepatic metastases from colorectal cancer. Clin Colon Rectal Surg. 2005; 18(3): 215–223, doi: 10.1055/s-2005-916282, indexed in Pubmed: 20011304.
2. Jegatheeswaran S, Mason JM, Hancock HC, et al. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. JAMA Surg. 2013; 148(4): 385–391, doi: 10.1001/jamasurg.2013.1216, indexed in Pubmed: 23715907.
3. Turdean S, Gurzu S, Turcu M, et al. Liver metastases: incidence and clinicopathological data. Acta Medica Marisiensis. 2012; 58: 254–258.
4. Görög D, Tóth A, Weltner J. Prognosis of untreated liver metastasis from rectal cancer. Acta Chir Hung. 1997; 36(1-4): 106–107, indexed in Pubmed: 9408305.
5. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006; 244(2): 254–259, doi: 10.1097/01.sla.0000217629.94941.cf, indexed in Pubmed: 16858188.
6. Hoe AL, Royle GT, Taylor I. Breast liver metastases--incidence, diagnosis and outcome. J R Soc Med. 1991; 84(12): 714–716, indexed in Pubmed: 1774744.
7. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005; 241(5): 715–22, discussion 722, doi: 10.1097/01.sla.0000160703.75808.7d, indexed in Pubmed: 15849507.
8. Wei AC, Greig PD, Grant D, et al. Survival after hepatic resection for colorectal metastases: a 10-year experience. Ann Surg Oncol. 2006; 13(5): 668–676, doi: 10.1245/ASO.2006.05.039, indexed in Pubmed: 16523369.
9. Ellis OV, Hornock SL, Bohan PM, et al. Impact of Hepatic Metastasectomy in the Multimodal Treatment of Metastatic Breast Cancer. J Surg Res. 2021 [Epub ahead of print]; 268: 650–659, doi: 10.1016/j.jss.2021.07.032, indexed in Pubmed: 34474214.
10. Kim M, Son S, Won Y, et al. Stereotactic Ablative Radiotherapy for Oligometastatic Disease in Liver. BioMed Res Int. 2014; 2014: 1–9, doi: 10.1155/2014/340478, indexed in Pubmed: 24868526.
11. Loi M, Desideri I, Dominici L, et al. Thermal Ablation versus SBRT in liver tumours: pros and cons. Med Oncol. 2020; 37(6): 52, doi: 10.1007/s12032-020-01377-7, indexed in Pubmed: 32350765.
12. Correa RJM, Salama JK, Milano MT, et al. Stereotactic Body Radiotherapy for Oligometastasis: Opportunities for Biology to Guide Clinical Management. Cancer J. 2016; 22(4): 247–256, doi: 10.1097/PPO.0000000000000202, indexed in Pubmed: 27441744.
13. Nieuwenhuizen S, Puijk RS, van den Bemd B, et al. Resectability and Ablatability Criteria for the Treatment of Liver Only Colorectal Metastases: Multidisciplinary Consensus Document from the COLLISION Trial Group. Cancers (Basel). 2020; 12(7), doi: 10.3390/cancers12071779, indexed in Pubmed: 32635230.
14. Wernecke K, Rummeny E, Bongartz G, et al. Detection of hepatic masses in patients with carcinoma: comparative sensitivities of sonography, CT, and MR imaging. AJR Am J Roentgenol. 1991; 157(4): 731–739, doi: 10.2214/ajr.157.4.1892027, indexed in Pubmed: 1892027.
15. Larsen LP, Rosenkilde M, Christensen H, et al. The value of contrast enhanced ultrasonography in detection of liver metastases from colorectal cancer: a prospective double-blinded study. Eur J Radiol. 2007; 62(2): 302–307, doi: 10.1016/j.ejrad.2006.11.033, indexed in Pubmed: 17194561.
16. Quaia E, D'Onofrio M, Palumbo A, et al. Comparison of contrast-enhanced ultrasonography versus baseline ultrasound and contrast-enhanced computed tomography in metastatic disease of the liver: diagnostic performance and confidence. Eur Radiol. 2006; 16(7): 1599–1609, doi: 10.1007/s00330-006-0192-7, indexed in Pubmed: 16552507.
17. Robinson PJ. The early detection of liver metastases. Cancer Imag. 2002; 2: 1–3.
18. Kulemann V, Schima W, Tamandl D, et al. Preoperative detection of colorectal liver metastases in fatty liver: MDCT or MRI? Eur J Radiol. 2011; 79(2): e1–e6, doi: 10.1016/j.ejrad.2010.03.004, indexed in Pubmed: 20392584.
19. Bluemke DA, Sahani D, Amendola M, et al. Efficacy and safety of MR imaging with liver-specific contrast agent: U.S. multicenter phase III study. Radiology. 2005; 237(1): 89–98, doi: 10.1148/radiol.2371031842, indexed in Pubmed: 16126918.

20. Ruers TJM, Langenhoff BS, Neeleman N, et al. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. J Clin Oncol. 2002; 20(2): 388–395, doi: 10.1200/JCO.2002.20.2.388, indexed in Pubmed: 11786565.
21. Fernandez FG, Drebin JA, Linehan DC, et al. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg. 2004; 240(3): 438–47; discussion 447, doi: 10.1097/01.sla.0000138076.72547.b1, indexed in Pubmed: 15319715.
22. Dagan R, Lo SS, Redmond KJ, et al. A multi-national report on stereotactic body radiotherapy for oligometastases: Patient selection and follow-up. Acta Oncol. 2016; 55(5): 633–637, doi: 10.3109/0284186X.2015.1118659, indexed in Pubmed: 27046290.
23. John R, Ho F, Appalanaido G, et al. Can radiotherapy finally "go live" in the management of liver metastases? Hepatoma Res. 2020, doi: 10.20517/2394-5079.2020.37.
24. Schefter TE, Kavanagh BD. Radiation therapy for liver metastases. Semin Radiat Oncol. 2011; 21(4): 264–270, doi: 10.1016/j.semradonc.2011.05.006, indexed in Pubmed: 21939855.
25. Palacios-Eito A, García-Cabezas S. Oligometastatic disease, the curative challenge in radiation oncology. World J Clin Oncol. 2015; 6(4): 30–34, doi: 10.5306/wjco.v6.i4.30, indexed in Pubmed: 26266098.
26. Høyer M, Swaminath A, Bydder S, et al. Radiotherapy for liver metastases: a review of evidence. Int J Radiat Oncol Biol Phys. 2012; 82(3): 1047–1057, doi: 10.1016/j.ijrobp.2011.07.020, indexed in Pubmed: 22284028.
27. Franzese C, Comito T, Viganò L, et al. Liver Metastases-directed Therapy in the Management of Oligometastatic Breast Cancer. Clin Breast Cancer. 2020; 20(6): 480–486, doi: 10.1016/j.clbc.2020.05.006, indexed in Pubmed: 32631769.
28. Romesser PB, Neal BP, Crane CH. External Beam Radiation Therapy for Liver Metastases. Surg Oncol Clin N Am. 2021; 30(1): 159–173, doi: 10.1016/j.soc.2020.08.006, indexed in Pubmed: 33220803.
29. Riou O, Llacer Moscardo C, Fenoglietto P, et al. SBRT planning for liver metastases: A focus on immobilization, motion management and planning imaging techniques. Rep Pract Oncol Radiother. 2017; 22(2): 103–110, doi: 10.1016/j.rpor.2017.02.006, indexed in Pubmed: 28490980.
30. Kowalchuk RO, Waters MR, Richardson KM, et al. A single-institutional experience with low dose stereotactic body radiation therapy for liver metastases. Rep Pract Oncol Radiother. 2020; 25(6): 987–993, doi: 10.1016/j.rpor.2020.09.010, indexed in Pubmed: 33100916.
31. Ohri N, Tomé WA, Méndez Romero A, et al. Local Control After Stereotactic Body Radiation Therapy for Liver Tumors. Int J Radiat Oncol Biol Phys. 2021; 110(1): 188–195, doi: 10.1016/j.ijrobp.2017.12.288, indexed in Pubmed: 29395629.
32. Kok END, Jansen EPM, Heeres BC, et al. High versus low dose Stereotactic Body Radiation Therapy for hepatic metastases. Clin Transl Radiat Oncol. 2020; 20: 45–50, doi: 10.1016/j.ctro.2019.11.004, indexed in Pubmed: 31886419.
33. Joo JiH, Park JH, Kim JC, et al. Local Control Outcomes Using Stereotactic Body Radiation Therapy for Liver Metastases From Colorectal Cancer. Int J Radiat Oncol Biol Phys. 2017; 99(4): 876–883, doi: 10.1016/j.ijrobp.2017.07.030, indexed in Pubmed: 29063852.
34. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer. 2011; 117(17): 4060–4069, doi: 10.1002/cncr.25997, indexed in Pubmed: 21432842.
35. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol. 2009; 27(10): 1572–1578, doi: 10.1200/JCO.2008.19.6329, indexed in Pubmed: 19255321.
36. Scorsetti M, Arcangeli S, Tozzi A, et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. Int J Radiat Oncol Biol Phys. 2013; 86(2): 336–342, doi: 10.1016/j.ijrobp.2012.12.021, indexed in Pubmed: 23433800.
37. Folkert MR, Meyer JJ, Aguilera TA, et al. Long-Term Results of a Phase 1 Dose-Escalation Trial and Subsequent Institutional Experience of Single-Fraction Stereotactic Ablative Radiation Therapy for Liver Metastases. Int J Radiat Oncol Biol Phys. 2021; 109(5): 1387–1395, doi: 10.1016/j.ijrobp.2020.12.012, indexed in Pubmed: 33340601.
38. Klement RJ, Abbasi-Senger N, Adebahr S, et al. The impact of local control on overall survival after stereotactic body radiotherapy for liver and lung metastases from colorectal cancer: a combined analysis of 388 patients with 500 metastases. BMC Cancer. 2019; 19(1): 173, doi: 10.1186/s12885-019-5362-5, indexed in Pubmed: 30808323.
39. Ahmed KA, Caudell JJ, El-Haddad G, et al. Radiosensitivity Differences Between Liver Metastases Based on Primary Histology Suggest Implications for Clinical Outcomes After Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys. 2016; 95(5): 1399–1404, doi: 10.1016/j.ijrobp.2016.03.050, indexed in Pubmed: 27319288.
40. Klement RJ, Guckenberger M, Alheid H, 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(2): 227–233, doi: 10.1016/j.radonc.2017.01.013, indexed in Pubmed: 28274491.
41. Andratschke N, Alheid H, Allgäuer M, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer. 2018; 18(1): 283, doi: 10.1186/s12885-018-4191-2, indexed in Pubmed: 29534687.
42. Méndez Romero A, Wunderink W, Hussain SM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase i-ii study. Acta Oncol. 2006; 45(7): 831–837, doi: 10.1080/02841860600897934, indexed in Pubmed: 16982547.
43. Comito T, Clerici E, Tozzi A, et al. Liver metastases and SBRT: A new paradigm? Rep Pract Oncol Radiother. 2015; 20(6): 464–471, doi: 10.1016/j.rpor.2014.10.002, indexed in Pubmed: 26696787.
44. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010; 37(8): 4078–4101, doi: 10.1118/1.3438081, indexed in Pubmed: 20879569.

45. Kothary N, Heit JJ, Louie JD, et al. Safety and efficacy of percutaneous fiducial marker implantation for image-guided radiation therapy. J Vasc Interv Radiol. 2009; 20(2): 235–239, doi: 10.1016/j.jvir.2008.09.026, indexed in Pubmed: 19019700.
46. Stick LB, Vogelius IR, Risum S, et al. Intrafractional fiducial marker position variations in stereotactic liver radiotherapy during voluntary deep inspiration breath-hold. Br J Radiol. 2020; 93(1116): 20200859, doi: 10.1259/bjr.20200859, indexed in Pubmed: 32915653.
47. Witt JS, Rosenberg SA, Bassetti MF. MRI-guided adaptive radiotherapy for liver tumours: visualising the future. Lancet Oncol. 2020; 21(2): e74–e82, doi: 10.1016/S1470-2045(20)30034-6, indexed in Pubmed: 32007208.
48. Gani C, Boeke S, McNair H, et al. Marker-less online MR-guided stereotactic body radiotherapy of liver metastases at a 1.5 T MR-Linac - Feasibility, workflow data and patient acceptance. Clin Transl Radiat Oncol. 2021; 26: 55–61, doi: 10.1016/j.ctro.2020.11.014, indexed in Pubmed: 33319073.
49. Hall WA, Straza MW, Chen X, et al. Initial clinical experience of Stereotactic Body Radiation Therapy (SBRT) for liver metastases, primary liver malignancy, and pancreatic cancer with 4D-MRI based online adaptation and real-time MRI monitoring using a 1.5 Tesla MR-Linac. PLoS One. 2020; 15(8): e0236570, doi: 10.1371/journal.pone.0236570, indexed in Pubmed: 32764748.
50. Rubio C, Hernando-Requejo O, Zucca Aparicio D, et al. Image guided SBRT for multiple liver metastases with ExacTrac Adaptive Gating. Rep Pract Oncol Radiother. 2017; 22(2): 150–157, doi: 10.1016/j.rpor.2016.07.006, indexed in Pubmed: 28490986.
51. Jarraya H, Mirabel X, Taieb S, et al. Image-based response assessment of liver metastases following stereotactic body radiotherapy with respiratory tracking. Radiat Oncol. 2013; 8: 24, doi: 10.1186/1748-717X-8-24, indexed in Pubmed: 23363610.
52. Høyer M, Swaminath A, Bydder S, et al. Radiotherapy for liver metastases: a review of evidence. Int J Radiat Oncol Biol Phys. 2012; 82(3): 1047–1057, doi: 10.1016/j.ijrobp.2011.07.020, indexed in Pubmed: 22284028.
53. Lee J, Shin IS, Yoon WS, et al. Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver malignancies: Meta-analyses and a systematic review. Radiother Oncol. 2020; 145: 63–70, doi: 10.1016/j.radonc.2019.12.004, indexed in Pubmed: 31923711.
54. Scorsetti M, Comito T, Clerici E, et al. Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up. Radiat Oncol. 2018; 13(1): 234, doi: 10.1186/s13014-018-1185-9, indexed in Pubmed: 30477560.
55. Menichelli C, Casamassima F, Panichi M, et al. SBRT for Liver Metastases: Results on 173 Treated Lesions. Int J Radiat Oncol Biol Phys. 2012; 84(3): S191, doi: 10.1016/j.ijrobp.2012.07.494.
56. Wulf J, Guckenberger M, Haedinger U, et al. Stereotactic radiotherapy of primary liver cancer and hepatic metastases. Acta Oncol. 2006; 45(7): 838–847, doi: 10.1080/02841860600904821, indexed in Pubmed: 16982548.
57. Lanciano R, Lamond J, Yang J, et al. Stereotactic body radiation therapy for patients with heavily pretreated liver metastases and liver tumors. Front Oncol. 2012; 2: 23, doi: 10.3389/fonc.2012.00023, indexed in Pubmed: 22645716.
58. Milano MT, Katz AW, Okunieff P. Patterns of recurrence after curative-intent radiation for oligometastases confined to one organ. Am J Clin Oncol. 2010; 33(2): 157–163, doi: 10.1097/COC.0b013e3181979238, indexed in Pubmed: 19770627.
59. Cacciola A, Parisi S, Tamburella C, et al. Stereotactic body radiation therapy and radiofrequency ablation for the treatment of liver metastases: How and when? Rep Pract Oncol Radiother. 2020; 25(3): 299–306, doi: 10.1016/j.rpor.2020.02.010, indexed in Pubmed: 32194349.
60. Lasley FD, Mannina EM, Johnson CS, et al. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy. Pract Radiat Oncol. 2015; 5(5): e443–e449, doi: 10.1016/j.prro.2015.02.007, indexed in Pubmed: 25899219.
61. Bae SH, Kim MS, Jang WII, et al. Low Hepatic Toxicity in Primary and Metastatic Liver Cancers after Stereotactic Ablative Radiotherapy Using 3 Fractions. J Korean Med Sci. 2015; 30(8): 1055–1061, doi: 10.3346/jkms.2015.30.8.1055, indexed in Pubmed: 26240482.
62. Hoyer M, Roed H, Traberg Hansen A, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol. 2006; 45(7): 823–830, doi: 10.1080/02841860600904854, indexed in Pubmed: 16982546.
63. Kim M, Son SH, Won YK, et al. Stereotactic ablative radiotherapy for oligometastatic disease in liver. Biomed Res Int. 2014; 2014: 340478, doi: 10.1155/2014/340478, indexed in Pubmed: 24868526.
64. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol. 2009; 27(10): 1585–1591, doi: 10.1200/JCO.2008.20.0600, indexed in Pubmed: 19255313.
65. Katz AW, Carey-Sampson M, Muhs AG, et al. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. Int J Radiat Oncol Biol Phys. 2007; 67(3): 793–798, doi: 10.1016/j.ijrobp.2006.10.025, indexed in Pubmed: 17197128.
66. Vautravers-Dewas C, Dewas S, Bonodeau F, et al. Image-guided robotic stereotactic body radiation therapy for liver metastases: is there a dose response relationship? Int J Radiat Oncol Biol Phys. 2011; 81(3): e39–e47, doi: 10.1016/j.ijrobp.2010.12.047, indexed in Pubmed: 21377292.
67. Habermehl D, Herfarth KK, Bermejo JL, et al. Single-dose radiosurgical treatment for hepatic metastases--therapeutic outcome of 138 treated lesions from a single institution. Radiat Oncol. 2013; 8: 175, doi: 10.1186/1748-717X-8-175, indexed in Pubmed: 23837905.
68. Rule W, Timmerman R, Tong L, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. Ann Surg Oncol. 2011; 18(4): 1081–1087, doi: 10.1245/s10434-010-1405-5, indexed in Pubmed: 21046264.