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Evidence-based clinical recommendations for hypofractionated radiotherapy: exploring efficacy and safety – Part 4: Liver and locally recurrent rectal cancer

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In this paper, we review the use of hypofractionated radiotherapy for gastrointestinal malignancies, focusing on primary and metastatic liver cancer, and recurrent rectal cancer. Technological advancements in radiotherapy have facilitated the direct delivery of high-dose radiation to tumors, while limiting normal tissue exposure, supporting the use of hypofractionation. Hypofractionated radiotherapy is particularly effective for primary and metastatic liver cancer where high-dose irradiation is crucial to achieve effective local control. For recurrent rectal cancer, the use of stereotactic body radiotherapy offers a promising approach for re-irradiation, balancing efficacy and safety in patients who have been administered previous pelvic radiotherapy and in whom salvage surgery is not applicable. Nevertheless, the potential for radiation-induced liver disease and gastrointestinal complications presents challenges when applying hypofractionation to gastrointestinal organs. Given the lack of universal consensus on hypofractionation regimens and the dose constraints for primary and metastatic liver cancer, as well as for recurrent rectal cancer, this review aims to facilitate clinical decision-making by pointing to potential regimens and dose constraints, underpinned by a comprehensive review of existing clinical studies and guidelines.

Keywords: Hepatocellular carcinoma, Hypofractionation, Liver neoplasms, Rectal neoplasms, Re-irradiation, Radiosurgery

Introduction

Radiotherapy is widely used for gastrointestinal (GI) malignancies. Clinical evidence increasingly supports the advantages of applying radiotherapy to hepatocellular carcinoma (HCC). In Korea, patients with HCC constitute the fifth most common group undergoing radiotherapy [1]. Moreover, given the efficacy of stereotactic body radiotherapy (SBRT) for HCC, various hypofractionation regimens

can be applied, depending on the target size and relevant organs-at-risk (OAR) [2]. Beyond HCC, radiotherapy for metastatic liver cancer has demonstrated its clinical advantages in the oligometastatic setting [3,4]. This review explores considerations for applying hypofractionated radiotherapy to HCC or metastatic liver cancer.

Neoadjuvant long-course concurrent chemoradiotherapy or short-course radiotherapy has become the standard of care for locally advanced cases of rectal cancer [5-7]. Despite the reduction in local recurrence achieved with these approaches, a substantial proportion of patients still experience local recurrence [8,9]. In situations requiring re-irradiation to enhance therapeutic gain, modalities such as hypofractionated radiotherapy including SBRT are considered [10]. Nevertheless, clear guidelines are currently not available for these scenarios. This review will discuss considerations that should be considered in radiotherapy in these situations.

Liver KQ1: What is the Applicable Hypofractionated Radiotherapy Regimen for Primary and Metastatic Liver Cancer?

1. Primary liver cancer

Liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related deaths worldwide [11]. HCC is the most common primary liver cancer, accounting for approximately 90% of cases, followed by intrahepatic cholangiocarcinoma (IHCC) and other primary liver cancers [12]. In the early stage of the disease, the mainstay of curative local therapy includes surgical resection, liver transplantation, and radiofrequency ablation (RFA). In the advanced stage, trans-arterial chemoembolization and/or systemic therapy are usually recommended [13,14]. However, these approaches are often limited due to tumor-related or patient-related factors, and their efficacies are often unsatisfactory [15]. In this context, radiotherapy has been increasingly utilized as an alternative treatment, or as part of a combination treatment for cure or palliation of primary liver cancer [16,17].

In the past, liver-directed radiotherapy was recognized as unsafe due to concerns about radiation-induced liver disease (RILD) or toxicity in the GI tract [18,19]. However, technical advances, including radiotherapy planning, and image-guided radiotherapy with respiratory motion control has led to safe and effective delivery of high-dose radiation [20]. Furthermore, the introduction of proton beam therapy has expanded the application of radiotherapy to primary liver cancer [21]. In particular, because HCC and IHCC require high-dose irradiation to achieve sufficient local control, this technical advance was critical for extending radiotherapy to the treatment of primary liver cancer [22]. Now, hypofractionated high-dose radiotherapy is a widely used regimen for the radiotherapy in primary liver cancer [23]. Nonetheless, high-dose liver-directed radiotherapy still raises concern about RILD and GI tract toxicity because patients with primary liver cancer tend to have underlying liver disease, poor liver function, and related gastroduodenopathy, which can be exacerbated by irradiation [24,25]. Therefore, the dose prescription depends on the tumor size, tumor location relative to the adjacent GI tract, underlying liver function, and estimated dose distribution in the normal liver parenchyma [2]. Hypofractionated regimens for HCC typically involve administration of 8–15 Gy per fraction over a course of 3–10 fractions [26]. Numerous prospective and retrospective studies employing this schedule have consistently shown an local control rate exceeding 90% across various research studies [26]. When determining the fraction size in radiotherapy for liver cancer, enhancement of the therapeutic ratio must be considered. This involves considering the dose–response of the tumor and the tolerance of OAR, to optimize the treatment parameters.

A clear dose–response relationship for guiding dose selection in HCC is controversial. Several studies have identified the relationship between local control rate and an equivalent dose in 2 Gy fractions (EQD_2). Lee et al. [27] reported a dose–response relationship, based on the EQD_2 with α/β ratio 10, in retrospective findings of radiotherapy in the caudate lobe. A local control rate of 100% has been observed with an EQD_2 >90 Gy. However, the correlation between higher doses and enhanced local control rates is controversial. Generally, excessively high doses may not always be necessary for small lesions [28,30]. Lee et al. [28]. reported the outcomes of ultra-hypofractionated radiotherapy with three fractions for HCC less than 3 cm showing that the local control was comparable between total doses of 45 Gy and 60 Gy. Furthermore Lee et al. [29] argued that the local control rates of hypofractionated radiotherapy for HCC were not associated with excessive dose above 100 Gy in biologically effective dose with α/β ratio 10 by reviewing the previous studies [30-34]. Further research is necessary to confirm the adequate dose regimen for optimal local control. In addition to considering the dose–response relationship of the tumor, the optimal dose regimen should take into account the baseline liver function. Decompensation of the liver frequently occurs following radiotherapy for HCC, particularly in cirrhotic patients or those with impaired liver function. Therefore, determining the optimal dose fractionation should be done while ensuring that the constraints of the normal liver, tailored to the Child-Pugh (CP) class, are met.

By summarizing the existing trials, a recent guideline from the American Society for Radiation Oncology (ASTRO) suggested hypofractionated radiotherapy doses and fractionation for HCC and IHCC, which are summarized in Table 1 [2]. Studies that primarily employed a 10-fraction hypofractionated schedule have mainly fo-

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Table 1. Recommended hypofractionated radiotherapy regimen for HCC and IHCC

Suggesting groups	Clinical situation	Total dose / fractionation
ASTRO	Ultra-hypofractionation	30–60 Gy in 3–5 fx[a,b]
		40–54 Gy in 6 fx
		50–66 Gy in 10 fx
	Moderate hypofractionation	48 Gy in 12 fx
		45–67.5 Gy in 15 fx
		60 Gy in 20 fx
		66–72 Gy in 22 fx
	Conventional fractionation	50.4 Gy in 28 fx[a]
		60 Gy in 30 fx
		77 Gy in 35 fx
PMRC	Tumors at >2 cm from the porta hepatis and GI tract	66 GyRBE in 10 fx
	Tumors at <2 cm from the porta hepatics and >2 cm from GI tract	72.6 GyRBE in 22 fx
	Tumors at <2 cm from the GI tract	77 GyRBE in 35 fx

HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; ASTRO, American Society for Radiation Oncology; PMRC, Proton Medical Research Center; GI, gastrointestinal; RBE, relative biological effectiveness; fx, fractions.
[a]Most common prescriptions used. [b]The recommended regimens are different according to the clinical situation as follows: 40–60 Gy in 3–5 fractions for noncirrhotic primary liver cancer (intrahepatic cholangiocarcinoma), 40–50 Gy in 3–5 fractions for Child-Pugh class A, and 30–40 Gy in 5 fractions for Child-Pugh class B7.

cused on the use of protons. Regarding proton beam therapy for primary HCC, the Proton Medical Research Center of the University of Tsukuba, Japan, has developed a dose regimen according to the location of primary tumor, relative to the porta hepatis and GI tract, which is also described in Table 1 [35].

2. Metastatic liver cancer

Metastatic liver cancer accounts for the majority of liver cancer cases and its proportion is higher than that of primary liver cancer [36,37]. Liver exhibits the highest frequency of metastases, as compared with that in other organs, primarily due to the unique characteristics of its circulation system, known as the dual supply by the portal vein and hepatic artery, which increases the chance for metastatic cancer cells to be deposited [37,38]. Because the existence of liver metastasis reflects systemic dissemination of the disease, systemic therapies are the mainstay of treatment [39]. However, for hepatic oligometastasis (HOM), local treatment modalities, including surgical resection, radiotherapy, and RFA, are actively applied. Among those modalities, the evidence about the benefit of surgical resection for HOM, particularly that arising from colorectal cancer, is the strongest and this treatment tends to be prioritized [3,40]. However, because surgical resection is limited by the operability of patients and resectability of the tumor, surgical resection is feasible in only to a small portion of patients with HOM [41]. Therefore, alternative less-invasive therapeutic approaches, such as RFA and radiotherapy, are also considered for ablation of HOM. Although RFA also shows good local control rates for HOM, RFA is only feasible for tumors located in visible areas on ultrasonography, i.e., areas accessible by a probe, not proximal to the vessels, and with size of 2–3 cm or less [42,43]. Radiotherapy can be another option for patients with HOM whose disease is not amenable to surgical resection and RFA.

As the radiotherapy technique for HOM, hypofractionated radiotherapy, mainly with ultra-hypofractionation, is currently widely used. However, no standardized regimen of hypofractionated radiotherapy is available for HOM [3]. Several prospective studies have reported the outcomes of hypofractionated radiotherapy for HOM derived from various primary cancers. Those studies adopted diverse dose regimens. The selected prospective studies are summarized in Table 2 [44-51]. Due to the diversity of the studies, including the study population, tumor characteristics, and treatment regimens, the reported outcomes were also heterogeneous. However, some factors, including metastatic tumor size, burden of metastatic disease, control of extrahepatic metastasis, and prescribed dose, were significantly and consistently associated with the oncological outcomes in various studies [44-46]. These factors identify HOM candidates for whom high-dose hypofractionated radiotherapy are suitable. As with primary liver cancer, hypofractionated proton beam therapy can be an attractive option for HOM, because of its physical property of reducing the irradiated volume to the liver and enabling dose escalation. Some prospective studies have reported the outcomes of hypofractionated proton beam therapy for patients with HOM showing good oncological outcomes and minimal toxicities [47,48].

Table 2. Selected prospective studies for stereotactic body radiotherapy or hypofractionated radiotherapy for liver metastasis

Study, year	Primary cancer (%)	Number of patients (lesions)	Number of tumors	Tumor size	Dose scheme	Outcomes	Toxicity
Rusthoven et al. [49], 2009	CRC (31.9) Lung cancer (21.3) Breast cancer (8.5) Ovarian cancer (6.4) Esophageal cancer (6.4) HCC (4.3) Others (21.3)	47 (63)	1–3	< 6 cm	36–60 Gy/3 fx	1-yr, 2-yr LC: 95%, 92% Median OS: 20.5 mo	Late: Gr ≥ 3 (2%)
Lee et al. [50], 2009	CRC (58.8) Breast cancer (17.6) Others (23.5)	68 (143)	1–8	Median TV: 75.2 mL (1.19–3,090 mL)	27.7–60 Gy/6 fx Median: 41.8 Gy/6 fx	1-yr LC: 71% Median OS: 17.6 mo	Acute: Gr ≥ 3 (10%) Late: Gr 4 (1.5%), Gr 5 (1.5%)
Chang et al. [44], 2011	CRC (100.0)	56 (102)	1–4	Median GTV: 30.1 mL (0.6–3,088 mL)	18–30 Gy/1 fx 36–60 Gy/3–6 fx Median: 41.7 Gy (22–60 Gy)	1-yr, 2-yr LC: 67%, 55% 1-yr, 2-yr OS: 72%, 38%	Acute: Gr 2 (14%), Gr 3 (3%) Late: Gr 2 (2%), Gr 3 (4%)
Scorsetti et al. [51], 2012	CRC (45.9) Breast cancer (18.0) Gynecological cancer (11.5) Others (22.9)	61 (76)	1–3	< 6 cm	75 Gy/3 fx	1-yr LC: 94.0% 1-yr OS: 83.5% Median OS: 19 mo	Late: Gr 3 (1.6%)
Scorsetti et al. [45], 2015	CRC (100.0)	42 (52)	1–3	Median: 3.5 cm (1.1–5.4 cm)	75 Gy/3 fx	3-yr LC: 85% 2-yr PFS: 48% 2-yr OS: 65%	Acute: Gr 2 (33%), Gr ≥ 3 (0%)
McPartin et al. [46], 2017	CRC (100.0)	70 (103)	1–3	Median GTV: 40.8 mL (0.6–3,089 mL)	22.7–62.1 Gy/5–6 fx	1-yr, 2-yr, 4-yr LC: 50%, 32%, 26% Median PFS: 10.8 mo Median OS: 16 mo	Acute: Gr 3 (6%)
Hong et al. [47], 2017	CRC (38.2) Pancreas cancer (14.6) Esophagogastric cancer (13.5) Others (33.7)	89 (143)	1–4	Median: 2.5 cm (0.5–11.9 cm)	30–50 GyRBE/5 fx	1-yr, 3-yr LC: 71.9%, 61.2% 1-yr, 3-yr PFS: 24.7%, 9.2% 1-yr, 3-yr OS: 66.3%, 20.8%	Gr ≥ 3 (0%)
Kim et al. [48], 2022	CRC (61.2) Gastroduodenal cancer (18.4) Esophageal cancer (2.0) Pancreatobiliary cancer (12.2) Lung cancer (2.0) Others (4.1)	46 (49)	1–3	Median: 2.5 cm (IQR 1.4–4.3 cm)	60 GyRBE/5 fx 70 GyRBE/10 fx	6-mo LC: 95.2%	Gr 2 (3.3%) Gr ≥ 3 (0%)

CRC, colorectal cancer; HCC, hepatocellular carcinoma; LC, local control; OS, overall survival; Gr, grade; TV, tumor volume; GTV, gross tumor volume; RBE, relative biological effectiveness; PFS, progression-free survival; IQR, interquartile range; fx, fractions.

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Liver KQ2: What are the Recommended Dose Constraints for Liver and Bowel Structures for Primary and Metastatic Liver Cancer?

Hypofractionated high-dose radiotherapy should be delivered safely while maintaining strict OAR dose constraints and employing adequate motion management [2]. Table 3 summarizes the reported OAR constraints based on fractionation from the American Association of Physicists in Medicine (AAPM) Task Group report [52], ASTRO guidelines [2], UK consensus [53], and the report by Timmerman [54].

In terms of normal liver volume, it is crucial to determine the radiation dose necessary to spare 700 mL of uninvolved liver volume, considering the parallel organ nature of the liver, as long as the mean liver dose is appropriate, particularly when applying a shorter schedule [16].

Cirrhotic liver patients with impaired baseline liver function are more sensitive to decompensation induced by radiotherapy [55,56]. Therefore, dose constraints according to the CP class should vary. In the ASTRO guidelines, liver dose constraints based on CP score were provided and presented in Table 3.

Strict adherence to dose constraints for GI structures is needed to prevent GI bleeding, which can lead to severe morbidity. Additionally, considering the movement of the liver, establishing appropriate planning OAR volume, and employing precise image guidance are essential for accurately assessing the radiation dose to GI structures [57]. Proficient experience in these aspects is crucial for minimizing GI toxicity. Tumors involving the porta hepatis demand meticulous attention, considering the ensuing biliary complications. These complications include biliary toxicity, characterized by biliary stricture and biliary obstruction, which may precipitate biliary sepsis. Hence, caution is needed when applying shortened fractionation in cases with portal vein tumor thrombosis. A more fractionated schedule is preferred when the tumor is close to the porta hepatis, and it is considered advisable to use a generous constraint for biliary structures when using a more fractionated regimen [58]. For moderate hypofractionation (10 or 15 fractions), current data on normal tissue constraints stem primarily from clinical study protocols utilizing proton therapy [59-61].

Rectum KQ 1: What are the Appropriate Hypofractionated Radiotherapy Schedules and Indications for Re-irradiation in Cases of Recurrent Rectal Cancer?

Local recurrence of rectal cancer, which refers to the recurrence of cancer within the pelvis after previous surgical resection, poses a

Table 3. Normal tissue constraint for liver and bowel structures for liver cancer

Organs-at-risk	3 fractions	5 fractions	10 fractions
Liver			
Noncirrhotic	D_{mean} < 12–15 Gy $D_{>700mL}$ < 19 Gy $D_{>700mL}$ < 17.7 Gy[a]	D_{mean} < 15–18 Gy $D_{>700mL}$ < 21 Gy $D_{>700mL}$ < 21.5 Gy[a]	$D_{>700mL}$ < 27 Gy[a]
Child-Pugh class A	D_{mean} < 10–12 Gy	D_{mean} < 13–15 Gy $D_{>700mL}$ < 15 Gy	D_{mean} < 15–20 Gy
Child-Pugh class B7	-	D_{mean} < 8–10 Gy $D_{>500mL}$ < 10 Gy	D_{mean} < 10–16 Gy
Bile duct	$D_{0.03mL}$ < 35.7 Gy	$D_{0.03mL}$ < 40.5 Gy	-
Stomach	$D_{0.03mL}$ < 22 Gy, 30 Gy[a] D_{5mL} < 22.5 Gy[a] D_{10mL} < 16.5 Gy	$D_{0.03mL}$ < 32 Gy, 35 Gy[a] D_{10mL} < 18 Gy D_{5mL} < 26.5 Gy[a]	$D_{0.03mL}$ < 45 Gy[a] D_{50mL} < 33.9 Gy[a]
Duodenum	$D_{0.03mL}$ < 22 Gy, 30 Gy[a] D_{5mL} < 16.5 Gy, 22.5 Gy[a] D_{10mL} < 11.4 Gy[b]	$D_{0.03mL}$ < 32 Gy, 35 Gy[a] D_{5mL} < 18 Gy, 26.5 Gy[a] D_{10mL} < 12.5 Gy[b]	$D_{0.03mL}$ < 45 Gy[a] D_{5mL} < 33.9 Gy[a]
Small bowel	$D_{0.03mL}$ < 25 Gy, 28.5 Gy[a] D_{5mL} < 18 Gy D_{30mL} < 20.7 Gy[a]	$D_{0.03mL}$ < 32 Gy, 35 Gy[b] D_{5mL} < 19.5 Gy D_{30mL} < 24 Gy[a]	$D_{0.03mL}$ < 41 Gy[a] D_{120mL} < 33.9 Gy[a]
Large bowel	$D_{0.03mL}$ < 28 Gy, 45 Gy[a] D_{20mL} < 24 Gy, 28.8 Gy[a]	$D_{0.03mL}$ < 34 Gy, 52.5 Gy[a] D_{20mL} < 25 Gy, 32.5 Gy[a]	$D_{0.03mL}$ < 60 Gy[a] D_{20mL} < 47 Gy[a]

D_{xmL} indicates a dose to x mL of the structure and D_{mean}, mean dose.
The data from the American Society for Radiation Oncology guidelines [54] are provided without specific denotation.
[a]Data from report by Timmerman [54]. [b]Data from the American Association of Physicists in Medicine Task Group report [52].

significant medical challenge, due to the associated morbidity. This includes pelvic pain, fistula, bleeding, fecal discharge, pelvic infection, and obstruction, all of which greatly impact the patient's quality of life [62]. Local recurrence rates remain approximately 10%, even after pelvic irradiation and surgery [63]. Curative resection of the local recurrence is crucial to improve survival. However, radical surgery often presents difficulties and leads to surgical morbidity if the tumor has a lateral location, is in proximity to the iliac vessels, or has invaded the sacrum or pelvic bone [64].

Hypofractionated radiotherapy, mainly with form of SBRT, represents a promising modality offering precise and highly conformal radiation delivery to the target area. However, SBRT for pelvic recurrence poses unique challenges. Many patients with local recurrence have previously received high-dose pelvic radiotherapy as part of the primary multimodal treatment, either as preoperative short-course radiotherapy (5 × 5 Gy) or as chemo-radiotherapy to 45–50 Gy (1.8–2.0 Gy/fraction). Factors such as previous radiation dose and field, and tumor proximity to OAR necessitate careful planning and precise dose calculation. The risk of late GI and genitourinary complications must be carefully considered.

1. Clinical outcomes of SBRT re-irradiation for pelvic recurrence from colorectal cancer

Re-irradiation with SBRT has demonstrated promising results in the management of recurrent rectal cancer in the pelvic area. Several studies have investigated the efficacy and safety of re-irradiation with SBRT (Table 4). Kim et al. [65] conducted a study involving 23 patients with recurrent rectal cancer who were treated with SBRT, of whom five had previously received pelvic irradiation. SBRT was administered at a dose of 30–51 Gy in 3 fractions. The study reported 4-year OS and local control rates of 24.9% and 74.3%, respectively, with one case of grade 4 rectal perforation. In cases of presacral recurrence, radical surgery is seldom a viable option, due to the predominant detection of recurrence as a fixed mass invading the sacrum and/or pelvic wall. DeFoe et al. [66] evaluated the safety and efficacy of re-irradiation with SBRT in 14 patients with presacral recurrences of rectal cancer. The patients received re-irradiation with SBRT at doses of 36 Gy in three fractions or 12 Gy, 16 Gy, or 18 Gy in 1 fraction. The study reported 1-year and 2-year local control rates of 90.9% and 68.2%, respectively, with no grade 3 or 4 toxicities observed. The 1-year and 2-year OS rates were 90.0% and 78.8%, respectively. Notably, SBRT provided complete pain relief from recurrent lesions in 57.1% of patients. Dagoglu et

Table 4. Studies reporting outcomes of stereotactic body radiotherapy re-RT for recurrent colorectal cancer

Study, period	Number of total/reRT patients	Median follow-up (month)	Previous RT dose	reRT dose	Treatment outcome			≥ Gr 3 toxicity
					OS	LC	PFS	
Kim et al. [65] 2002–2006	23/5	31	45 Gy	30–51 Gy/3 fx	4-yr OS: 24.9% 5-yr OS: 23.2% Median OS: 37 mo	4-yr LC: 74.3%	4-yr PFS: 51.1% Median PFS: 55 mo	Acute: Gr 4 rectal perforation (n = 1) Late: none
DeFoe et al. [66] 2003–2008	14/14	16.5	Median: 50.4 Gy	36 Gy/3 fx, 12 Gy/1 fx, 16 Gy/1 fx, 18 Gy/1 fx	1-yr OS: 90.0% 2-yr OS: 78.8%	1-yr LC: 90.9% 2-yr LC: 68.2%	NR	Acute: none Late: none
Dagoglu et al. [67] 2006–2012	18/18	38	Median: 50.4 Gy	25 Gy/5 fx	1-yr OS: 76.8% 2-yr OS: 65.9% 3-yr OS: 59.3% Median OS: 40 mo	1-yr LC:100% 2-yr LC: 93.7% 3-yr LC: 85.9%	NR	Acute or late: Gr 4 small bowel perforation (n = 1); Gr 3 neuropathy (n = 1); Gr 3 hydronephrosis from ureteric fibrosis (n = 1)
Smith et al. [10] 2015–2019	35/35	24.5	45–50.4 Gy	30 Gy/5 fx	1-yr OS: 95.0% 2-yr OS: 84.4% Median OS: 28.3 mo	1-yr LC: 84.9% 2-yr LC: 69.0%	Median PFS: 12.1 mo	Acute: none Late: Gr 3 pain (n = 1)
Johnstone et al. [68] 2015–2020	69/69	28	45–52.5 Gy	30 Gy/5 fx	2-yr OS: 77.0% Median OS: 38.7 mo	NR	2-yr PFS: 28.0% Median PFS: 12.1 mo	NR

reRT, re-irradiation; RT, radiotherapy, OS, overall survival; LC, local control; PFS, progression-free survival; fx, fractions; Gr, grade; NR, not reported.

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al. [67] reported on the outcomes of re-irradiation with SBRT in 18 patients with pelvic recurrences from colorectal cancer. SBRT was administered at a dose of 25 Gy in 5 fractions. The study reported 1-year and 2-year local control rates of 100% and 93.7%, respectively, and 1-year and 2-year OS rates of 76.8% and 65.9%, respectively. However, the study also noted some grade 3 and 4 toxicities, including one case of small bowel perforation, one case of neuropathy, and one case of hydronephrosis resulting from ureteral fibrosis. These findings highlight the importance of careful patient selection and monitoring. Smith et al. [10] investigated SBRT re-irradiation for locally recurrent rectal cancer in 35 patients. SBRT was delivered at a dose of 30 Gy in 5 fractions. The study reported 1-year and 2-year local control rates of 84.9% and 69%, respectively, and 1-year and 2-year OS rates of 95.0% and 84.4%, respectively. Acute and late toxicities were minimal, with only one patient experiencing grade 3 pain. In addition, patient-reported quality of life scores improved after SBRT. In a multicenter retrospective analysis by Johnstone et al. [68], 69 patients treated with SBRT re-irradiation for locally recurrent rectal cancer were evaluated, making it the largest series of studies to date. The study reported a 2-year OS rate of 77.0% and a 2-year PFS rate of 28.0%. Although the cancer types were not limited to colorectal cancer, a systematic review conducted by Murray et al. [69], which analyzed 17 studies that investigated pelvic re-irradiation using SBRT, demonstrated that, out of a total of 205 patients, 13 patients experienced grade 3–4 toxicities. They also reported 1-year local control rates ranging from 51% to 100%.

Overall, these studies suggested that re-irradiation with SBRT can achieve favorable local control rates with acceptable toxicity profiles in patients with recurrent rectal cancer in the pelvic area. However, the number of reports is limited, and all reflect small retrospective studies. Therefore, further research, including prospective studies, is warranted to establish the role of SBRT as an alternative to surgery in this population and to optimize treatment techniques.

2. Considerations for dose prescription in SBRT pelvic re-irradiation

The optimal dose and fractionation of SBRT for pelvic re-irradiation have not been established and vary across the literature. The dose regimen of SBRT should be determined on an individual basis, considering the previous irradiation doses and constraints of the surrounding normal tissues. Currently, no clear consensus on the recommended dose constraints for normal pelvic organs in pelvic re-irradiation is available. Nevertheless, some studies have proposed principles for determining dose constraints during SBRT re-irradiation. Murray et al. [69] suggested applying traditional dose constraints cumulatively. This approach ensures that the sum of doses from the original treatment and re-irradiation does not exceed traditional tolerance limits. However, if these limits prevent the delivery of a meaningful target dose, a degree of repair could be assumed, influenced by the time to re-irradiation. For example, Robinson et al. [70] have proposed a fixed 15% per annum tissue recovery for acceptable OAR constraints. Therefore, the previous dose is converted to EQD_2, with a yearly reduction of 15%, which accounts for the cumulative dose. Then, the re-irradiation dose was determined based on the cumulative dose and their national consensus OAR constraints [53]. Using this process, they have proposed an isotoxic dose prescription in locally recurrent rectal cancer, where the dose is escalated until the maximum pre-defined OAR constraints are met. Furthermore, an international Delphi consensus for pelvic SBRT re-irradiation suggests that acceptable dose fractionation schedules for SBRT in the pelvis are 30–37.5 Gy in 5–6 fractions or 21–27 Gy in 3 fractions, with treatment delivered on alternate days [71]. In the consensus, the maximum cumulative dose in EQD_2 to 0.5 mL for each OAR is shown based on the first treatment of 45 Gy in 25 fractions (EQD_2, 43.2 Gy3). For example, based on the AAPM report of 101 dose constraints [52], the maximum cumulative doses for the bladder, small bowel, cauda equina/sacral plexus, and colon/rectum are 80 Gy, 70 Gy, 67 Gy, and 80 Gy, respectively, when assuming no recovery. Assuming a recovery of 25% after a time interval of at least 12 months following irradiation, the maximum cumulative doses are 91.4 Gy, 80.8 Gy, 77.9 Gy, and 91.4 Gy, respectively. Assuming a 50% recovery, the maximum cumulative doses are 102.2 Gy, 91.6 Gy, 88.6 Gy, and 102.2 Gy, respectively. This international Delphi consensus also suggested other dose constraints based on the published literature from Abusaris et al. [72], Smith et al. [10], and Paradis et al. [73].

Conclusion

Hypofractionated radiotherapy is an effective option for primary and metastatic liver cancer and recurrent rectal cancer, enabled by advancements in precise radiation delivery. While it shows promise in achieving local control and providing re-irradiation options, challenges such as RILD and GI complications require careful dose planning. This review highlights potential regimens and constraints to guide clinical decision-making, emphasizing the need for further research and consensus to optimize outcomes.

Statement of Ethics

As this study did not involve any human subjects, Institutional Review Board approval and informed consent were not required.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

Conceptualization, HKB, GSY, SYS, KSK, JHS, BHK, YKK, KYJ, YSK; Investigation and methodology, HKB, GSY, KSK; Project administration, SYS, YSK; Resources, HKB, GSY, KSK; Supervision, YSK; Writing of the original draft, HKB, GSY, KSK; Writing of the review and editing, HKB, GSY, KSK; Software, HKB, GSY, KSK; Validation, HKB, GSY, KSK; Formal analysis, HKB, GSY, KSK; Data curation, HKB, GSY, KSK; Visualization, HKB, GSY, KSK. All the authors have proofread the final version.

Data Availability Statement

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

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