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Radiotherapy for the Primary Tumor in Patients with Metastatic Rectal Cancer

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Abstract Patients with metastatic rectal cancer (mRC) have a poor prognosis and suffer from several symptoms like bleeding, pain, and obstruction. Radiation therapy (RT) has been used both for palliation and improvement of overall survival (OS) in potentially curable patients. However, treatment in this setting is debated and a recent literature review included only studies published before 2000. Therefore, an analysis of literature was performed including only studies published in recent years (2010–2016) to better evaluate the effect of modern RT in these patients.

The analysis of nine reviewed studies (six retrospective and three phase II) showed that RT is able to achieve pain, bleeding, and obstruction response rate of 79, 87, and 78%, respectively. Moreover, in patients receiving radio-chemo-surgical combined modality treatment, median survivals ranging between 30 and 38 months were recorded, with 5-year survival up to 55% of patients. RT was generally well tolerated with the most common reported side effect being diarrhea/proctitis.

Further studies in this field are needed to establish the best therapeutic sequences, to define the optimal RT dose and fractionation, and to evaluate the clinical results in terms of quality of life (QoL).

Keywords Radiotherapy · Rectal cancer · Synchronous metastases · Literature review

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Introduction

Although a progressive decrease in both incidence and mortality has been recorded in Europe, colorectal cancer still represents one of the cancers with a higher incidence worldwide [1, 2]. In patients with rectal cancer (RC), synchronous distant metastases are diagnosed in approximately 15–20% of patients [3]. Treatment of these patients is challenging because of their poor prognosis and the high incidence of pelvic symptoms (e.g., bleeding, pain, and obstruction) which impacts Quality of Life (QoL).

Radiotherapy (RT) is effective in controlling disease-related symptoms. A literature review reported a pooled overall symptom response rate of 75%, while that of pain, bleeding/discharge, and mass effect being 78, 81, and 71%, respectively [4•]. However, this systematic analysis included studies published between 1949 and 1999 reporting data of patients treated between 1937 and 1991. Therefore, it was not able to describe the results of modern RT within the framework of current drug therapy.

Furthermore, the treatment strategy in these patients is debated and the role of RT is not totally clear. If metastases are unresectable, the treatment of the primary tumor is palliative, with chemotherapy as the backbone of therapy to improve QoL and survival. It is still unclear as whether to reserve RT only for symptomatic patients [5].

Therefore, aim of this literature review is to analyze recent publications about RT on primary tumor in patients with metastatic rectal cancer (mRC).

Literature Review

Methodology

The literature search was performed using PUBMED including recent studies published after 2010. Only studies reporting results on mRC treated with RT to the primary tumor were included.

Study Characteristics

Overall, nine studies were included in this analysis. Six series were retrospective [6–11] and three were prospective phase II trials [12•, 13•, 14•]. The number of enrolled patients ranged between 18 and 99 (median 50). The inclusion criteria were highly variable. Two studies enrolled patients with stage IV disease [7, 8]. Two series included only symptomatic patients with stage IV disease [6, 12•]. Two studies included symptomatic locally advanced rectal cancer, with or without metastases [11, 14•]. Particularly, one of them enrolled only patients with obstructive symptoms [14•]. One series enrolled patients with cT3–4 stage and unresectable metastases [9]. One study included patients with cT3–4 tumors and potentially resectable metastases [10]. Finally, one trial enrolled patients with locally advanced disease and liver-only metastases [13•]. In four studies, the treatment aim was symptomatic palliation [6, 11, 12•, 14•] while in three studies, the aim was curative [9, 10, 13]. In one study, patients were treated both for cure or palliation [8•] and in one study, the treatment aim was not specified [7]. In two studies, the median follow-up was not reported [7, 8] while in the other series, it ranged between 5 and 36 months (median 22) [6, 9, 10, 11•, 12•, 13, 14•] (Table 1).

Treatment

In five studies, patients underwent combined modality treatment with RT or chemoradiation, and chemotherapy eventually followed by surgical resection of primary tumor and metastatic lesions [7–10, 13]. In the other four series, patients underwent RT in some cases associated with chemotherapy [6, 11•, 12•, 14•]. In two studies, the median RT dose was not reported [8•, 11]. In the other series, the median dose ranged between 25 and 50.4 Gy (median 25) and dose per fraction ranged between 1.8 and 8 Gy (median 5 Gy) [6, 7, 9, 10, 12, 13•, 14•]. The most frequently used chemotherapy scheme was FOLFOX [7, 10, 13•, 14•]. Concurrent chemotherapy was not prescribed in five studies [10, 11, 12•, 13•, 14•], four of which used short course RT (25 Gy) [10, 12•, 13•, 14•], and the most commonly used drug was capecitabine in the other series [6, 8, 9].

Toxicity

Acute toxicity was not reported in three studies [7, 8•, 12•]. Other two series showed only minimal incidence of G ≥ 3 acute toxicity (0–3%) [6, 11] and in the other studies, the most frequent G ≥ 3 toxicity was diarrhea-proctitis (6–35%) [10, 13•, 14•]. Results in terms of late toxicity were not reported in all studies.

Clinical and Symptomatic Response

Clinical response was not reported in four series [6, 8, 11, 12•]. In one study, 100% response rate defined as partial response + stable disease (PR + SD) was reported [10]. In the other three series, the response rate defined as PR + complete response (PR + CR) ranged between 58.7 and 73.7% (median 66.7%) [7, 9, 14•]. Symptomatic response was not reported in five series [7–10, 13]. One series showed a rate of symptomatic CR and PR of 30 and 35%, respectively [12•]. Three studies reported the symptomatic response related to different symptoms [6, 11•, 14•]. Response of bleeding ranged between 83 and 100% (median 86.7%). Response of pain was 79–87.5% (median 79.3%) and response of obstruction was 62.5–83.3% (median 78%). In one study with 38% of patients showing near-obstructing lesions, only 17.5% of patients required palliative surgery [12•]. Furthermore, in the study enrolling only patients with obstructive symptoms 1-year, 2-year, and 3-year colostomy-free survival were 100, 71.4, and 47.6%, respectively [14•].

Outcome

Only one study reported the rate of local relapse being 1/26 in patients with tumor resection after chemotherapy and RT [13•]. Three series showed median progression-free survival ranging between 9 and 16 months (median 13) [9, 10, 13]. Median overall survival (OS) ranged between 6 and 37.4 months across eight studies reporting this outcome (median 30 months) [6–9, 11•, 12, 13•, 14•]. No studies reported QoL results. In terms of prognostic factors, one study reported an improved symptomatic response in patients receiving concurrent chemotherapy or a biologically equivalent dose ≥40 Gy [6]. On the contrary, another series reported no evidence of dose-response relationship for symptoms control [11]. An improved OS was recorded in patients receiving curative resection of all lesions in one study [9]. Finally, another series showed improved OS in patients receiving preoperative chemoradiation on the primary tumor but only if subsequent metastasectomy was performed [7].

Table 1 Characteristics and findings of analyzed studies

Authors/ year	Study design	No. of patients	Inclusion criteria	Treatment intent	Median follow-up, months (range)	Treatment	Median RT dose, Gy (range) [dose/fraction, Gy]	Chemotherapy	Concurrent chemotherapy
Bae SH et al. 2011; [6]	Retrospective	80	Symptomatic stage IV	Palliative	5 (1–44)	RT (CRT 23.0%) Adjuvant CT 33.0%	36 (8–60) [1.8–8.0]	Capecitabine or 5-FU or oral tegafur-uracil	Capecitabine or 5-FU or oral tegafur-uracil
Lin JK et al. 2012; [7]	Retrospective	63	Stage IV	NR	NR	CH + CRT + CH ± SR and metastasectomy	45–50 [1.8–2.0]	FOLFOX or DeGramont or FOLFIRI, + cetuximab or bevacizumab[a]	FOLFOX or DeGramont or FOLFIRI, + cetuximab or bevacizumab[a]
Tyc-Szczepaniak et al. 2013; [12•]	Prospective, phase II	40	Symptomatic stage IV[b]	Palliative	26 (19–34)	RT + CH	25 (25–30) [5.0]	CAPOX until progression or severe toxicity[c]	Not prescribed
Jung M et al. 2014; [8•]	Retrospective	28	Stage IV	Curative 22 pts Palliative 6 pts	NR	Curative: CH + RT + SR and metastasectomy	Curative 25 [5.0] or 50.4 [1.8] Palliative: NR	Curative: capecitabine + oxaliplatin (or irinotecan) ± bevacizumab palliative: oxaliplatin + capecitabine ± bevacizumab	Long course RT: capecitabine
Liu KT et al. 2016 [9]	Retrospective	76	$cT_{3–4}$ and unresectable metastases	Curative	36 (10–88)	CRT ± SR and metastasectomy + CH	50.4 (45–54) [1.8]	6 mo capecitabine-based before or after surgery	Capecitabine-based
Yoon HI et al. 2016; [10]	Retrospective	50	$cT_{3–4}$ and potentially resectable metastases	Curative	22 (9–59)	CH + RT + CH ± SR and metastasectomy	25 [5.0]	4–9 upfront cycles of FOLFOX or FOLFIRI ± bevacizumab or cetuximab; 0–8 cycles of same CH between RT and SR	Not prescribed
Kim KH et al. 2016; [13•]	Prospective phase II	32	Locally advanced rectal ca. and only liver metastases	Curative	30 (9–58)	4 cycles CH + RT + 4-cycle s CH ± SR and metastasectomy	25 [5.0]	8 cycle mFOLFOX6	Not prescribed
Picardi V et al. 2016; [14•]	Prospective phase II	18	Symptomatic locally advanced rectal ca, M0–1[d]	Palliative	11.5 (3–36)	RT (pre- + post-RT CH: 22.2%)	25 [5.0]	FOLFOX in 22.2% of patients before and after RT	Not prescribed
Chia D et al. 2016; [11]	Retrospective	99	Symptomatic locally advanced or recurrent rectal ca	Palliative	6.9	RT (pre- or post-RT CH 10%)	NR (18–54) [1.8–3.0]	Not prescribed	Not prescribed

Patients received chemoradiation

CRT concurrent chemoradiation, *CH* chemotherapy, *NR* not reported, *RT* radiotherapy, *SR* surgical resection

[a] 1–2 courses of up-front chemotherapy followed by chemoradiation followed by the same chemotherapy

[b] 38% of patients had a near-obstructing lesion

[c] Or other oxaliplatin-based schedules or capecitabine alone

[d] All patients had obstructive symptoms

Discussion

This literature review confirmed the palliative efficacy of RT in symptomatic advanced RC. In fact, our analysis showed response rates of 79, 87, and 78% for pain, bleeding, and obstructive symptoms, respectively. Interestingly, RT seems able to reduce the need of palliative surgery (colostomy) in patients with obstructive neoplasms based on the results of two trials [12•, 14•]. This result could challenge the current guidelines for patients with neoplastic obstruction. In fact, based on the American College of Radiology (ACR) appropriateness criteria for mRC "any patient with an obstructing tumor should undergo surgical diversion prior to initiating combined-modality therapy" [15].

Furthermore, our review showed that patients treated with combined modality treatment including RT or chemoradiation of the primary tumor can achieve prolonged OS. In fact, in four studies with treatment including RT of primary tumor, chemotherapy, and possibly surgical resection of primary and metastatic lesions, median OS ranged between 30 and 38 months [7–9, 13•]. Moreover, in the study enrolling only patients with potentially resectable metastases, 5-year OS was 55.1% [10].

Our analysis, due to the characteristics of included studies, has obvious limitations. Most series are retrospective and randomized trials are lacking. In addition, within the individual studies, there is major disparity in inclusion criteria, prescribed treatment, and RT dose and fractionation. However, even with these limitations, some considerations can be drawn.

The only study reporting a significant incidence (15.8%) of skin toxicity was the Liu and colleagues trial based on long course RT (50.4 Gy) combined with concurrent capecitabine [9]. In addition, the study reporting the highest incidence of hematologic toxicity was the Kim and co-workers trial based on short course RT delivered after 4 cycles of chemotherapy [13•].

The highest diarrhea/proctitis rates were recorded in the series of Yoon and colleagues [10] and Picardi and colleagues [14•] (35 and 16.7%, respectively) both based on short course RT. On the contrary, in the study by Kim and colleagues, who used the same RT regimen, the incidence of diarrhea was only 6% [13•]. From these comparisons, it is difficult to draw conclusions on the impact of the RT characteristics on short-term toxicity.

In terms of clinical response, the results recorded in two studies [7, 9] based on long course RT (58.7%, 73.3%) were substantially similar to those reported in a study [14•] based on short-course (66.7%) RT. This comparison suggests that in terms of local response, the two different protocols are probably equivalent.

The symptomatic response evaluated in terms of pain, bleeding, and obstruction was very similar (Table 2) in the three studies reporting this data [6, 11•, 14•] despite that in two studies doses up to 60 Gy [6] and 54 Gy [11] were used while in the third study the total dose was 25 Gy [14•]. The absence of a relationship between dose and symptomatic response is confirmed by the analysis of Chia and colleagues, who did not observe significant differences in this regard [11]. On the contrary, in the analysis of Bae and coworkers [6], a higher symptomatic control rate was recorded in patients undergoing RT with BED ≥40 Gy. Therefore, further analyses aimed to clarify this issue are needed.

The highest progression-free survival (PFS) was recorded in the study by Yoon and colleagues [10] (median 16 months) while the lowest PFS was reported in the series by Kim and co-workers [13•] (median 9 months) despite the similarity of combined modality treatment and RT dose. This difference can be explained by the fact that in the study by Yoon and colleagues, only patients with potentially resectable metastases were enrolled [10].

As expected, in studies based on treatment with curative purposes [8•, 9, 13•], median OS was higher (30–38 months, median 31 months) compared to series [6, 11•, 12•, 14•] of palliative RT (6–25 months, median 9.2 months). Two studies reported results in terms of 5-year OS, both based on combined modality therapy with curative purposes [9, 10]. The results from Yoon and colleagues' study [10] (55.1%) were higher compared to those of Liu and collaborators' series [9] (20.3%). Even in this case, the difference could be explained by enrollment of only patients with potentially resectable metastases in the first study.

Despite the different publication time of the analyzed papers (1949–1999 versus 2011–2016), the results of our analysis do not differ from the previous literature analysis of Cameron and colleagues [4•]. The response rates of pain were 78 and 79% in their review and in ours respectively, while the bleeding response rates were 81 and 87%, respectively. This comparison suggests that the palliative effect of RT is not affected by the use of "modern" drugs or use of likely more advanced RT techniques. In addition, the quality of scientific evidence shows several analogies. In both analyses, most of the studies are retrospective, toxicity data are lacking, and there are no evaluations on QoL. Therefore, it is desirable that innovative studies will be drawn to provide a more accurate assessment of RT efficacy.

In patients with obstructive symptoms due to advanced mRC, alternative treatments have been proposed such as self-expandable metallic stents or thermal ablative treatments (laser or argon plasma coagulation endoscopic treatments) [16, 17]. However, these treatments are not always feasible and not complication-free in terms of stent migration, fever, and anal pain or bleeding [18–20]. On the contrary, even with the limitations mentioned above related to lack of late toxicity data, RT seems associated to an acceptable incidence of significant side effects.

Table 2 Study results

Authors/ year	Acute toxicity, G3–4 (scale)	Late toxicity (scale)	Response (scale)	Symptoms control	Local control	Median PFS (months)	Median OS (months)	Notes
Bae SH et al. 2011; [6]	0% (CTCAE v.3)	NR	NR	Bleeding 83% Pain 79% Obstruction 78%	NR	NR	6 1-year 22.1%	BED ≥40Gy and CRT associated with improved symptoms control rate
Lin JK et al. 2012; [7]	NR	NR	58.7% (RECIST)	NR	NR	NR	37.4	CRT improves OS only in patients receiving metastasectomy
Tyc-Szczepaniak et al. 2013; [12•]	NR	NR	NR	CR 30% PR 35%	NR	NR	11.5	Palliative surgery at 2 years in only 17.5% of pts
Jung M et al. 2014; [8•]	NR	NR	NR	NR	NR	NR	Curative 31 palliative NR	–
Liu KT et al. 2016; [9]	Radiation dermatitis 15.8% Hematologic 2.6% Fatigue 1.3% (CTCAE v.3)	NR	Primary tumor 73.7% Metastases 46.1% (RECIST)	NR	NR	13 5-year 5.9%	30 5-year 20.3%	Curative resection of all lesions after CRT prolonged survival
Yoon HI et al. 2016; [10]	Diarrhea 35% (CTCAE v.4)	NR	Primary tumor PR + SD 100% (NR)	NR	NR	16 2-year 34.8%	NR 5-year 55.1%	Median survival not reached in patients receiving SR
Kim KH et al. 2016; [13•]	Neutropenia 28% Hypokalemia 3% Hyperglycemia 3% Nausea 3% Diarrhea 6% Pain 3% Infection 3% (CTCAE v.3)	NR	Liver metastases PR 47.0% Rectum pCR 11.0% (RECIST)	NR	1 local recurrence after SR[a]	9 2-year 17.0%	38 2-year 65.0%	<4 liver metastases and not PD after 4 cycles of CT higher resectability rate
Picardi V et al. 2016; [14•]	Proctitis 16.7% (CTCAE v.3)	NR	PR + CR 66.7% PR + SD 94.4% (RECIST)	Bleeding 100% Pain 87.5% Obstruction 83.3%	NR	NR	25 3-year 39.8%	1-, 2-, and 3-year colostomy-free survival rates 100, 71.4, and 47.6%, respectively.
Chia D et al. 2016; [11]	3% (CTCAE v.3)	NR	NR	Bleeding 86.7% Pain 79.3% Obstruction 62.5%	NR	NR	6.9 1-year 30.6%	No evidence of dose response relationship

BED biological equivalent dose, *CR* complete response, *CT* chemotherapy, *CRT* concurrent chemoradiation, *NR* not reported, *OS* overall survival, *pCR* pathological complete response, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *pts* patients, *SD* stable disease, *SR* surgery

[a] Out of 26 patients receiving primary tumor resection

Conclusion

In conclusion, RT is able to achieve a high symptomatic response rate in patients with RC and unresectable metastases or unfit for curative treatment due to other reasons (age and/or comorbidities). The results of the recent literature, in this setting, do not differ from those reported in studies published in the previous era. Moreover, RT may be considered in potentially curable patients with resectable metastases. In this case, as for non-metastatic patients, neoadjuvant RT should be recommended to reduce toxicity and improve disease local control. A short course treatment, in this setting, seems to be preferable since it eliminates any delays in chemotherapy commencement.

Further studies are needed in order to define the best sequence of combined modality treatments and to define the RT optimal dose and fractionation. These studies should include as an end-point of the evaluation of QoL, possibly using Patients Reported Outcome Measures. In addition, to improve treatment tailoring (curative versus palliative), the development of predictive models in this setting would be useful. Finally, it could be tested, together with RT of the primary tumor, the use of treatments of metastatic lesion less invasive compared to surgery, such as stereotactic RT almost in selected patients.

Compliance with Ethics Standards

Conflict of Interest Milly Buwenge, Lucia Giaccherini, Alessandra Guido, Alessandra Arcelli, Gabriella Macchia, Francesco Deodato, Savino Cilla, Lorenzo Fuccio, Andrea Farioli, Silvia Cammelli, and Alessio G. Morganti declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest published recently are denoted with:
- • Of importance
- •• Of major importance

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