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FULL PAPER

Stereotactic/hypofractionated body radiation therapy as an effective treatment for lymph node metastases from colorectal cancer: an institutional retrospective analysis

¹CIRO FRANZESE, MD, ¹ANTONELLA FOGLIATA, MSc, ¹TIZIANA COMITO, MD, ¹ANGELO TOZZI, MD, ¹CRISTINA IFTODE, MD, ¹ELENA CLERICI, MD, ¹DAVIDE FRANCESCHINI, MD, ¹PIERINA NAVARRIA, MD, ¹ANNA MARIA ASCOLESE, MD, ¹LUCIA DI BRINA, MD, ¹FIORENZA DE ROSE, MD, ¹GIUSEPPE R D'AGOSTINO, MD, ^{1,2}LUCA COZZI, PhD and ^{1,2}MARTA SCORSETTI, MD, Prof

¹Department of Radiotherapy and Radiosurgery, Humanitas Research Hospital and Cancer Center, Milan-Rozzano, Italy

²Department of Biomedical Sciences, Humanitas University, Milan-Rozzano, Italy

Address correspondence to: Antonella Fogliata
E-mail: antonella.fogliata@humanitas.it

Objective: The colorectal cancer (CRC) might present loco-regional recurrence, including lymph-node metastasis. Stereotactic body radiotherapy (SBRT) is a non-invasive and well-tolerated ablative treatment. Aim of the present study is to evaluate efficacy and toxicity of SBRT with volumetric modulated arc therapy (VMAT) in this setting.

Methods: 35 patients presenting a total of 47 nodal recurrences from CRC, treated with VMAT-SBRT from 2008 to 2015, were selected. About three fourth of the treatments delivered 45 Gy in 6 daily fractions. End-points were the detection of toxicities, overall survival (OS), local control (LC), disease progression free incidence (DPFI) and disease free survival (DFS). Tumour response was assessed according to the RECIST criteria.

Results: Only Grade 1 and 2 toxicities were recorded. Median follow-up was 15 months (range 2–68). Local relapse was reported in 6 patients, regional relapse in 10 patients. Complete remission was reported in 20 cases (53%), partial remission in 14 (37%). Rates of LC at 1, 2 and 3 years were 85.3, 75.0 and 75.0%, respectively. At 1 year the actuarial OS was 100%, at 2 and 3 years was 81.4%. Median DFS was estimated in 16 months, with an incidence of 69.4, 33.3 and 19.4% at 1, 2 and 3 years, respectively.

Conclusion: The use of the VMAT-SBRT in lymph-node recurrence of CRC could prevent severe complications and achieve satisfying rates of disease control.

Advances in knowledge: The use of VMAT-SBRT is a viable approach for lymph-node recurrence of CRC.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of cancer-related death worldwide.¹ Even if the management of CRC has continued to evolve during the last century, approximately 20–50% of patients will develop recurrence after definitive treatment for primary tumour.^{2–4}

The improvement of both surgical techniques and of radiotherapy (RT) and chemotherapy approaches, decreased the rate of local recurrence to 4–8%.⁵ However, the risk of loco-regional and distant metastases still persist.

Recurrences from CRC often present as solitary disease or a limited number of metastases.³ This pattern of recurrence

was described as oligometastatic state for the first time by Hellman and Weichselbaum.⁶ It can be considered an intermediate state between local disease and widespread disease, and could be still amenable of a local treatment. Lateral pelvis (LPLN) and paraortic lymph node (PALN) can be site of metastases from CRC. While PALN are considered as M1 stage by the American Joint Committee for Cancer (AJCC),⁷ LPLN are considered regional lymph nodes. Kobayashi et al⁸ demonstrated that the risk of lymph node metastases to the LPLN is about 16.5% in T3 and 37.2% in T4 disease. Lower is the risk of PALN, with an overall incidence of 1.7%.⁹ Although liver and lung resection in oligometastatic CRC is recognized as an effective approach, surgical dissection of lymph node metastasis is not widely accepted due to the lack of clinical evidence and to the high post-operative morbidity.

The improvement in the last decades of the RT treatments increased the possibility to approach on isolated metastatic foci with stereotactic body radiation therapy (SBRT). SBRT is a non-invasive and well-tolerated ablative treatment, and its role in oligometastatic CRC has been extensively investigated. Hoyer *et al*¹⁰ published the results of a phase II study investigating the role of SBRT in oligometastatic CRC patients. 64 patients with a total number of 141 lesions were enrolled (44 in the liver, 12 in the lungs, 3 lymph nodes, 1 adrenal gland and 4 in two organs) and after 2 years, actuarial local control (LC) was 86 and 63% in tumour and patient based analysis, respectively.

We previously published our experience with the use SBRT and volumetric modulated arc therapy (VMAT) for the treatment of abdominal lymph node metastases from different histologies. We included 71 patients with a total of 79 lesions, treated with a dose of 45 Gy delivered in 6 daily fractions of 7.5 Gy each. In our analysis disease control was achieved in 97.5% of the lesions with an actuarial LC rate at 1 year of 83%.¹¹

Few reports describe the role of SBRT specifically for the treatment of lymph node metastases in oligometastatic CRC. One of the first data were published by Kim *et al*.¹² They only included 7 patients with PALN recurrence, and the reported 1- and 3-year overall survival (OS) rates were 100 and 71.4%, respectively.

Aim of the present study is to evaluate the efficacy and pattern of toxicity of SBRT with VMAT for the treatment of lymph node metastasis in oligometastatic CRC patients.

METHODS AND MATERIALS

Patient selection

A cohort of 35 patients presenting nodal recurrence from CRC, treated with SBRT and VMAT technique in our institution from November 2008 to December 2015, was selected for this study. All patients signed informed consent at registration in the hospital for the use of data for scientific purposes. No ethics approval was required.

Inclusion criteria were: no more than three lymph node metastases; maximum diameter 5 cm on CT or MRI scan; no evidence of progressive or untreated gross disease outside the lymph node; no concurrent chemotherapy, interrupted at least 1 week before; primary tumour was resected or under control; other sites of metastatic disease, different from lymph node, were accepted if amenable of ablative treatment or surgery. Minimum age 18 years old. Patients were excluded if the lesions were bigger than 5 cm in maximum diameter; if the lesions were treated with other local approaches or if they had other abdominal illnesses that contraindicate RT, as inflammatory bowel disease or bowel ulcers.

Three of those patients (males) were treated for different nodal recurrences in two treatments separated by 8, 9 and 27 months. The analysis is hence conducted on 38 treatments. A total of 47 lymph nodal lesions, of which almost half presenting in the paraortic region, have been treated in the patient group. A median latency time of 45 months was evaluated from the date of primary tumour diagnosis to the treatment of the nodal

Table 1. Patient and treatment characteristics

No. of patients		35
No. of treatments		38
No. of lesions		47
Age	Median, range (y.o.)	66, 32–89
Sex	Male	24
	Female	11
Follow-up	Median, range (months)	15, 2–68
Primary tumour	Colon	26
	Rectum	9
Type of nodal metastasis	Solitary	17
	Oligometastatic	21
Site of nodal metastasis	Paraortic	24
	Pelvic	12
	Other sites of abdomen	11
CTV volume	Median, range (cm ³)	8, 0.2–568
CTV diameter	Median, range (cm ³)	2.6, 0.8–10.3
PTV volume	Median, range (cm ³)	28, 4–882
PTV diameter	Median, range (cm ³)	3.8, 1.9–11.9
Latency time	Median, range (months)	45, 7–86
PS	0	32
	1	6
Prescription doses	6 × 7.5 Gy = 45 Gy	28
	6 × 6.0 Gy = 36 Gy	5
	6 × 5.0 Gy = 30 Gy	2
	5 × 6.0 Gy = 30Gy	1
	10 × 4.0 Gy = 40Gy	1
	13 × 3.0 Gy = 39 Gy	1

metastasis. Patient and treatment characteristics are summarized in Table 1.

Dose prescription and radiation treatment

The gross tumour volume (GTV) was delineated on simulation CT, co-registered with MRI or PET scan when available. Clinical target volume (CTV) was equal to GTV with no additional margin. An isotropic margin of 5 mm was added to CTV to obtain the planning target volume (PTV).

All patients received VMAT planning and treatment delivery (in its Varian, RapidArc form) with 6 or 10 MV Flattening Filter Free Beams (FFF) from either Varian Clinac DHX, TrueBeam or Edge unit, equipped with a Millennium 120-MLC (5-mm leaf width at isocenter on TrueBeam and Clinac) or an HD-120MLC (2.5-mm leaf width at isocenter on TrueBeamSTx and Edge). Plans were generated with two coplanar VMAT arcs using the Eclipse treatment planning system, the Progressive Resolution Optimizer PRO for inverse planning optimization and Anisotropic Analytical Algorithm AAA for final dose calculation,

with versions varying from 8.5 to 11. The use of the 10 MV FFF beam allowed to keep the beam on time of two minutes, thanks to the high dose rate (2400 MU min^{-1}). The prescribed dose was not unique for all analysed patients, depending on target characteristics such as number of lesions, dimensions and proximity to organs at risk (Table 1). However, about three fourth of the treatments were delivered in 6 daily fractions of 7.5 Gy, for a total dose of 45 Gy. When the 6 fractions were used, doses to organs at risk (OAR) were limited according to the internal general protocol as follows: small bowels: $V_{36\text{Gy}} < 3 \text{ cm}^3$ (structure volume receiving 36Gy should be less than 3 cm^3); stomach and duodenum: $V_{36\text{Gy}} < 1 \text{ cm}^3$; kidneys (each): $V_{15\text{Gy}} < 35\%$; $\geq 700 \text{ cm}^3$ of normal liver should receive $\leq 21 \text{ Gy}$. For target coverage and homogeneity, PTV dosimetric requests are $D_{98\%} > 95\%$ (the dose received by at least 98% of the PTV volume should be larger than 95% of the prescribed dose), and $D_{2\%} < 107\%$. If, for anatomical and overlapping reasons, it is not possible to fulfil all the dose-volume criteria, the OAR sparing would prevail on the PTV coverage.

All the patients were positioned supine, with a thermoplastic mask. An abdominal compression was used for the upper abdomen lymph nodes to minimize the internal organ movement. No fiducial markers were implanted for tumour localization. The patient position was carefully evaluated daily with CBCT imaging before each treatment session.

Toxicity

All patients had weekly clinical evaluation during the treatment. The first evaluation was planned at about 3 months after the end of the RT. Follow-up visits were scheduled every 3 months for the first year and then every 6 months from the 2nd to the 5th year after RT. At each follow-up visit, a history was obtained with the evaluation of treatment-related morbidity and diagnostic examination (CT, MRI or PET scan according to the physician's discretion). End-points were the evaluation of the feasibility of the treatment, the detection of acute and late toxicities, graded according to the Common Toxicity Criteria CTCAE version 3.

Gastro-intestinal related toxicities were attempted to correlate with dosimetric data as dose received by 5, 10, 20 and 50 cm^3 of the bowels.

Survivals and tumour response

OS was computed from the end of the SBRT treatment to the last follow-up or patient death (no deaths for causes not disease related in the analysed group), using the Kaplan–Meier analysis. LC was evaluated from the end of the RT treatment to the local progression (no regional progression nor distant metastases), censoring to the last follow-up. Disease free survival (DFS) was analysed from the end of the SBRT until death or disease progression, censoring to the last follow-up. All statistical calculations were performed using SPSS, version 21.0 (SPSS Inc, Chicago, IL).

Tumour response was assessed according to the Response Evaluation and Criteria for Solid Tumors (RECIST).¹³ An increase of the tumour size or the development of new lesions in the treatment field were considered as local progression. The development

of new lesions out of the treatment field are defined as regional failure.

RESULTS

Toxicity

No acute toxicity was developed for 33 of the 38 analysed treatments. Grade 1 was recorded in two cases: nausea was reported by one patient with isolated lymph node metastases located at the liver hilum, and one patient with a peri-pancreatic node treated. Grade 2 was recorded for three patients: diarrhoea, nausea/pain and asthenia/diarrhoea, in all cases after a paraortic node treatment. All the reported toxicities were resolved with the temporary use of medications.

No correlation was found between small bowel dose level and the toxicity expression. As an example, the mean $D_{5\text{cm}^3}$ values were $25.7 \pm 8.7 \text{ Gy}$ and $24.4 \pm 6.0 \text{ Gy}$ for Grade 1 and Grade 2 toxicity patients, respectively.

Outcome

The data here reported refers to a median follow-up of 15 months (range 2–68 months).

Local relapse was reported in six patients, at a median time of 11 months (range 4–20) from the SBRT treatment. Regional relapse was developed in 10 patients at a median latency time of 7 months (range 2–27). Distant metastases were reported in 23 cases, developed after a median of 7 months (range 1–36): 12 liver metastases (within a median of 5 months, range 1–8), 11 lung metastases (within a median of 5 months, range 1–36), one bone, pancreatic and peritoneal metastases.

The treated tumour was in complete remission in 20 cases (53% of the treatments), partial remission in 14 (37%), presented a stable disease in 3 patients, and one case was progressing at the first evaluation after SBRT. Rates of LC at 1, 2 and 3 years were 85.3, 75.0 and 75.0%, respectively (Figure 1).

Figure 1. Kaplan–Meier curve for local control.

Figure 2. Kaplan–Meier curve for overall survival.

The Kaplan–Meier curve of the OS is reported in Figure 2. At 1 year the actuarial survival rate is 100%, at 2 and 3 years is 81.4%. In Figure 3 the DFS is reported as Kaplan–Meier curves.

At both LC and OS, a plateau was observed after about 2 years. This finding could be explained the majority of local relapses occurring within approximately 2 years from SBRT. The recurrence a can be associated to a more aggressive disease, which can then affects the survival. Median DFS was estimated in 16 months, with an incidence of 69.4, 33.3 and 19.4% at 1, 2 and 3 years, respectively.

DISCUSSION

The treatment of isolated lymph node recurrence from CRC is nowadays not established and the literature is still limited. Local treatment became a standard of care in liver metastases

from CRC. Some large surgical series demonstrated the possibility to reach 5 years survival rates of 37% after resection of liver metastases.^{14,15}

Subsequently less invasive approaches have been introduced for liver metastasis. Solbiati et al¹⁶ published the outcome of 179 metachronous liver metastases from CRC, treated with radiofrequency ablation (RFA). Estimated 2- and 3-year survival rates were 69 and 46%, respectively. The evolution of SBRT in the spectrum of local treatments allowed physician to treat lesions previously unachievable with other techniques, for site or dimension of the disease. The SBRT takes advantage of the tumour cell biology, killing the malignant cells directly and indirectly causing stromal and vascular damages.¹⁷ The high-dose SBRT, including single or few fractions, is able to ablate the tumour with an efficacy similar to that achieved with surgery, especially for small lesions.^{18,19} At our institution, SBRT has been widely used in the last years to treat oligometastatic patients characterized by a limited burden of disease.^{20–22} We published in 2016 the outcome and toxicity of 71 patients treated on 79 lymph node recurrences in abdomen or pelvis. The lesions originated from different primaries, and were treated with a homogeneous dose of 45 Gy in 6 consecutive fractions. Patients were treated if they have a maximum of three recurrences. LC was achieved in 97.5% of the lesions with an actuarial rate at 1 year of 83%. No Grade 3 or 4 toxicities were observed.¹¹ Here we aimed to analyse all lymph node recurrences from CRC treated with SBRT at our institution, as in this setting is quite heterogeneous. Shibata et al²³ published in 2002 a small series of 25 patients operated for isolated retroperitoneal recurrences from CRC. 20 patients underwent resection and 5 patients were deemed unresectable at the time of operation. The observed median survival was 31 months for the operated group compared with 3 months in those patients who did not undergo resection ($p = 0.0001$). However, lymph node metastases in the abdomen or pelvis are rarely considered amenable of surgery, so traditionally patients are directed to chemotherapy. Conventional chemotherapy including a combination of fluoropirimitidine, irinotecan or oxaliplatin in combination with one targeted therapy, led to a median survival of about 20 months.²⁴

In the present study, optimal survival rates are reported for the treated patients, with 2 and 3 years rate of 81.4%. Kim et al¹² analysed a small group of 7 patients treated with SBRT on PALN recurrences. 1 and 3-years OS rates were 100 and 71.4%, respectively, with median survival of 37 months. Kang et al²⁵ reported the results of a study including 59 patients affected by CRC (31 within the nodal area). Globally the 3- and 5-year LC rates were 66 and 24%, respectively. Focusing to lymph node metastatic patients progression-free survival was 25% at 3 years and 19% at 5 years. In the present study, the local control rates at 1 and 2 years were 85.3 and 75% and DFS at 1 and 2 years were 69.4 and 33.3%. In-field relapse was observed in only 6 patients while out-field lymph node progression was observed 10 patients. Higher is the number of patients with progression as distant metastases after the SBRT, with a median time of 7 months. At both LC and OS, a plateau was observed after about 2 years. This finding could be explained the majority of local relapses occurring within approximately 2 years from SBRT.

Figure 3. Kaplan–Meier curves for disease free survival.

The recurrence can be associated to a more aggressive disease, which can then affect the survival. This figure brings the attention to the selection of patients who will benefit from a local treatment, including SBRT. While on one hand we know that SBRT allows long-term disease control, and therefore maintenance of an adequate quality of life (QoL), on the other hand it is necessary to understand which patients will benefit the most from RT in the oligometastatic setting. Even if the SBRT has potentially the same indications of metastasectomy, patients do not need to be extremely fit as for surgery. Criteria for the use of SBRT have been specified in the last years, including patients with controlled primary tumour, favourable histology, good performance status and a limited number of metastases (commonly less than 5).²⁶ Moreover the improvement of the imaging such as MRI and PET scan allows a better identification of real oligometastatic patients.

Complications after RT can be an issue as lymph node metastasis are located generally very close to healthy tissue such as kidney, liver or duodenum. Compared to conventional RT, the SBRT is able to deliver high dose to the disease while sparing healthy tissue. Bae et al²⁷ suggested for bowel the absolute volume to receive 20, 25, 30 or 35 Gy and D_{max} as valuable predictor of severe intestinal toxicity. At D_{max} below 37 Gy was not associated with severe toxicity. While Rusthoven et al²⁸ suggested a D_{max} below 30 Gy in 3 fractions, Timmerman²⁹ used a more restrictive constraint of 27 Gy for D_{max} .

In the study of Kim et al,¹² one patient experienced a Grade 4 bowel toxicity, likely due to the maximum dose of 53 Gy received by the bowel in 3 fractions, particularly higher than the established dose constraint. In our series, we adopted a more cautious dose constraint of $D_{max} \leq 36$ Gy in 6 fractions, for the bowel, stomach and duodenum. This and all the other constraints criteria were met in the whole group. In fact, toxicity was very mild with no Grade 3 or more events observed. Most commonly patients reported mild nausea, diarrhoea and asthenia. Moreover, we treated all patients with the SBRT with the VMAT; this technique is able to reduce the treatment time to about 2 min. The reduction of the beam-on-time allows the operator to deliver

the prescribed dose of radiation with greater safety, as the movement of the patients and of the internal organs is theoretically smaller. Moreover the very good pattern of toxicities could be conducted to the selection of the patients that is very crucial in this setting. In fact patients with poor performance status, with bowel inflammatory disease or bowel ulcers near the irradiation area were excluded from the treatment.

Limitations of this study are the retrospective nature of the analysis, the limited number of included patients and the heterogeneity of the series.

However, we think that sharing of the experience can be of help to the scientific community in order to improve the survival and quality of life of these patients, and above all give rise to the creation of international prospective studies.

CONCLUSION

Lymph node recurrence of CRC may deteriorate life of patient due to invasive approaches. The use of the SBRT as a local treatment could both prevent the diffusion of disease by an ablative effect and at the same time preserve QoL thanks to its minimal invasiveness. Local control and low profile toxicity can be achieved with BED less than 100 Gy and more than 5 fractions when treating lymph node oligometastases of CRC. Prospective trials are warranted to prove the above result.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

CONFLICT OF INTEREST

L. Cozzi acts as Scientific Advisor to Varian Medical Systems and is Clinical Research Scientist at Humanitas Cancer Center. All other co-authors declare that they have no conflict interests.

ETHICAL APPROVAL

All procedures were in accordance with the ethical standards and the Helsinki declaration.

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