FULL PAPER

Brain metastases from primary colorectal cancer: is radiosurgery an effective treatment approach? Results of a multicenter study of the radiation and clinical oncology Italian association (AIRO)

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Objectives: The prognosis of brain metastatic colorectal cancer patients (BMCRC) is poor. Several local treatments have been used, but the optimal treatment choice remains an unresolved issue. We evaluated the clinical outcomes of a large series of BMCRC patients treated in several Italian centers using stereotactic radiosurgery (SRS).

Methods: 185 BMCRC patients for a total of 262 lesions treated were evaluated. Treatments included surgery followed by post-operative SRS to the resection cavity, and SRS, either single-fraction, then hypofractionated SRS (HSRS). Outcomes was measured in terms of local control (LC), toxicities, brain distant failure (BDF), and overall survival (OS). Prognostic factors influencing survival were assed too.

Results: The median follow-up time was 33 months (range 3–183 months). Surgery plus SRS have been performed in 28 (10.7%) cases, SRS in 141 (53.8%), and HSRS in 93 (35.5%). 77 (41.6%) patients received systemic therapy. The main total dose and fractionation used were 24 Gy in single fraction or 24 Gy in three daily fractions. Local recurrence occurred in 32 (17.3%) patients. Median, 6 months,1-year-LC were 86 months (95%CI 36-86), 87.2% ± 2.8, 77.8% ± 4.1. Median,6 months,1-year-BDF were 23 months (95%CI 9-44), 66.4% ± 3.9, 55.3% ± 4.5. Median,6 months,1-year-OS were 7 months (95% CI 6–9), 52.7% ± 3.6, 33% ± 3.5. No severe neurological toxicity occurred. Stage at diagnosis, Karnofsky Performance Status (KPS), presence and number of extracranial metastases, and

disease-specific-graded-prognostic-assessment (DS-GPA) score were observed as conditioning survival.

Conclusion: SRS/HSRS have proven to be an effective local treatment for BMCRC. A careful evaluation of prognostic factors as well as a multidisciplinary evaluation is a valid aid to manage the optimal therapeutic strategy for CTC patients with BMs.

Advances in knowledge: The prognosis of BMCRC is poor. Several local treatments was used, but optimal treatment choice remains undefined. Radiosurgery has proven to be an effective local treatment for BMCRC. A careful evaluation of prognostic factors and a multidisciplinary evaluation needed.

INTRODUCTION

Colorectal cancer (CRC) is the third most common primary cancer, and the fourth leading cause of cancer-related deaths worldwide.[1–5] Treatment advances have led to an improved survival of CRC patients over time, and the incidence of brain metastasis (BMs) has gradually increased as well.[6–9] The reported incidence of BMs ranges from 0.6 to 4.2%, usually occurring in advanced stages of the disease, concomitant with liver (50%) or lung (80%) involvement.[10] The prognosis of brain metastatic CRC (BMCRC) patients is poor, with median survival between 4 and 6 weeks for untreated ones, and 6–9 months in cases of active treatments.[11–18] Several local treatment approaches have been used and investigated, including neurosurgical resection, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and hypofractionated stereotactic radiosurgery (HSRS).[19,20] The choice of one over the other is usually determined by the disease status, the patient performance status, the previous response to treatments, the site and size of BMs. Published studies suggest that a combined treatment, including surgery plus WBRT, is associated with better outcomes, albeit this advantage is also attributed to a better patient selection.[21] Unfortunately, the large number of BMCRC patients are unsuitable for surgical resection in relation to age, and/or presence of wide extracranial metastatic disease. In this setting, radiation therapy (RT) could be a valid alternative local treatment. Several RT modalities can be employed. Over the last few years, SRS has become the preferred treatment modality for patients with small BMs and minimal mass effect, with outcomes appearing to be comparable to those of surgical resection. The advantages of this treatment are its minimal invasiveness, a low rate of post-treatment complications compared to WBRT, and a high rate of local tumor control.[22–26] In addition, SRS is able to deliver selectively, high ablative RT doses, in single or few fractions, without delaying the administration of systemic therapy.[27,28] To date, limited literature data are available on this topic, with a low number of patients evaluated, and treated in different ways. Thus, to date the management of BMCRC patients is still an unresolved issue, and an important healthcare challenge. Based on this lack of evidence, we evaluated the outcome of a large series of BMCRC patients treated in several Italian centers. The main objectives were to evaluate the efficacy of SRS/HSRS in terms of local control (LC) and treatment-related toxicities, and to identify prognostic factors eventually conditioning outcome. Brain distant progression (BDP), progression free survival (PFS), and overall survival (OS) were evaluated as well.

METHODS AND MATERIALS

Patients and procedures

The present retrospective study includes patients with limited BMs (up to 4) from CRC treated with SRS/HSRS. Selected patients received surgical resection followed by SRS/HSRS. In detail: i) surgical resection followed by SRS/HSRS on the surgical cavity was performed in case of patients with KPS 90–100, and/or controlled extra cranial disease, and/or single brain lesion with maximum diameter ≥21 mm, and/or presence of 2 BMs in which one was larger and conditioning mass effect, and/or life expectancy longer than 3 months, and/or progressive neurological deficits; ii) SRS alone in case of small or multiple BMs; iii) HSRS alone in case of large BMs unsuitable for surgical resection for older age, poor general conditions or uncontrolled extra cranial disease. All patients were treated in agreement with the Helsinki declaration. This study was based on a retrospective analysis of treatment charts and received approval by local Ethical Committee.

Treatment: SRS/HSRS

For SRS/HSRS, enhanced T1MRI sequences and post-contrast CT scan were used and co-registered to precisely delineate the target volume. Frame or frameless system were used for patient immobilization and repositioning. All scans, extending from the top of the skull to the third cervical vertebra, were acquired with 1 mm slice thickness. The gross target volume (GTV) corresponded to the BM volume; the planning target volume (PTV) was defined as an isotropic expansion from GTV of 0–3 mm. The delineated organs at risk (OARs) were brain, brainstem, optic nerves, chiasm and lenses. No margins were added to OARs. Several prescribed total doses and fractionation was employed in relation to the size of BMs, and/or to the close proximity of OARs, and/or to the center preference. The main total dose and fractionation employed was 24 Gy in single fraction or 24 Gy in 3 daily fractions. Patients were treated with the volumetric modulated arc technique RapidArc (LINAC, CyberKnife), Tomotherapy, or with Gamma Knife (GK) in relation to the center availability. The dose was prescribed at an isodose line that ensured that more than 98% of PTV receives 95% of prescribed dose. For GK SRS, the dose was administered at the 50% isodose line. Exactrac (Brainlab) and/or cone beam CT imaging was performed daily for patient set up and positioning verification.

Systemic therapy

No concomitant chemotherapy or target therapy have been employed during SRS/HSRS, in relation to the short time period of treatment. Patients received a systemic adjuvant therapy after BMs local treatments. Different regimen were used in relation to

Table 1. Patients, tumor and treatment characteristics of CRC patients at diagnosis

	No	%
PATIENTS	185	100
Gender		
Male	111	60
Female	74	40
Median age	62 years (range 32–86 years)	
KPS		
90–100	173	93.6
80	10	5.4
<80	2	1
Primary tumors		
Colon	148	80
Rectum	37	20
Biomolecular status		
KRAS		
Mutated	53	28.6
Wild type	20	10.8
Not available	112	60.6
BRAF		
Mutated	7	3.8
Wild type	25	13.5
Not available	153	82.7
Microsatellite instability		
Positive	3	1.6
Negative	8	4.3
Not available	174	94.1
Treatments at diagnosis		
Surgery plus chemotherapy	105	56.7
Surgery only	26	14.1
Surgery plus chemotherapy plus radiation therapy	26	14.1
Chemotherapy only	11	5.9
Surgery plus radiation therapy	7	3.8
No treatment	10	5.4
Stage at diagnosis		
I-III	111	60
IV	74	40
IV only brain	4	5.4

(Continued)

Table 1. (Continued)

	No	%
IV EC metastases	58	78.4
IV Brain + EC	12	16.2
Median IT between diagnosis and appearance of BMs	33 months (range 0–226 months)	

BMs, brain metastases; CRC, colorectal cancer; EC, extracranial; IT, interval time in months; KPS, Karnofsky performancestatus; KRAS, Kirsten rat sarcoma viral oncogene homolog.

previous treatments received, consisting in standard oxaliplatin- or irinotecan-fluoropyrimidine regimens with or without anti vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) antibodies according to national guidelines. All patients treated with an anti-VEGF antibody received bevacizumab.

Outcome evaluation

Clinical outcome was evaluated by neurological examination and brain MRI performed 2 months after RT and then every 3 months. Local progression was defined as radiographic increase of the enhancing abnormalities in the irradiated volume recorded in two consecutive MRI conducted 2 months apart; in cases of suspected radionecrosis, perfusion and diffusion MRI sequences, and/or FDGPET, have been utilized. BDP was determined as the presence of new BMs or leptomeningeal enhancement outside the irradiated volume. When needed tumor progression was defined according to Response Assessment in Neuro-Oncology (RANO) working group.[29] Toxicities were graded according to Common Terminology Criteria for Adverse Events v. 4.0. Systemic disease was evaluated by contrast-enhanced total body CT-scan, and/or 18-FDG CT-PET.

Statistical analysis

Standard descriptive statistics were used to describe the general data behavior. Survival and recurrence time observations were computed according to the method of Kaplan and Meier, starting from the date of BMs diagnosis. In order to investigate the prognostic role of different individual variables, the log-rank test or univariate Cox regression were used, respectively, for categorical and numerical variables age, gender, KPS, stage at diagnosis, histological subtype, Kirsten rat sarcoma viral oncogene homolog (KRAS)/BRAF mutation and microsatellite instability status, interval time between primary tumor diagnoses and appearance of BMs, disease-specific graded prognostic assessment (DS-GPA) score, presence of other metastatic site at time of BMs, number, site and size of BMs. Multivariate Cox model was used as a method to estimate the independent association of a variable set with LC, BDP, PFS, and OS. Statistical analysis was performed by the use of the Medcalc software, v. 17.7 (MedCalc software, Ostend, Belgium).

Table 2. Patient, tumor and treatment characteristics at BMs occurrence

	No	%
Patients	185	100
Presence of EC metastases		
Yes	158	85.4
No	27	14.6
No. of organs interested by EC metastases in 158 EC metastatic patients		
1		
2	66	41.8
3	57	36.1
4	24	15.2
5	10	6.3
	1	0.6
DS-GPA score		
0–1	51	27.6
2	30	16.2
2.5–3	48	25.9
03-05-2004	56	30.3
No. BMs for patient		
1	138	74.6
2	24	13
3	15	8.1
4	8	4.3
No of BMs treated	262	100
BMs LOCATION		
Supratentorial	184	70.2
Infratentorial	78	29.8
Median BMs diameter (range)	20 mm (range 3–64 mm)	
Median BMs volume (range)	4.0 cm^3 (range 0.04–81.60 cm^3)	
TREATMENTS		
Surgery plus SRS	28	10.7
SRS single fraction	129	49.2
HSRS	105	40.1
Schedules median Gy (range Gy)		
SRS single fraction 24 (10–26.25)	141	53.8
HSRS		
2 frs 20 (15-30)	6	2.3
3 frs 24 (15-30)	72	27.5
4 frs 32 (20-32)	15	5.7

(Continued)

Table 2. (Continued)

	No	%
5 frs 30 (20-40)	28	10.7

BM, brain metastasis; BMs, brain metastases; DS-GPA, diseasespecific graded prognostic assessment; EC, extracranial; HSRS, hypofractionated stereotactic radiosurgery; SRS, single dose stereotacticradiosurgery; frs, fractions.

RESULTS

Patients and treatments

From September 2004 to December 2018, among 213 patients treated, 185 evaluable patients were included in this analysis. 74 (40%) were female and 111 (60%) male with a median age of 62 years (range 32–86 years). At diagnosis, the greater number of patients had a KPS 90–100 (93.5%), primary colon adenocarcinoma (97.2%), stage I-III (60%) disease, and underwent surgery followed by chemotherapy (56.7%). KRAS status was available in 73 (39.4%) cases of whom 53 (72.6%) were mutated and 20 (27.4%) wild type, BRAF status in 32 (17.2%) of whom 7 (21.8%) were mutated and 25 (78.2%) wild type; microsatellite instability status was available in 11 (5.9%), 3 (27.3%) were positive and 8 (72.7%) negative. Patient, tumor and treatment characteristics at diagnosis are shown in Table 1. The median interval time between the diagnosis of primary CRC and the appearance of BMs was 33 months (range 0–226 months). At the time of BMs, 158 (85.4%) patients had other extra cranial metastases, 27 (14.6%) BMs only, and the large number had DS-GPA score 2.5–4 (56.2%). The total BMs irradiated were 262. The most of patients had 1–2 BMs (87.5%), and supratentorial location (83.2%). The treatments performed were: surgical resection followed by HSRS on the tumor bed in 28 (10.7%) cases, SRS in 141 (53.8%), and HSRS in 93 (35.5%). 77 (41.6%) patients received systemic therapy after BMs treatment consisted in FOLFIRI, FOLFOX, Capecitabine, Bevacizumab, Irinotecan, and Regorafenib. Patient, tumor and treatment characteristics at BMs occurrence are shown in Table 2.

Local control (LC), distant brain progression (BDP), progression free survival (PFS), and overall survival (OS) analysis

The median follow-up time from BMs treatment for the entire cohort was 33 months (range 3–183 months) and 37 months (range 9–183 months) for alive patients. 32 (17.3%) patients had local recurrence in site of treatment at a median time of 6 months (range 1–86 months). The median LC time, 6 months, 1, 2 and 3 years LC rates were 86 months (95% CI 36–86), 87.2% ± 2.8, 77.8% ± 4.1, 68.7% ± 5.6, and 63% ± 7.5, respectively. BDP occurred in 71 (38.4%) patients at a median time of 3 months (range 1–82 months). The median BDP time, 6 months, 1, 2 and 3 years BDP rates were 23 months (95% CI 9–44), 66.4% ± 3.9, 55.3% ± 4.5, 47.5% ± 5.3, 38% ± 7.3, respectively. The median PFS time, 6 months, 1, 2 and 3 years PFS rates were 3 months (95% CI 2–5), 38.6% ± 3.6, 26% ± 3.4, 14.6% ± 3, 11% ± 2.9, respectively. The median OS time, 6 months, 1, 2 and 3 year OS rates were 7 months (95% CI 6–9), 52.7% ± 3.6, 33% ± 3.5, 16.8% ± 2.9, 12.1% ± 2.7, respectively. At the last observation time, 26 (14.1%) patients are alive and 159 (85.9%) dead; 96 (60.4%) for extracranial progression, 48 (30.2%) for extracranial and brain

progression, 11 (6.9%) for diffuse brain and meningeal progression only, and 4 (2.5%) for tumor unrelated cause. Figure 1 shows LC rate and BDP; Figure 2 shows PFS, and OS for the all patients treated. Among different RT treatment modality performed, no statistically significant differences were observed on LC, BDF, PFS, and OS. Indeed, the median LC time, 6 months, 1, 2 and 3 years LC rates were nr, 88.8% ± 3.4, 77.3% ± 5.0, 67.7% ± 7.7, and 56.4% ± 12.2, for patients received SRS, 86 months, 82.8% ± 4.2, 77.7% ± 5.3, 69.1% ± 7.4, and 69.1% ± 7.4 for those underwent HSRS, and 86 months, 83.4% ± 7.6, 72.9% ± 9.6, 54.7% ± 11.6, and 54.7% ± 11.6 in cases of surgical resection followed by SRS/HSRS, respectively (*p*-value 0.229). The median BDP time, 6 months, 1, 2 and 3 years BDP rates were 34 months (95% CI 13–36), 67.9% ± 4.6, 61.1% ± 5.1, 51.8% ± 6.8, and 31.1% ± 12.1, for patients received SRS, 7 months (95% CI 7–82), 63.7% ± 5.5, 47.4% ± 6.5, 47.4% ± 6.5, and 47.4% ± 6.5 for those underwent HSRS, and 10 months (95% CI 3–82), 65.3% ± 9.4, 41.0% ± 10.5, 35.9% ± 10.4, and 35.9% ± 10.4 in cases of surgical resection followed by SRS/HSRS, respectively (*p*-value 0.157). The median PFS time, 6 months, 1, 2 and 3 years PFS rates were 3 months (95% CI 2–4), 34.1% ± 4.7, 27.8% ± 4.6, 15.5% ± 4.1, and 9.0% ± 3.7, for patients received SRS, 3 months (95% CI 2–7), 41.2% ± 6.6, 18.8% ± 5.7, 10.6% ± 4.9, and 10.6% ± 4.9 for those underwent HSRS, and 7 months (95% CI 3–15), 52.2% ± 10.4, 34.8% ± 9.9, 19.9% ± 8.6, and 19.9% ± 8.6 in cases of surgical resection followed by SRS/HSRS, respectively (*p*-value 0.495). The median OS time, 6 months, 1, 2 and 3 year OS rates were 6 months (95% CI 4–9), 49.3% ± 4.9, 30.1% ± 4.6, 18.0% ± 4.0, and 11.0% ± 3.5, for patients received SRS, 7 months (95% CI 5–9), 50.5% ± 6.6, 26.5% ± 5.9, 13.0% ± 4.9, and 10.4% ± 4.6 for those underwent HSRS, and 13 months (95% CI 10–17), 73.9% ± 9.1, 60.9% ± 10.2, 21.7% ± 8.6, and 21.7% ± 8.6 in cases of surgical resection followed by SRS/HSRS, respectively (*p*-value 0.175).

Prognostic factors analysis

No factors were recorded as influencing LC. Regarding BDP, the site of primary tumor (colon *vs* rectum), and the number of BMs have had statistically significant value in our analysis. On univariate and multivariate analysis, stage at diagnosis, KPS, presence and number of EC metastases at the time of BMs occurrence, and DS-GPA score were observed as conditioning survival. Details about prognostic factors analyzed and their statistical relevance are shown in Table 3.

Salvage treatment for intracranial/local progression

Among 32 local brain relapse patients, 15 received further treatment: nine surgical resection, 2 WBRT, and 4 SRS. About 71 patients with BDF, 40 were treated: 2 underwent surgical resection followed by HSRS, 14 WBRT, 3 HSRS, and 21 SRS. Systemic

Figure 1. A LC in site of BMs treatment; B. BDF. BDF, brain distant failure; BM, brain metastasis; LC, local control.
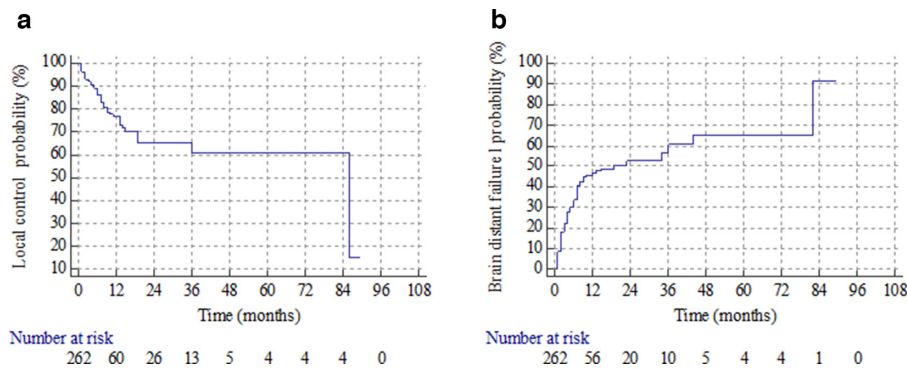
therapy was performed in five patients using different regimen in relation to previous treatment.

Toxicity

Acute treatment related toxicities, consisting in nausea Grade 1-2(G1-2), vomit G2, and headache G1, occurred in 10 patients. Partial or generalized G1-2 seizure arose in 12, and G2 motor deficit in 6, Grade 1–2 radionecrosis, requiring corticosteroid treatment, has been recorded in 9 patients and Grade 3 in 1. The latter undergone surgical resection.

DISCUSSION

The occurrence of BMs from primary CRC is a rare and late event over the disease history, and patients generally present with diffuse extracranial metastatic involvement at the time of BMs existence.[1–4] Among these, patients with mutated RSA tumors present a different metastatic spread, and a higher risk to develop BMs compared with those harboring wild type RAS tumors. The studies that looked at the effect of RAS mutations in metastatic CRC demonstrated that the presence of this mutation predicted a worse OS ($p < 0.01$).[30,31] However, the prognosis of the entire population is poor with median OS ranged from 2 to 12 months, as reported in different published series.[8,12,15] More recently, given the more frequent employ of molecular targeted therapies such as anti-VEGF antibodies, anti-EGFR antibodies, and immunotherapies the number of long-term survivors patients are increasing, with a further potential risk of BMs occurrence. Due to the poor life expectancy and the potential fear of intracranial hemorrhage from some novel biologics,

patients with BMs have often been excluded from clinical trials assessing novel therapies. Therefore, limited data on their clinical activity, clinical predictive markers to guide patient selection and safety of these agents exist in patients with BMs from CRC. Some groups reported a potential improved outcome in patients receiving biologic agents after the development of BMs, but the timing and benefit of the local RT treatments and systemic therapy integration remains an open question to investigate.[32,33] WBRT represents the preferred treatment in cases of multiple brain localizations or meningeal involvement.[7,14] Over the past decade, the use of SRS in place of WBRT, for limited brain disease, is emerging as the first treatment choice..[14,19,22–28] Unfortunately, considering the rarity of BMs incidence in CRC patients, and the short life expectancy, there are a paucity of literature data on this topic. Most of them evaluated the incidence of BMs in CRC patients, others analyzed prognostic factors, and the minority assessed the role of local treatment on outcome. Exactly for these reasons, the optimal therapeutic strategy in these cases is not yet defined. Besides, few data are available about the role of SRS/HSRS on LC in these poor prognosis patients. Paix et al, evaluating 15 patients underwent SRS or HSRS, showed a 6 and 12 months LC rates of 78 and 52%, respectively, without Grade III toxicity or more.[34] Matzunaga et al reported a series of 154 patients treated with SRS. The 2 years local tumor control, defined as suppression of tumor growth, was 60% without impairment of patients quality of life (QOL).[35] Similarly, Schoegg et al demonstrated an early neurological improvement in 82% of patients treated with SRS, and a 6 months local tumor control rate of 94%.[36] With the aim of providing a contribution about

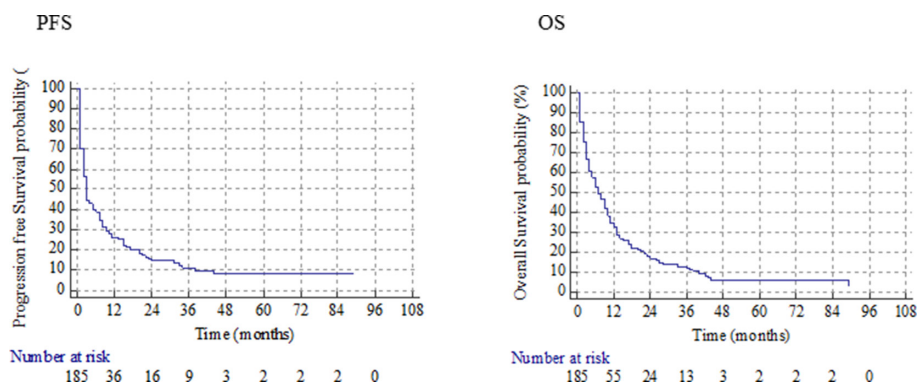Figure 2. PFS and OS. OS, overall survival; PFS, progression free survival.

Table 3. Prognostic factors influencing OS

Prognostic factors	Patients	Median OS months (months 95% CI)	6 months OS (95% CI)	1 year OS (95% CI)	2 year OS (95% CI)	3 year OS (95% CI)	p-value Univariate	HR multivariate (95% CI)	p-value Multivariate
	185	7 (6–9)	52.7 (±3.6)	33 (±3.5)	16.8 (±2.9)	12.1 (±2.7)			
KPS									
90–100	173	8 (6–10)	54.2 (±3.8)	34.5 (±3.6)	17.2 (±3.0)	11.1 (±2.7)	0.002	-	ns
80	10	3 (1–12)	37.5 (±16.1)	12.5 (±11.5)	12.5 (±11.5)	12.5 (±11.5)			
<80	2	1 (n.e.)	0	0	0	0			
Stage at diagnosis									
I-III	112	11 (9–13)	65 (±4.5)	45.3 (±4.8)	23 (±4.3)	18.9 (±4.2)	<.0001	1.67 (95% CI 1.22–2.29)	0.001
IV	73	4 (3–6)	34.2 (±5.5)	15.1 (±4.1)	7.6 (±3.1)	3.0 (±2.1)			
No. of metastatic organs									
1	31	5 (3–9)	38.7 (±8.7)	25.8 (±7.8)	11.3 (±5.9)	7.5 (±5.0)	0.02	-	ns
2	24	6 (3–9)	45.8 (±10.2)	12.5 (±6.7)	8.3 (±5.6)	4.1 (±4.0)			
3	13	3 (2–4)	15.4 (±10.0)	0	0	0			
4	5	4 (4–28)	20.0 (±17.9)	20.0 (±17.9)	20.0 (±17.9)	0			
DS-GPA score									
0–1	51	8 (4–11)	52.7 (±7.0)	31 (±6.7)	19.7 (±5.8)	14 (±5.3)	<.0001	-	ns
2	30	3 (2–6)	23.3 (±7.7)	3.3 (±3.2)	0	0			
2.5–3	48	10 (6–13)	59.8 (±7.1)	35.9 (±7.3)	12.5 (±6.1)	8.3 (±5.3)			
03-05-2004	56	9 (6–16)	62.5 (±6.4)	47.9 (±6.7)	25.3 (±5.9)	19.4 (±5.4)			
EC metastases at BMs occurrence									
No									
Yes	27	16 (13–38)	77.8 (±8.0)	70.0 (±8.9)	40.7 (±9.9)	40.7 (±9.9)	0.0002	1.89 (95%CI 1.12–3.16)	

(Continued)

Table 3. (Continued)

Prognostic factors	Patients	Median OS months (months 95% CI)	6 months OS (95% CI)	1 year OS (95% CI)	2 year OS (95% CI)	3 year OS (95% CI)	HR multivariate (95% CI)	*p*-value Univariate	*p*-value Multivariate
	185	7 (6–9)	52.7 (±3.6)	33 (±3.5)	16.8 (±2.9)	12.1 (±2.7)			
	158	6 (4–8)	48.4 (±4.0)	26.7 (±3.6)	12.6 (±2.8)	6.8 (±2.3)			0.01

BMs, brain metastases; EC, extracranial; GPA, diseasespecific graded prognostic assessment; KPS, Karnofsky performance scale; OS, overall survival; n.r., not reached; ns, not significant. Cox proportional-hazards regression.

this matter, we reviewed a series of CRC patients with limited BMs, treated with SRS or HSRS in several Italian centers. Local control rate, treatment-related toxicities, OS rate, and prognostic factor conditioning outcomes have been analyzed. By use of this approach, the 1 year local control was obtained in about 80% of patients without severe toxicities or neurological impairment. Indeed, the large part of our patients showed G1-G2 acute or late side-effects; only one had Grade 3 radionecrosis requiring surgical resection. Although different total doses and fraction-ations have been employed no significant differences on LC have been recorded. Probably these data are related to the fact that single dose SRS was delivered in more than half of patients, and in cases of larger BMs, requiring an hypofractionated schedule, and adequate biological effective doses have been prescribed and administered. Unlike literature results, in our cohort the employ of surgical resection followed by SRS/HSRS has not proven of influencing local control. In order to highlight these data, among 28 patients who had undergone surgical resection, 10 which had local relapse showed synchronous BDP, and extracranial disease progression, at the same time. Survival rates compare favor-ably with previous reports, with an OS of 33 and 17% at 1 and 2 years, respectively. In this poor prognostic scenario, to identify prognostic factors positively impacting on survival is needed. Matsunaga et al reviewing the medical records of 152 patients who had undergone GK SRS identified a lower KPS score (*p* = 0.026), and the presence of extracranial metastases (*p* = 0.004) as factors significantly correlated with poor overall survival time.[35] Similarly, Del Carpio Huerta et al, in their retrospective analysis regarding 28 BMCRC patients, showed the presence of progres-sive metastatic extracranial disease (*p* = 0.056), and the number of metastatic extracranial locations (*p* = 0.015) as features influencing outcome.[37] In addition, a greater benefit has been recorded by the use of surgical resection compared to RT alone (*p* = 0.019). Other small published series showed the number of BMs, and the local treatment performed, surgery *vs* SRS alone or SRS/HSRS *vs* WBRT, as factors conditioning survival. However, the low number of patients included in these evaluation, and the heterogeneity of treatments performed do not provide consoli-date evidences regarding the optimal therapeutic choice for these patients.[38] A recent published review showed a better survival using SRS, but authors suggested that more robust data are needed to confirm this point.[39] On the other hand, in the large series published in literature, Michi et al failed to identify any factors that correlated with prognosis.[18] Thus, to date the identification of prognostic factors influencing outcome is an open and chal-lenging topic to investigate. The results of our analysis, assessing prognostic factors eventually conditioning prognosis, identified good KPS, the absence of metastatic disease at diagnosis, the high DS-GPA score, the absence or the presence of limited extra-cranial metastases at BMs occurrence time, as factors influencing survival. Particularly, patients without EC metastatic localization (27 in our series) had the better outcome with a median OS time 1, 2, 3 OS rates of 16 months, 70,40 and 40%, respectively, compared to 6 months, 27, 13 and 7% for EC metastatic ones (*p*-value = 0.0002). Would seem that in these subgroup of patients, a most aggressive BMs treatment, could positively influence the outcome, as well. The number of BMs did not result to affect survival in our series, but these data are probably related to the

low number of patients with more than one brain lesion (25%). In addition, considering that all patients received SRS/HSRS and only few patients (14%) surgical resection, no comparative data are provided. In addition, the RAS tumor status has not proven to influence survival probably in relation to the lack of these data in our series. We are aware that the present study has all the limits due to its retrospective nature, and the collection of patients data treated in different centers with different radiosurgery modality. However, to our knowledge, this is the larger study, assessing the role of SRS/HSRS for BMsCRC, and evaluating prognostic factors conditioning survival. Our results underline that SRS/HSRS is a safe and feasible treatment with a satisfactory local control and negligible toxicity. In a potentially radioresistant tumor such as CRC, a high RT doses delivered in a short treatment time could be the way to control brain disease maintaining a good patients QoL. The identification of a subgroup of patients

to a more favorable prognosis could provide a valid aid for future prospective studies in order to maximize survival maintaining an optimal neurological status, while avoiding unnecessary treatments. A clear consensus on the topic is more requisite than ever.

CONCLUSIONS

Our analysis confirmed that the occurrence of BMs from primary CRC define a disease status to poor prognosis. Considering the control of brain disease pivotal to allow an acceptable QoL and to enable the carrying out systemic therapy, the choice of an adequate local treatment can significantly impact on survival. In our experience, SRS/HSRS have proven to be an effective and safe local treatment. A careful evaluation of prognostic and predictive factors, as well as a multidisciplinary evaluation, is a valid aid to manage the optimal therapeutic strategy for CRC patients with BMs.

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