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Feasibility and safety of single-fraction sub-ablative radiotherapy with systemic therapy in colorectal cancer patients with ≤ 10 metastases: A multicenter pilot study (NCT05375708)

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ABSTRACT

Colorectal cancer patients with ≤10 unresectable metastases were treated with single-fraction sub-ablative radiotherapy in addition to standard of care systemic therapy in a single-arm, open-label, multicenter, pilot study (SIRIUS) to assess feasibility and safety. Results indicate that radiotherapy combined with systemic therapy is feasible and safe in this population.

Introduction

Metastatic colorectal cancer (mCRC) patients with no curative intent treatment options are treated with systemic therapy to prolong survival while maintaining quality of life (QoL) [1]. The current standard first line therapy is a fluoropyrimidine based combination chemotherapy plus bevacizumab or an epidermal growth factor inhibitor (EGFR-inhibitor) [2–5]. After achieving stable disease or partial response with chemotherapy and targeted therapy, maintenance therapy with either capecitabine and bevacizumab or fluorouracil, leucovorin and targeted therapy is the preferred strategy to extend disease control [6]. Disease progression often stems from advancing existing lesions (macroscopic disease) [7], indicating that maintenance systemic therapy more effectively controls microscopic disease than macroscopic disease. Adding radiotherapy to systemic therapy in patients with mCRC could be beneficial in suppressing macroscopic disease.

Radiotherapy can be effective as palliative treatment to alleviate symptoms or as ablative stereotactic body radiation therapy (SBRT) in patients with oligometastatic disease to improve survival. Observational studies in patients with one to three metastases and varying primary tumors [8], in patients with oligometastatic non-small cell lungcarcinoma [9] and lung oligometastatic colorectal cancer patients [10] demonstrate effectiveness and support the use of SBRT in this population. Finally, the efficacy of SBRT is demonstrated in the landmark SABR-COMET trial, in which patients with 1–5 metastatic lesions from various primary tumor types obtained a median overall survival (OS) of 28 months (95 %: CI 18–39 months) in the control arm versus 50 months (95 % CI: 29–83 months) in the experimental arm [11]. SBRT of oligometastatic colorectal cancer is considered an effective and safe ablative therapy with curative intent according to the European Society for Medical Oncology (ESMO) Guidelines Committee [1].

Recent developments in radiation oncology have made it possible to

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deliver high precision radiotherapy up to 10 metastases with limited side effects [12]. An observational study with non-small cell lung carcinoma patients and maximum of 8 lesions demonstrated favorable overall survival results [13] and another study showed that stereotactic radiosurgery in patients with 5–10 brain metastases was non-inferior to 1–4 brain metastases in terms of overall survival, while treatment was well tolerated [14]. Patients with more than 10 macroscopic tumor sites probably have a more important systemic component, will potentially benefit less from local treatment, and will have an increased treatment burden with local therapy. The exact number of metastases that might benefit from local treatment remains subject of scientific research, here we pragmatically chose 10 metastases [15–17]. We suggest that radiotherapy's role extends beyond oligometastatic disease with curative intent and symptom relief, to patients with limited polymetastatic disease (Fig. 1). We hypothesize that maintenance systemic therapy suppresses microscopic disease sufficiently whilst disease control can be prolonged by adding radiotherapy to suppress macroscopic disease in mCRC patients with ≤10 unresectable metastases. This novel conceptual approach might postpone 2nd line intensive systemic therapy and progression of disease, maintain or improve quality of life (QoL), and potentially extend OS.

Since feasibility and safety of radiotherapy in combination with systemic therapy in patients with up to 10 metastases is currently unknown, a pilot study (SIRIUS) was initiated before conducting a large multicenter, randomized trial. Our aim was to determine the feasibility and safety of this combination in patients with limited polymetastatic CRC (≤10 metastases).

Methods

A single-arm, open-label, multicenter, pilot study was conducted in four hospitals in the Netherlands. Feasibility, the primary endpoint, required confirmation in five out of six patients. Eligible patients had mCRC with ≤10 metastases and stable disease or partial response (according to RECIST 1.1) after two to four months of initial systemic therapy with capecitabine, oxaliplatin, and bevacizumab (CAPOX-B), fluorouracil, leucovorin, oxaliplatin, and bevacizumab (FOLFOX-B) or fluorouracil, leucovorin, oxaliplatin, irinotecan, and bevacizumab (FOLFOXIRI-B), and had a performance status of 0 or 1 (Fig. 2). Exclusion criteria were: eligible for curative-intent local treatment, peritonitis carcinomatosa, pleuritis carcinomatosa, known brain metastases, or substantial overlap with a previously treated radiation volume (NCT05375708). Written informed consent was obtained, and the study was approved by the Committee on Human-Related Research NedMec (21/742) and local institutional review boards.

Patients received a single 15 Gy fraction to each of the macroscopic tumor sites, including the primary tumor if present. The therapy was delivered in an image-guided way, either on a conventional linear accelerator (LINAC) or a 1.5 T MR-LINAC, whichever had the best targeting according to the treating radiation oncologist. The planning target volume (PTV) included the macroscopic tumor volume (GTV), expanded with a per tumor site dependent margin. Dose constraints followed established literature for single-fraction treatments [18–20]. To mitigate hemorrhage risk, the first two cycles of maintenance therapy excluded bevacizumab, ensuring a 28-day bevacizumab-free interval before and 14 days after radiotherapy. Oral fluoropyrimidines were continued, however if 5-FU maintenance therapy was given, a 7-day therapy gap was planned.

The trial's primary endpoint was feasibility, defined as 5 out of 6 patients in whom: (1) radiotherapy was delivered as planned, (2) > 90 % of the planned dose on all disease sites was received in 95 % of the PTV and (3) the total radiotherapy treatment window would be ≤5 consecutive working days. The secondary endpoint was safety: the number of grade II adverse events (AEs) of specific interest (pain of any type, pneumonitis, proctitis and colitis) and grade III and IV AEs were registered according to CTCAE 5.0 up to 90 days post-radiotherapy, and serious AEs until the end of follow-up. Exploratory objectives included:

- Progression-free survival (PFS), defined as time from radiotherapy to progression of disease, according to RECIST 1.1, or death from any cause.
- Time to treatment failure (TTF), defined as time from radiotherapy to progression of disease not amenable for radiotherapy. If progression of disease occurred that was amenable for radiotherapy this was highly encouraged.
- Intensive systemic therapy free survival (iSTFS), defined as time from radiotherapy to start of intensive systemic therapy.
- Type of progression, defined as progression based on growth of existing lesions, new metastatic lesions or a combination.
- Local control, defined as the number of previously radiated lesions without progression, growth or new metastasis directed treatment. At start of systemic therapy patients were censored. One-year local control was also determined.
- Overall survival (OS), defined as time from radiotherapy to death from any cause.

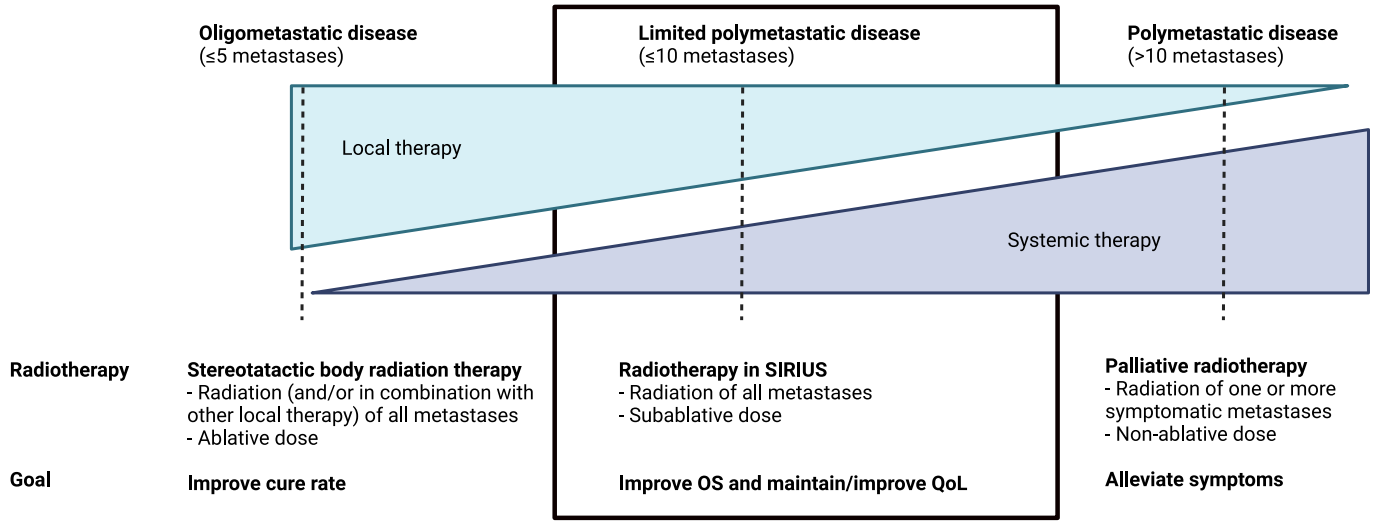
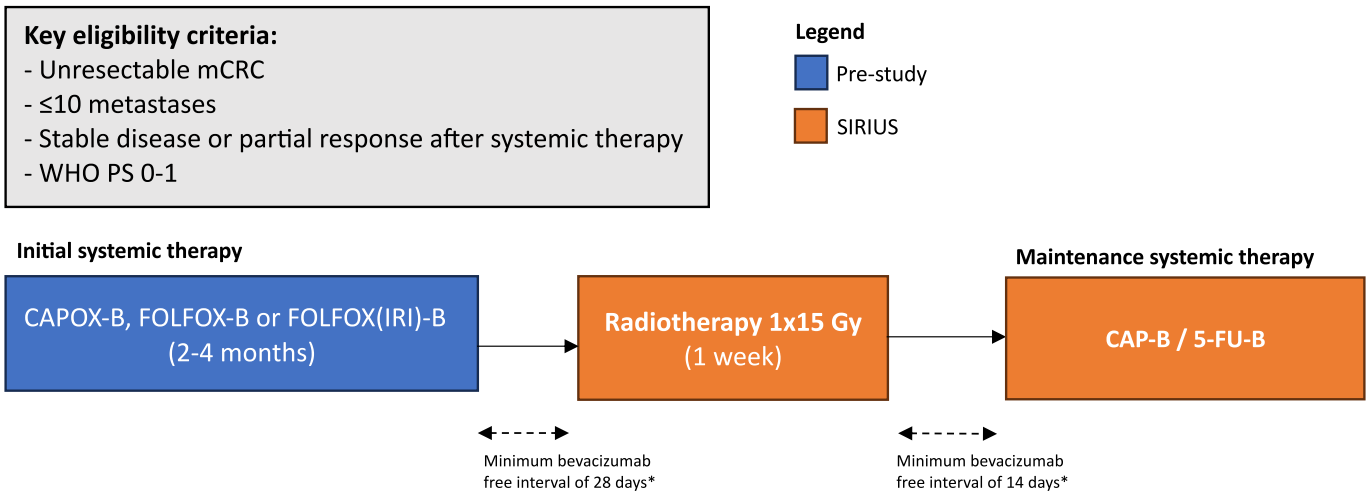


Fig. 1. Spectrum of metastatic disease and the role of local therapy and systemic therapy. In SIRIUS it is hypothesized to improve OS and maintain/improve QoL by adding radiotherapy in patients with limited polymetastatic disease.



*Fluoropyrimidine maintenance therapy was continued. Abbreviations: 5-FU-B = 5-fluorouracil, leucovorin and bevacizumab; CAP-B = capecitabine and bevacizumab; CAPOX-B = capecitabine with oxaliplatin and bevacizumab; FOLFOX-B = fluorouracil, leucovorin, oxaliplatin and bevacizumab; FOLFOXIRI-B = fluorouracil, leucovorin, oxaliplatin, irinotecan and bevacizumab; mCRC = metastatic colorectal cancer; WHO PS = World Health Organization performance score

Fig. 2. SIRIUS eligibility and design.

Results

Six patients were included and as of the data cutoff date (April 17th, 2024) had a median follow-up of 16.6 months (IQR: 10.7-N/A). Median age was 53 years (range 32–72 years) and three were male (50 %) (Table 1). Before initial systemic therapy, a median of 4 lesions (range 2–6) were present, with 38 % vanished during systemic therapy, and a median of 2.5 lesions (range: 1–5) was radiated. Based on the location, distribution, number and or/size of lesions, curative-intent treatment was considered not feasible by the central tumor board.

Table 1
Patient, tumor, and radiotherapy characteristics.

Age in years, median (min, max)	53 (32–72)	**Respons to first line systemic therapy**	
Sex, male	3 (50 %)	Stable disease	1 (17 %)
WHO performance score		Partial response	5 (83 %)
0	3 (50 %)	**Number of treated metastases**	
1	3 (50 %)	1–3	4 (67 %)
Time to metastases, synchronous	2 (33 %)	4–5	2 (33 %)
Site of primary tumor		6–10	0
Right-sided	2 (33 %)	**Location of treated metastases**	
Left-sided/rectum	4 (67 %)	Liver	7/16 (44 %)
Primary tumor resection	6 (100 %)	Lymph node	5/16 (31 %)
Adjuvant chemotherapy	2 (33 %)	Lung	3/16 (19 %)
BRAF^{V600E} mutation	1 (17 %)	Soft tissue	1/16 (6 %)
RAS mutation	3 (50 %)	**Median GTV in cm^3 (IQR)**	1.9 (1.4–5.6)
Number of metastases before systemic therapy		**Median PTV volume in cm^3 (IQR)**	15.8 (6.2–26.9)
1–3	1 (17 %)	**Median V100%GTV (IQR)**	100 % (97.0–100.0)
4–5	3 (50 %)	**Median V95%PTV (IQR)**	97.2 % (96.3–98.8)
6–10	2 (33 %)	**Median number of hospital visits (min–max)** (incl. preperation visit)	2 (2–3)

GTV = gross tumor volume; SD = standard deviation; PTV = planning target volume; WHO = world health organization.

All patients received radiotherapy as planned. More than 90 % of the planned dose was delivered to 95 % of the PTV in all patients with a median V95 %PTV of 97.2 % (IQR: 96.3 %–98.8 %). All patients were treated within the radiotherapy treatment window (equal or less than 5 consecutive working days) with a median of 2 hospital visits for each patient, including a preparation visit. Patient ID1 opted out of maintenance therapy after radiotherapy for personal reasons unrelated to the treatment. Systemic therapy delays were minimal, except for two patients. One patient had two weeks delay due to the patient's planned holiday and one patient had one week delay due to hand foot syndrome. Feasibility endpoints were met for all patients.

No grade III or grade IV events were reported within 90 days. One grade II event of specific interest (non-specific thoracic pain) had been reported, which was unrelated to radiation. One patient died nine months after radiotherapy. This was due to recurrence of a rectal tumor and painful abscesses in the pelvis; the patient opted out of further oncologic treatments. There was no relation to the radiation since the rectal tumor had been resected prior to the study and was not irradiated.

Two patients (ID4 and ID6) remained progression-free after a follow-up of eleven and nine months respectively (Fig. 3), four patients had progressive disease. Progression was based on different types of progression: Two patients (ID1 and ID3) had progression based on new metastatic lesions after eight respectively twelve months. One patient (ID5) had progression based on recurrence of an earlier resected rectal tumor after six months. One patient (ID2) had progression of an existing, re-irradiated lesion after fifteen months.

Four patients were radiated during follow-up due to minimal growth of an existing lesion (ID2, ID3 and ID5) and new lesions (ID1). Two of these patients (ID1 and ID2) showed an ongoing iSTFS of 18 and 16 months, respectively. For all 6 patients the median PFS was 12.0 months (95 % CI: 7.8-N/A), median TTF was 14.5 months (95 % CI: 12-N/A), and median iSTFS or OS were not reached.

Local control, assessed for each individual radiated lesion, was 69 % (11/16). The one-year local control rate was 56 %. On an important note, three out of four patients with irradiated liver metastases showed radiologic post-radiation effects mimicking progression on CT-scan. These post-radiation effects remained asymptomatic, however should be recognized by radiologists as no true progression of disease by

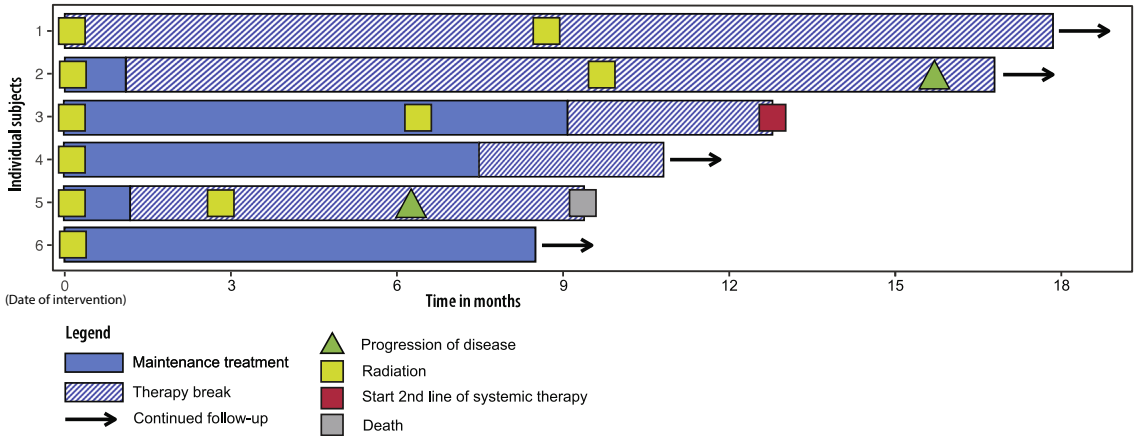


Fig. 3. Swimmerplot of SIRIUS lead-in.

considering the radiation plan when assessing previously radiated lesions. In equivocal cases, additional MR imaging, including diffusion weighted sequences, can aid in distinguishing post-radiation effects from true progression.

Discussion and conclusion

Single-fraction sub-ablative radiotherapy combined with systemic therapy for patients with limited polymetastatic (≤10 metastases) CRC is feasible and safe. All patients in this pilot study received the planned dose within a week without clinically relevant delays in systemic therapy. Our findings support the successful integration of radiotherapy into the treatment of patients with unresectable limited polymetastatic disease.

In our study, we administered a sub-ablative single-fraction dose of 15 Gy, akin to 25 Gy in 5 fractions used with short-course radiotherapy for rectal cancer. We aimed to prolong local control with at least three months in PFS/TTF, aligning with the ESMO magnitude of clinical benefit scale [21]. Additionally, standard of care systemic therapy can be administered without clinically relevant delays and QoL is expected to be maintained [22]. Higher radiation doses risks increased toxicity and could delay standard systemic therapy, while it can be questioned if a higher dose would postpone second-line systemic therapy [11].

Single-fraction radiotherapy minimizes dose delays of systemic therapy and hospital visits, thereby preserving QoL. Our concept of a sub-ablative dose with the aim of postponing second- line intensive systemic therapy, while maintaining QoL, is evidently different compared to the interventional arm of the SABR COMET-10, in which an ablative dose (20–35 Gy) with curative intent is given in patients with 4–10 metastases of different tumor types.

Although underpowered for efficacy assessment, our pilot study showed promise with median PFS, after initial systemic therapy, of 12.0 months and TTF of 14.5 months. Median iSTFS or OS were not reached after a median follow-up of 16.6 months. In comparison to patients treated with systemic therapy alone: median PFS for mCRC patients with ≤10 metastases receiving CAPOX-B followed by CAP-B maintenance was 9.9 months [23], while 4 out of 6 patients in our study surpassed this duration despite total maintenance therapy exposure being surprisingly low at the request of the participating patients and not because of radiation toxicity. Sub-ablative dose radiation therapy could therefore reduce systemic therapy treatment and related costs. The small sample size of this study and the lack of an active control group are important limitations for efficacy assessment. Consequently, these findings should not be extended to the current standard of care.

Our intended study population were patients with 4–10 metastases. However, patients in the study had a maximum of 6 metastases before initital systemic therapy. Additionally, due to effective initial systemic therapy, 38 % of lesions vanished inducing oligopersistence (1–3 metastases) in 4 out of 6 patients. To assess feasibility and safety in patients with more irradiated lesions, we will execute a follow-up study with adjusted in- and exclusion criteria: counting malignant lesions will occur after initial systemic therapy instead of before. Upon confirming safety and feasibility, a randomized trial will evaluate efficacy and QoL (as QoL was not measured in this preliminary study).

Selecting the primary endpoint for this subsequent trial is challenging. While improving QoL and OS are crucial patient goals, they pose difficulties in oncology trials due to various factors like response shift, missing data, large sample size, long-term follow-up, and post-trial therapies [24,25]. For systemic therapies, PFS is clearly defined and implemented in clinical trials. However, clinical trials of metastasis-directed local therapy (MDT) often adopt PFS as a trial endpoint without recognizing the fundamental difference between systemic and local treatments. TTF or iSTFS might provide more relevant endpoints, potentially reflecting improved QoL by delaying intensive systemic therapy. Yet, iSTFS has drawbacks as an endpoint because the decision to start a new line of systemic therapy is subjective as it involves shared decision-making between physicians and patients. In conclusion, an international consensus statement is needed for clinically relevant primary endpoints in local therapy trials for oligo- and/or polymetastatic disease.

In summary, we demonstrate that the concept of single-fraction sub-ablative radiotherapy in combination with systemic therapy in patients with limited polymetastatic (≤10) CRC is feasible and safe. This synergistic approach, controlling macroscopic disease with single-fraction sub-ablative radiotherapy and controlling microscopic disease with maintenance systemic therapy, may postpone second-line intensive systemic therapy, disease progression, improve QoL, and potentially extend OS. Randomized tumor-specific studies with feasible, clinically relevant primary endpoints are essential to implement this treatment paradigm in routine clinical practice.

CRediT authorship contribution statement

K. Zwart: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **M.N.G.J.A. Braat:** Investigation, Methodology, Resources, Supervision, Writing – review & editing. **F.H. van der Baan:** Methodology, Writing – review & editing. **A.M. May:** Supervision, Methodology, Writing – review & editing. **J.M.L. Roodhart:** Resources, Writing – review & editing. **D. Al-Toma:** Data curation, Investigation, Project administration, Writing – review & editing. **J.M.M.B. Otten:** Resources, Writing – review & editing. **M. Los:** Resources, Writing – review & editing. **T. Oostergo:** Resources, Writing – review & editing. **R.J.A. Fijneman:** Writing –

review & editing. **J.M. van Dodewaard-de Jong:** Resources, Writing – review & editing. **C.J.A Punt:** Writing – review & editing. **G. Meijer:** Writing – review & editing. **J.J.W. Lagendijk:** Conceptualization, Writing – review & editing. **M. Koopman:** Supervision, Resources, Writing – review & editing. **M. Intven:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **G.M. Bol:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [K. Zwart: No disclosures of interest. M.N.G.J.A. Braat: No disclosures of interest. F.H. van der Baan: Institutional financial interests: Personal Genome Diagnostics. A.M. May: No disclosures of interest. J.M.L. Roodhart: Institutional scientific grants: Bayer, GSK, Servier, Cleara, HUB 4 organoids, Pierre Fabre, Servier, Xilis, DoMore diagnostics, Delphi, PGDx. Advisory role: BMS, Merck-Serono, AMGEN, Bayer, Servier, GSK, Nutricia. D. Al-Toma: No disclosures of interest. J.M.M.B. Otten: No disclosures of interest. M. Los: No disclosures of interest. T. Oostergo: No disclosures of interest. R.J.A. Fijneman: Scientific grants and non-financial support from Labcorp (Personal Genome Diagnostics); DELFI Diagnostics; Solvias (Cergentis BV); grants from MERCK BV; non-financial support from Natera. In addition, RJAF has several patents pending. J.M. van Dodewaard-de Jong: No disclosures of interest. C.J.A Punt: Advisory role: Nordic Pharma. G. Meijer: No disclosures of interest. J.J.W. Lagendijk: Stock and travel/accomodation: Elekta. M. Koopman: Advisory role: Eisai, Nordic Farma, Merck-Serono, Pierre Fabre, Servier. Institutional scientific grants: Bayer, Bristol Myers Squibb, Merck, Personal Genome Diagnostics (PGDx), Pierre Fabre, Roche, Sirtex, Servier. Non-financial interests: chair of the ESMO RWD-DH working group, co– chair: DCCG, PI PLCRC (national observational cohort study), involved in several clinical trials as PI or co-investigator in CRC. M. Intven: Institutional scientific grants: Dutch cancer society, Elekta. Personal financial grants: Elekta. Advisory role: Dutch Society for Radiotherapy and Oncology, Elekta. G.M. Bol: Institutional scientific grants from Bayer, Servier, Pierre Fabre and Terumo].

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