Inoperable *de novo* metastatic colorectal cancer with primary tumour *in situ*: Evaluating discordant responses to upfront systemic therapy of the primary tumours and metastatic sites and complications arising from primary tumours (experiences from an Irish Cancer Centre)

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Received March 25, 2021; Accepted November 22, 2021

DOI: 10.3892/mco.2021.2472

Abstract. Systemic therapy is the mainstay of treatment for *de novo* metastatic colorectal cancer (mCRC). Heterogeneity between primary tumours and metastases may lead to discordant responses to systemic therapy at these sites. The aim of the present study was to examine these discrepancies and to evaluate the rates of complications arising from the primary tumour and the strategies employed to manage these complications. Electronic medical records were screened for patients eligible for data analysis between January 1st, 2014 and December 31st, 2019. All patients diagnosed with *de novo* mCRC with primary tumour *in situ* at the time of initial systemic therapy were included in data analysis. Responses in primary tumour and metastatic sites (according to the Response Evaluation Criteria In Solid Tumours v1.1), discrepancies in these responses and rates of complications arising from primary tumours were assessed along with patient, pathological or molecular factors that may be associated with these discrepant responses or primary tumour complications. A total of 50 patients were identified (median age, 62 years). Right-colon, left-colon and rectal primary tumours comprised 34, 44 and 22% of CRC cases, respectively. All patients received 5-fluorouracil-based chemotherapy (either alone or in combination with oxaliplatin or irinotecan). Disease response (DR), stable disease (SD) and progressive disease (PD) were observed as the first response to systemic therapy in 24, 62 and 12% of primary tumours and in 36, 18 and 44% of metastatic sites, respectively. Only 36% of patients demonstrated concordant responses between the primary tumours and metastases, while the remaining 62% demonstrated discordant responses between the primary tumour and distant metastases (22% had DR with SD; 36% had DR or SD with PD; and 4% had PD with SD in the primary tumour and metastases, respectively). Restaging images were not available for 2% of the patients. Approximately 30% of patients developed complications from primary tumours, including bowel obstruction (6.12%), perforation (6%), rectal pain (6%) and rectal bleeding (10%). Approximately 10% of patients underwent palliative stoma creation. Additionally, 12% required palliative radiotherapy to the primary tumour (due to localized complications arising from the tumour). Discordant responses to systemic therapy between primary tumours and metastases occurred in 60% of patients with *de novo* mCRC (with primary tumour *in situ* at the time of first systemic therapy). The observations of the present study have potential implications for molecular tissue analysis to help guide systemic therapy. Tissue from metastatic sites may be preferable to confirm biomarker status in mCRC based on this study.

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Key words: colon cancer, primary tumour, metastases, chemotherapy, discordant response, complication, interventions

Introduction

According to global cancer statistics, colorectal cancer (CRC) is the third most common type of cancer diagnosed worldwide, accounting for just over 10% of all diagnosed cancers. This is surpassed only by cancers of the lung and breast (the latter in women). CRC is the second leading cause of cancer-related mortality, accounting for just over 9% of cancer-related deaths (1). Approximately 20% of patients with CRC demonstrate metastases at initial diagnosis (metastatic CRC; mCRC), whether detected on imaging or confirmed during biopsy,

with up to 80% of such patients deemed unresectable at initial diagnosis (2,3).

Systemic therapy is the mainstay of treatment for patients with inoperable CRC. Localized therapy in the palliative setting (namely surgical resection and irradiation of the primary tumour) is commonly limited to patients suffering from primary tumour complications. These can include bowel obstruction, perforation, localized pain and bleeding from the tumour (4,5).

Chemotherapeutic agents typically employed in mCRC consist of the antimetabolite 5-fluorouracil (5FU) (6,7), the pyrimidine analogue capecitabine (8), the topoisomerase inhibitor irinotecan (9) and the alkylating agent oxaliplatin (10). EGFR-targeting monoclonal antibodies include cetuximab (11) and panitumumab (12) for confirmed KRAS/NRAS wild-type tumours and VEGF-targeting bevacizumab (13) and ramucirumab (14), the latter typically in combination with chemotherapy using the FOLFIRI regimen (15).

Oxaliplatin-containing regimens, such as FOLFOX (16,17) or XELOX (18,19) and irinotecan-containing regimens, such as FOLFIRI (20-22) and XELIRI (23-25), have both been established equally effective in terms of progression-free and overall survival as first-line palliative systemic therapy in mCRC (26). Oxaliplatin-containing regimens may be preferred over irinotecan-based regimens as first-line therapy in mCRC due to their slightly more favourable median overall survival and toxicity profiles (21,27,28), including in elderly patients (29).

This may vary in patients for whom either oxaliplatin or irinotecan are contraindicated as first-line therapy due to their varying toxicity profiles. In patients deemed unsuitable for additional oxaliplatin and irinotecan with 5FU or capecitabine (such as patients of advanced age, with co-morbidities or poor performance status), single-agent 5FU or capecitabine may be preferred. Such single-agent 5FU regimens include the Roswell Park (30,31) and QUASAR (32,33) regimens and capecitabine (34,35) in either the adjuvant (36) or palliative (37) setting.

Combined nucleic acid analogue/thymidine phosphorylase inhibitor TAS-102 (tipiracil hydrochloride) (38) and the multikinase inhibitor regorafenib (39) are typically reserved for patients in whom 5FU-based chemotherapy in combination with oxaliplatin or irinotecan has failed (or if the patient is deemed clinically unsuitable to receive these treatments). Depending on the patient, irinotecan- or oxaliplatin-based chemotherapy may be rechallenged in the palliative setting if a significant interval has elapsed since completing a previous course of treatment, provided cumulative toxicity allows for this approach (40,41).

The targeted tyrosine kinase inhibitors encorafenib and binimetinib may be considered in BRAF V600E mutant tumours in combination with other systemic therapies (42). Immune checkpoint inhibitors are reserved for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumours (43); these include the monoclonal antibody inhibitors nivolumab (44,45) and pembrolizumab (46), which inhibit programmed death receptor 1, and ipilimumab (47), which inhibits cytotoxic T-lymphocyte-associated protein 4.

Tumour heterogeneity exists in mCRC, whether within the primary tumour (intra-tumoural heterogeneity) or between the primary and metastatic tumours (inter-tumoural heterogeneity) (48-50). Intra- or inter-tumoural heterogeneity has been implicated in the mechanisms underlying resistance to systemic therapy (51). Tumour heterogeneity in mCRC can vary during the course of the disease (52).

Inter-tumoural heterogeneity accounts for identifiable discordances in scientifically validated tests of advanced CRC. These discordances may include differentiation of adenocarcinoma (53,54), in which cancer stem cells play a role (55), mutation status (56-59), including KRAS/NRAS (60-62) and BRAF (63,64) status, MSI status (65) and dMMR status (66,67). This may lead to discordances in biomarker profiles between the primary tumour and metastases. Inter-tumoural heterogeneity appears to be more prevalent in mCRC with certain pathological and molecular features, such as confirmed MSI (68,69).

Among diagnosed CRCs, 30-40% of carry a pathogenic somatic KRAS mutation (70), 10% carry a NRAS mutation (71) and 10% carry a BRAF mutation (72). dMMR is identified in 10-20% (73-75) and MSI is identified in 10-20% of diagnosed colon cancers (76,77). Approximately 3% of colon cancers arise from germline mutations leading to MSI (78), a condition known as Lynch syndrome or hereditary non-polyposis CRC. Approximately 1% of cases result from germline defects in the α-fetoprotein gene (79), a condition known as familial adenomatous polyposis. Hypermethylation of the MLH1 gene promoter occurring in tumours with the CpG island methylator phenotype appears to be the predominant somatic mechanism of action of MSI-H in colorectal tumours (80).

Discordant responses between the primary tumour and metastatic sites in mCRC may arise from this underlying heterogeneity between tumour sites. Tumour cells at the metastatic sites may harbour clones that have gained (or lost) mutations advantageous to their survival compared to those residing at the primary site, or vice versa (81,82). These molecular discrepancies in mCRC are not yet fully understood; clonal evolution, cancer stem cells and 'The Big Bang' model have all been hypothesized to play a role (83-85).

The incidence of these biomarker discordances in mCRC varies depending on the resources consulted. Part of the literature, including meta-analysis studies, suggests that the rate of biomarker concordance is high between primary tumours and metastases in mCRC (86,87). These studies further suggest that tissues from either the primary tumour or metastatic site are sufficient for confirming the biomarker status of mCRC to help guide the systemic therapy approach (88). However, more recent studies suggest that the rate of these discordances increases if next-generation sequencing is used (89,90). There is high concordance (>90%) between immunohistochemical analysis and molecular testing of dMMR (91).

The rates of molecular discordances between the primary tumour and metastatic sites in mCRC may be as high as 10-15%, depending on the study (86,92). The rate of discrepancies in MSI or MMR status tends to be low (<5%) upon comparison (93,94). The expression of other specific biomarkers, such as programmed death ligand 1 (PD-L1), may vary more markedly between primary tumour and metastatic sites in up to one-third of patients (95).

Evaluating molecular characteristics between primary and metastatic tumours separately in a single patient with mCRC

can demonstrate variable biological behaviour and response to systemic therapy due to these identified subclones (96). Non-genetic factors, such as post-translational modification, epigenetics and the tumour microenvironment, also contribute to this phenomenon. Comparing such predictive or prognostic molecular signatures between the primary and metastatic tumours in mCRC has yielded different results. For example, mutant KRAS status exhibits concordance between the primary tumour and distant organ metastases in up to 90% of patients with mCRC (97). Conversely, comparisons between the primary tumour and lymph node metastases demonstrate lower concordance rates with a KRAS mutant status of ~37% (98).

The role of pre-emptive localized therapies in patients with relatively asymptomatic primary tumours remains controversial and has demonstrated an inconsistent clinical benefit (99-101). Radiation to rectal and rectosigmoid cancer primary tumours has been associated with a reduced risk of death in one retrospective study (102). Previous findings have demonstrated no additional benefit, reduced risk of complications or death when radiation treatment is administered before systemic therapy (103), while other findings suggest that prior resection of the colorectal primary in mCRC offers benefit in selected patients (104). However, this should not be routinely considered in asymptomatic patients, as it offers no additional benefit (105), taking into account the currently available systemic therapies (106).

Materials and methods

Study design. A retrospective review of patients was conducted using ARIA v15.6 software (https://www.varian.com/; supplied by Varian Medical Systems). The terms 'colon cancer' and 'rectal cancer' were utilized to narrow the search and identify patients suitable for inclusion in the study. Patient records were assessed between January 1st, 2014 and December 31st, 2019. Any patients initiated on up-front systemic therapy prior to January 1st, 2014, or beyond December 31st, 2019, were excluded from the study. Data events (radiological progression and overall survival) were not recorded beyond December 31st, 2019.

Ethics approval was obtained from the local hospital Medical Research Ethics Committee prior to data collection (REC Ref: 113/2020). Patient data were anonymized during data collection and analysis. Informed consent (written or oral) was not required, since this was a retrospective chart review (as outlined per Health Research Consent Declaration Committee Guidelines, Ireland). All data collection procedures followed the General Data Protection Regulation and the Data Protection Act, 2018.

Patient characteristics. The analysis included patients with a radiologically and pathologically confirmed diagnosis of metastatic *de novo* mCRC, with the primary tumour *in situ* treated with up-front palliative systemic therapy. Non-curative status was confirmed through multidisciplinary meeting discussion (in applicable cases requiring discussion with surgical specialists based on imaging findings). Patients considered to have operable/potentially curable mCRC at initial diagnosis per multidisciplinary meeting discussion were excluded from the analysis. Patients with a prior history of early-stage CRC treated with radical management strategies (including surgery or high-dose radiotherapy) were excluded. Patients diagnosed with *de novo* mCRC requiring up-front localized management strategies for primary tumours (radiotherapy, endoscopy or surgery) prior to palliative systemic therapy were excluded.

Mutation status and response to therapy. KRAS, NRAS and BRAF status were confirmed through next-generation sequencing CRC mutation panel test (107). MSI and MMR status were confirmed using a multiplex PCR approach followed by DNA fragment analysis and immunohistochemistry (using BenchMarckULTRA IHC/ISH by Roche Diagnostics).

The responses of primary tumours and metastases to up-front systemic chemotherapy were observed separately and discordant responses to therapy were documented based on routine interval radiological assessments. Molecular characteristics possibly associated with these discordant responses were also analysed and the incidence of complications from the primary tumours and subsequent interventions were evaluated.

Factors including patient age, sex, primary tumour location, molecular panel status and interval of response to first-line systemic therapy were recorded. Responses to systemic therapy in primary tumour and metastatic sites were recorded separately using Response Evaluation Criteria In Solid Tumours, v1.1 (108). Furthermore, the incidence of complications, types of complications arising from primary tumours and subsequent management strategies for such complications were also recorded, whether this involved conservative management (such as endoscopy, surgery, or radiotherapy, or a combination of these interventions).

Study endpoints. Primary endpoints included documented response rates to first-line up-front chemotherapy (in both primary and metastatic sites) and the rates of discordance between these responses. Primary endpoints also included evaluation of molecular and pathological factors that may be associated with the discordant radiological responses. Secondary endpoints included documenting the rate of complications arising from the primary tumour (during up-front palliative systemic therapy), the types of complications encountered and the management strategies employed.

Statistical analysis. Non-parametric tests were used to compare groups, investigate the statistical significance of the associations and analyse survival (McNamara, Friedman's and Kaplan-Meier analyses). $P<0.05$ was considered to indicate statistically significant differences.

Results

Characteristics of primary and metastatic tumours. A total of 50 patients were identified and included in the analysis (median age, 62 years; interquartile range, 55-69 years). A total of 30 patients (60%) were male. Primary tumours confined to the right colon (including the caecum, ascending and transverse colon), left colon (including the descending and sigmoid colon) and rectum were observed in 34% (n=17), 44% (n=22) and 22% (n=11) of the patients, respectively (Table I).

Table I. Patient, tumour and molecular tissue characteristics with associated treatment modalities employed (n=50).

Characteristics	No. (%)
Demographics	
Male sex	30 (60)
Female sex	20 (40)
Age (years), median (IQR)	62 (55-69)
Location of primary tumour	
Right colon	17 (34)
Left colon	33 (66)
Sites of metastasis	
Liver	44 (88)
Lung	20 (40)
Peritoneum	10 (20)
Lymph nodes	11 (22)
Other/bone	1 (2)
Mutations	
None	19 (38)
KRAS	24 (48)
NRAS	2 (4)
BRAF	2 (4)
Microsatellite instability	1 (2)
NA/sample not sufficient for test	5 (10)
Chemotherapy	
5FU/oxaliplatin (FOLFOX)	28 (56)
Median number of cycles (IQR)	8.5 (4-12)
5FU/irinotecan (FOLFIRI)	17 (34)
Median number of cycles (IQR)	9 (4-12)
Capecitabine/irinotecan (XELIRI)	3 (6)
Median number of cycles (IQR)	3 (3-6)
Single-agent 5FU	1 (2)
Median number of cycles	30 weekly cycles
5FU/oxaliplatin (FLOX)	1 (2)
Concurrent anti-VEGF antibody (bevacizumab)	9 (18)
Concurrent anti-EGFR-antibody (cetuximab/panitumumab)	12 (24)

IQR, interquartile range; 5FU, 5-fluorouracil.

The most common site of metastasis at diagnosis of mCRC was the liver (n=44, 88%), followed by the lung (n=20, 40%) and peritoneum (n=10, 20%). Only 1 patient had bone metastasis. In 18 (36%) and 2 (4%) patients, the liver and lung were the only sites of metastasis, respectively. Finally, 10 patients (20%) had both liver and lung metastases at diagnosis (Table I).

Metastasis involving one, two and three or more organ sites were present in 23 (46%), 20 (40%) and 7 (14%) patients, respectively, at the time of diagnosis of non-curative mCRC. KRAS, NRAS and BRAF were found to be mutated in 24 (48%), 2 (4%) and 2 (4%) cases, respectively. Furthermore, 2 patients (4%) had synchronous KRAS and BRAF mutations. Only 1 patient (2%) harboured KRAS mutation with MSI, and 5 patients (10%) could not have their mutation panels performed due to insufficient tissue available for diagnosis (Table I).

Treatment and response. All patients received 5FU-based chemotherapy. A total of 28 patients (56%) received concurrent oxaliplatin (FOLFOX regimen) and 17 (34%) received concurrent irinotecan (FOLFIRI regimen) as first-line treatment, with an observed median treatment duration of 17 and 19 weeks, respectively. Furthermore, 3 patients (6%) received concurrent capecitabine with irinotecan (XELIRI regimen) with a median treatment duration of 6 weeks, while 1 patient received single-agent 5FU (QUASAR regimen) for up to 30 weeks (Table I).

VEGR-targeted monoclonal antibody therapy (bevacizumab) was used in 9 patients (18%), whereas EGFR-targeted monoclonal antibody therapy (cetuximab and panitumumab) was used in 12 patients (24%), concurrently with first-line chemotherapy (Table I). Over half of the patients had received one line of systemic therapy for mCRC (n=27, 54%), 11 (22%) had received up to two lines of chemotherapy, and 11 patients (22%) had received three or more lines of chemotherapy (by data cut-off).

Radiological assessment of response to palliative systemic therapy demonstrated significant discordant responses between the primary tumour and metastatic sites. Primary tumours demonstrated disease response (DR), stable disease (SD) and progressive disease (PD) in 24, 62 and 12% of patients on first-line palliative systemic therapy, respectively.

By contrast, metastatic lesions demonstrated DR, SD and PD on first-line chemotherapy in 36, 18 and 44% of patients, respectively (Table II). Only 18 (36%) of the patients demonstrated concordant responses in both the primary tumour and metastatic sites on first-line palliative systemic therapy. A total of 11 patients (22%) demonstrated discordant responses consisting of SD with DR, n=2 (4%) had PD with SD, and n=18 (36%) had either DR or SD with PD in the primary tumour and metastatic sites respectively (Table III). Discordant responses between the primary tumour and metastatic sites did not vary significantly according to the KRAS/NRAS/BRAF mutant ($P>0.05$).

A total of 15 patients (30%) developed complications arising from the primary tumours during the course of up-front first-line systemic therapy. As regards complications arising from the primary tumour requiring intervention, 6 patients (12%) developed bowel obstruction and 3 patients (6%) developed bowel perforation; an additional 8 patients (16%) developed either pain or bleeding from the primary tumour, necessitating local intervention. Only 1 patient developed a primary tumour-associated abscess requiring drainage and surgical resection. An outline of complications from the primary tumour and the management strategies employed is outlined in Table IV.

Of the 50 patients, 38 (76%) did not develop any complications from their primary tumour requiring intervention while receiving palliative systemic therapy or by the time of data cut-off. A total of 3 patients (6%) initially deemed inoperable/non-curable at diagnosis ultimately proceeded to undergo surgery with curative intent with resection of the primary tumour, metastasectomy, or other local therapies (e.g.,

Table II. Radiological assessment after first-line chemotherapy.

Type of response	Primary sites, n (%)	Distant metastatic sites, n (%)
Disease progression	6 (12)	22 (44)
Stable disease	31 (62)	9 (18)
Disease response	11 (22)	18 (36)

Table III. Difference in response between primary and metastatic sites among patients.

Type of response	Primary site	Metastatic sites	%	Total %
Concordant response	PD	PD	8	36
	SD	SD	12	
	DR	DR	16	
Discordant response with SD or DR	SD	DR	20	22
	DR	SD	2	
Discordant response with PD at one site	DR	PD	6	40
	SD	PD	30	
	PD	SD	4	

PD, progressive disease; DR, disease response; SD, stable disease.

Table IV. Complications arising from primary colorectal tumour and localized interventions employed.

Complications of primary tumour sites	No. (%)
Type of complication	
Obstruction	6 (12)
Obstruction and perforation	3 (6)
Abscess	1 (2)
Pain	3 (6)
Bleeding	5 (10)
Type of intervention	
Curative surgical resection of primary/ metastatic site (metastasectomy)	3 (6)
Palliative radiotherapy only	6 (12)
Palliative stoma creation (colostomy/ ileostomy)	5 (10)
Stoma creation with radiotherapy	1 (2)

radiation) to metastatic sites. These management strategies were undertaken considering marked radiological treatment response following repeat multidisciplinary team meeting discussions.

A total of 5 patients (10%) required emergent defunctioning stoma creation (colostomy or ileostomy) for bowel obstruction, or perforation. A total of 6 patients (12%) required local radiotherapy for primary tumour *in situ*, most often for rectal bleeding or localized pain. Only 1 patient underwent both stoma creation and local irradiation (Table IV).

Left-sided primary tumours were associated with a significantly higher rate of complications requiring local intervention compared with right-sided tumours (P<0.001), with complications arising in 17 (34%) and 9 (18%) cases, respectively. The median overall survival was 14.0 months (95% CI: 10.0-36.0; Fig. 1). At the time of data cut-off (December 31st, 2019), 7 patients (14%) remained alive, 3 of whom were receiving their third line of systemic therapy, 2 were receiving their fourth line and 2 were off treatment (undergoing active clinical follow-up with radiological surveillance).

Discussion

The present study demonstrated that up-front palliative systemic therapy can effectively control primary tumours in patients with *de novo* mCRC with primary tumours *in situ* that are deemed inoperable/non-curable at initial diagnosis. However, while up-front systemic therapy with palliative intent is predominantly effective in mCRC with primary tumour *in situ*, 24% of patients in our study required localized intervention due to complications arising from the primary tumour (on first-line systemic therapy).

Other studies have demonstrated a reduced risk of primary tumour-related complications and the need for emergent surgical intervention with up-front localized interventions prior to undertaking palliative systemic therapy (3,101). Most international guidelines currently recommend combination chemotherapy as the initial treatment for unresectable mCRC with primary *in situ* (109,110). Local interventions for primary tumours are typically reserved for when complications arise from the primary tumour after palliative systemic therapy

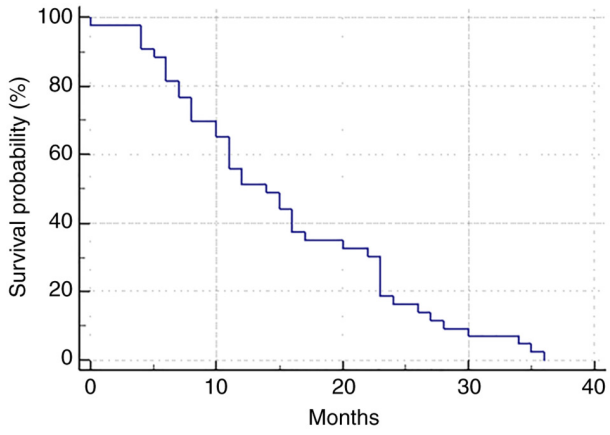

Figure 1. Kaplan Meier curve demonstrating a median overall survival of 14 months (95% CI: 10.0-36.0).

has already been employed (including bowel obstruction, perforation, significant pain, or bleeding from the primary tumour) (111,112).

In the present study, higher rates of radiological response were observed in primary tumours compared with metastatic tumour sites. Nonetheless, the rate of complications arising from the primary tumour requiring intervention during systemic therapy remained high (up to 25% of cases in this patient cohort).

In a retrospective study involving 233 patients with mCRC receiving combined chemotherapy with or without bevacizumab as up-front first-line systemic therapy (113), only 7% of these patients required emergent surgical intervention, and 4% required emergent non-surgical intervention (radiation and endoscopic stenting) while on systemic therapy. On the other hand, the remaining 213 patients (89%) never required local intervention for their primary tumour. Another study observed that, among 83 asymptomatic patients with non-curable mCRC treated with first-line chemotherapy (114), only 5% required surgery, while 4% required colonic stenting to manage complications arising from the primary tumour.

Conversely, other studies support prophylactic surgical resection of the primary tumours in non-curable mCRC before undertaking palliative-intent systemic therapy to reduce the future risk of primary tumour complications (2,3,101). One meta-analysis reviewed eight retrospective studies including 1,062 patients (101) and observed that up-front primary tumour resection was associated with reduced rates of primary tumour-associated complications requiring emergent localized intervention and increased overall survival rate. This was compared to patients receiving up-front palliative systemic therapy alone, who were 7.3 times more likely to suffer acute complications requiring localized interventions while on palliative systemic therapy.

Current randomized control trials, such as the SYNCHRONOUS trial (ISRCTN30964555) and the iPACS study (JCOC1007) are comparing up-front palliative chemotherapy alone with up-front primary tumour resection followed by palliative chemotherapy in patients with non-curative mCRC with asymptomatic primary tumours at diagnosis (115,116).

Multiple studies have observed conflicting results when addressing the concordance rates *of KRAS, NRAS and BRAF* mutation status between the primary colorectal tumour and metastatic sites. While some results showed no significant difference in mutation status (namely KRAS) between the primary tumours and corresponding metastases, others showed discordant results in 4-32% of the patients (16). One study including 305 patients demonstrated a high concordance rate of KRAS mutation status (96.4%) between primary colorectal tumours and corresponding liver metastases (23,24). Mutation status discordance rates of ≤25% between the primary tumour and the lymph node metastases were also observed (117).

There were certain limitations to the present study. Certain patient variables (such as past medical history, ethnicity, dietary history, smoking history, and whether patients did or did not attend a colorectal screening program) were not assessed as part of the analysis, as they were considered to be outside the scope of this study, and due to relatively small patient number. This is further taking into account the small number of patients accrued in this data analysis, which limits the validity of statistical associations observed. Further research (ideally a meta-analysis) is required to assess and, ultimately, validate the associations observed in this study.

In the present study, statistically appreciable rates of discordant radiological responses to up-front palliative systemic therapy were observed between the primary tumour and metastatic tumour sites in patients with inoperable/non-curative *de novo* mCRC (in up to 60% of our patient cohort). Approximately one-third of the patients demonstrating radiological control of the primary tumour otherwise demonstrated progression at metastatic sites while on first-line up-front single-modality palliative systemic therapy at the first interval restaging imaging.

This has implications for molecular analyses of the tissues obtained from patients diagnosed with mCRC. Our analysis suggests that standard molecular panels performed in mCRC (including KRAS, NRAS and BRAF status with MMR and MSI analyses) should preferentially be performed on tissue from metastatic sites rather than on tissue from the primary tumour.

Up-front localized management strategies, such as palliative radiation to the primary tumour, surgical interventions (including stoma formation) and endoscopic procedures (such as colonic stenting) should be considered in certain patients with inoperable mCRC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RAH: Conception and design of the study, data collection and analysis, writing and drafting the manuscript. SM: Participation in manuscript writing and collection of references. HM and HI: Critical revision of the manuscript for important intellectual content. SA: Assessment of radiological responses according to RECIST criteria. RK and GK: Critical revision and editing of the manuscript. NO: Conception and design of the study, manuscript editing and critically revising the work for important intellectual content. All authors have read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Ethics approval was obtained from the local hospital Medical Research Ethics Committee prior to data collection (REC Ref:113/2020). Patient data were anonymized during data collection and analysis. Informed consent (written or oral) was not required, since this was a retrospective chart review (as outlined per Health Research Consent Declaration Committee Guidelines, Ireland). All data collection procedures followed the General Data Protection Regulation and the Data Protection Act, 2018.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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