

WJG 20th Anniversary Special Issues (5): Colorectal cancer**Prognostic and predictive response factors in colorectal cancer patients: Between hope and reality**

Chiara De Divitiis, Guglielmo Nasti, Massimo Montano, Rossella Fisichella, Rosario Vincenzo Iaffaioli, Massimiliano Berretta

Chiara De Divitiis, Guglielmo Nasti, Massimo Montano, Rosario Vincenzo Iaffaioli, Medical Oncology, Abdominal Department, National Cancer Institute G. Pascale Foundation, 80131 Napoli, Italy

Rossella Fisichella, Department of Surgery, University of Catania, Policlinico Universitario "G. Rodolico", 95123 Catania, Italy

Massimiliano Berretta, Department of Medical Oncology, National Cancer Institute of Aviano, 33081 Aviano, Italy

Massimiliano Berretta, Euro-Mediterranean Institute of Science and Technology (IEMEST), 90139 Palermo, Italy

Author contributions: De Divitiis C, Nasti G, Montano M, Fisichella R, Iaffaioli RV and Berretta M contributed equally to this work, designing and performing the research, and writing the paper.

Correspondence to: Massimiliano Berretta, MD, PhD, Department of Medical Oncology, National Cancer Institute of Aviano, Via Franco Gallini 2, 33081 Aviano, Italy. mberretta@cro.it
Telephone: +39-95-7179966 Fax: +39-95-3782912

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Abstract

Colorectal cancer (CRC) represents one of the most commonly diagnosed cancers worldwide. It is the second leading cause of cancer death in Western Countries. In the last decade the survival of patients with metastatic CRC has improved dramatically. Due to the advent of new drugs (irinotecan and oxaliplatin) and target therapies (*i.e.*, bevacizumab, cetuximab and panitumab), the median overall survival has risen from about 12 mo in the mid nineties to 30 mo recently. Many questions needing of right collocations and more clearness still exist regarding the prognostic factors and the predictive factors of response to therapy. Despite advances in dosing and scheduling of chemotherapy in both adjuvant and advanced settings, and a greater emphasis on early detection, the outlook still remains

poor for most patients. Molecular analyses have shown that the natural history of all CRCs is not the same. Individual patients with same stage tumours may have different long term prognosis and response to therapy. In addition, some prognostic variables are likely to be more important than others. Here we review the role of prognostic factors and predictive factors according to the recently published English literature.

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Key words: Colorectal cancer; Prognosis; Prognostic factors; Therapy; Metastases; Molecular analyses

Core tip: Colorectal cancer (CRC) represents one of the most commonly diagnosed cancers worldwide. It is the second leading cause of cancer death in Western Countries. In the last decade the survival of patients with metastatic CRC has improved dramatically. Due to the advent of new drugs and target therapies the median overall survival has risen from about 12 mo in the mid nineties to 30 mo recently. Many questions still exist regarding the prognostic factors and the predictive factors of response to therapy needing of right collocations and more clearness.

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INTRODUCTION

Over the past 30 years, there has been a great interest in

clinical and molecular prognostic factors in metastatic (m) colorectal cancer (CRC).

This interest is even greater today with the advent of molecularly targeted agents that have changed dramatically the treatment algorithms and the survival for patients with mCRC.

CRC is one of the most commonly diagnosed cancers in the world and remains the second leading cause of cancer death in Western countries.

Approximately 50% of patients with CRC present, at diagnosis, distant metastases. From the late 1990s the median overall survival (OS) for patients with mCRC has increased from about 12 mo, for those treated with a 5-fluorouracil (5-FU)-based chemotherapeutic regimens, to approximately 18 mo with the addition of irinotecan and oxaliplatin^[1-5].

The availability of targeted biologics, in fact, next to the results obtained with chemotherapy alone, has increased the OS of mCRC to more than 24 mo, median.

The use of monoclonal antibodies such as cetuximab, panitumumab and bevacizumab has improved the treatment options and the OS, but, on the other hand, has made the planning of treatment strategies increasingly articulated and complex. Furthermore, it is understood that the natural history of mCRC is not always the same; patients with mCRC may have various long term prognosis and respond differently to the same treatment. All this justifies the frantic search for biological, prognostic and predictive markers able to implement the knowledge on the biology of the tumour and drive the clinician in an increasingly personalized decision-making process.

Therefore the information on the biology of CRC, together with the identification of markers with prognostic and predictive value play today a crucial role in the management of advanced disease and in the treatment of early-stage forms, offering new tools to estimate the possibility of cure and, more generally, the overall outcome of patient.

It seems clear that the promise of personalized medicine in the treatment of mCRC is becoming a reality thanks to new knowledge of genetics that have allowed, at times, to change clinical practice.

CLINICAL PROGNOSTIC FACTORS

The extreme heterogeneity in survival rate^[6], that often emerges from the results of clinical trials probably stems from the differences in the characteristics of patients and from the prognostic factors.

In addition to the Eastern Cooperative Oncology Group (ECOG) performance status (PS), patients in clinical trials are also stratified according to several prognostic factors that are likely to have a significant role in influencing their survival.

Although the analysis of several studies, most of which have not included more than 400 patients, have stressed the importance of several clinical parameters

such as PS^[7], or elevated levels of lactate dehydrogenase, white blood cell (WBC)^[8], serum albumin^[6], liver transaminases^[8], haemoglobin^[9], platelets, tumour markers like CEA^[8] and CA 19-9 and the pathological grading^[9] or various localization of the primary tumour^[10], today there is no general consensus in considering each of these parameters as valid and reliable prognostic factors.

Köhne's prognostic classification is based on ECOG PS, alkaline phosphatase (ALP) level, number of metastatic sites and WBC cells count. However, the validity and applicability of this score is not universally recognized.

In fact, while Díaz *et al*^[11] demonstrated the validity of Köhne's classification in a small number of patients treated with irinotecan- or oxaliplatin-based first-line chemotherapy, Sanoff *et al*^[12], on the other hand, subsequently confirmed the validity of the score.

Also the values of ALP may have prognostic significance. In the GERCOR OPTIMOX 1 study^[13], patients with increased levels of ALP (3-5 times the upper limit value) showed a median progression-free (PFS) and OS significantly reduced compared to patients with less elevated ALP values.

Regarding the prognostic value of CEA levels, while in the adjuvant setting CEA remains the best tumour marker available to be used as an independent prognostic factor and as a monitor for recurrence of disease after primary tumour resection^[14], its role as prognostic factor in mCRC is unclear.

High levels of serum CEA on diagnosis has been associated with a worse prognosis in some studies, while others have found no significant correlation between CEA and prognosis.

In the mCRC, the role of CEA in relation to the expression of other molecules seems to be more interesting.

Baek *et al*^[15] assessed the relationship between serpin B5 and CEA expression in CRC.

They showed that the expression of serpin B5 in 377 patients with CRC is associated with CEA levels, histology, stage, lymph node metastasis, lymphatic and perineural invasion, and especially with a reduced DFS ($P = 0.001$) and OS ($P = 0.017$). These results indicate that in patients with mCRC, increased levels of serpin B5 could represent a negative prognostic marker correlated with the levels of CEA.

Selcukbiricik *et al*^[16] aimed to determine the prognostic role of initial CEA and CA 19-9 values in mCRC patients according to the status of *KRAS*. In particular, they have questioned whether the high initial CEA and CA 19-9 levels could be associated with the presence of *KRAS* mutation in patients with mCRC.

Between 2000 and 2010, a total of 215 patients with mCRC treated and followed up in Turkey, have been analyzed. Smokers have been excluded from the study. The clinic-pathological findings and initial CEA and CA 19-9 values have been determined.

KRAS mutation analysis has been performed using quantitative PCR evaluation of the DNA from the tumour tissues^[17].

KRAS mutations have been detected in 99 of the patients (46%). *KRAS* has been found to be wild type in 116 patients (54%). Significant differences have been detected between the *KRAS* wild-type and mutant groups with respect to age and the initial serum CEA levels. The median OS time and 3-year OS rate for patients with a high initial CEA level (> 5 ng/mL) have been significantly shorter than those of patients with a low initial CEA level (< 5 ng/mL) (50.5 mo and 61.8% *vs* 78.6 mo and 79.1%, $P = 0.014$). Multivariate analysis has indicated stage at the time of diagnosis ($P < 0.001$) and low initial serum CEA level ($P = 0.037$) as independent prognostic factors of OS. For *KRAS* mutant patients, the stage at diagnosis ($P = 0.017$), low initial serum CEA level ($P = 0.001$), and low initial serum CA 19-9 level have been found to be independent prognostic indicators of OS. Thus, they have demonstrated for the first time that the presence of a *KRAS* mutation correlates with high initial CEA and CA 19-9 levels in patients with mCRC.

They concluded that the patients with high initial CEA and CA 19-9 levels may potentially predict the presence of a *KRAS* mutation, and this prediction may guide targeted therapies in these patients.

CA 19-9, which is called sialyl Lewis a (sLa), is another alternative marker for CRC^[18,19].

The increase of CA 19-9 has demonstrated a significantly higher frequency of metastasis and distinctly lower survival rate, making it an adverse prognostic factor for CRC patients^[19].

It is commonly accepted that CA 19-9 is used as a marker of hematogenous metastasis and a predictor of prognosis in CRC^[20]. However, the significance of elevated CA 19-9 in CRC remains to be clarified. For example, the increase of CA 19-9 has been reported as a risk factor for extra hepatic metastasis in CRC patients with liver metastasis (LM)^[21]. For CRC patients with normal CEA, CA 19-9 has been a valuable prognostic factor and might help predict lung metastasis^[22]. Elevated CA 19-9 has also been reported to be related with the peritoneal metastasis of CRC^[23].

Furthermore, both CEA and CA19-9 have been found to be independent and significant predictors for OS in unresectable CRC LM^[24].

Dong *et al*^[25] aimed to explore the value of CA 19-9, CEA and some biochemical enzymes in indicating LM of CRC.

A total of 493 patients with metastatic cancers have been retrospectively evaluated. Three groups of eligible patients have been identified: CRC patients with LM (CRC-LM) or without LM (CRC-NLM), and non-CRC patients with LM (NCRC-LM). All metastatic lesions have been identified by CT or MRI. Data on characteristics of the patients, the primary site, the locations of metastasis, CA 19-9, CEA, and biochemical parameters have been collected for analysis.

Some biochemical enzymes have been found to be significantly higher in groups with LM than without CRC-LM or NCRC-LM *vs* CRC-NLM. Both CEA and CA

19-9 resulted much higher in CRC-LM than CRC-NLM or NCRC-LM. For CRC patients, CA 19-9, γ -glutamyl transpeptidase, CEA and alcohol consumption have been identified as independent factors associated with LM.

This analysis has suggested that CA 19-9 might be a potential valuable indicator for LM of CRC in the clinic.

Recently some authors have reported that the concomitant diagnosis of HIV-infection and CRC represents an independent and poor prognostic factor in this particular setting of patients^[26-29].

Conversely old age does not represent, after accurate evaluation (Comprehensive Geriatric Assessment) of elderly CRC patient, a poor prognostic factor^[30-35].

HISTOLOGY

Regarding the histology, the majority of CRC is represented by adenocarcinomas.

The variants "Mucinous" and "signet ring" adenocarcinoma, have a poor prognosis^[36], and constitute approximately 10%, with signet ring cell carcinoma comprising 1%-2.4%. Mucinous cancers are characterized by the presence of abundant extracellular mucin (more than 50% of the tumour mass).

Not only patients with mucinous mCRC have a poor prognosis, but they also have reduced response to chemotherapy and targeted agents^[37].

Therefore, this pathological feature can be considered as prognostic markers and used as a stratification factor for clinical trials in mCRC.

PERITONEAL INVOLVEMENT

The peritoneal involvement is an important independent pathological prognostic parameter and may supersede other parameters in current usage in CRC prognosis.

The prognosis of these patients is poor with reduced survival from 18.1 mo to 6.7 mo from^[38]. Often they present at diagnosis with PS expired, ascites and weight loss. The goal of treatment in this case is therefore palliation, reserving the systemic chemotherapy when the diagnosis is made before surgery.

In fact, surgery or chemotherapy alone do not improve the patients' survival and results in a median survival of 5-7 mo. In recent years, a new therapeutic alternative approach based on the combination of surgery with chemotherapy has been developed as a treatment for peritoneal disease.

Some studies^[39,40] indicated that the only real treatment options to improve the survival of patients with peritoneal disease at the time seem to be represented by the cytoreductive surgery and hyperthermic intraperitoneal chemotherapy^[39]. But it must be considered that these procedures are burdened with significant morbidity and mortality. It is therefore essential a careful selection of the patients that can actually tolerate and benefit from these types of treatments rather aggressive. In any case the prognosis in these patients is conditioned by the ex-

tents of carcinomatosis, by Sugarbaker's peritoneal cancer index, by the possibility of obtaining a complete cytoreduction and by the opportunity to perform a postoperative systemic chemotherapy.

MOLECULAR PROGNOSTIC AND PREDICTIVE MARKERS

In order to accurately treat the molecular markers (prognostic and predictive) it must be remembered that the development of CRC is a multistep and complex process. It occurs as a result of the accumulation of different and many genetic and epigenetic alterations that negatively affect the process of regulation, control of cell proliferation and differentiation, apoptosis, and angiogenesis.

KRAS-NRAS-BRAF

While the expression of EGFR and the presence of *EGFR* gene mutations do not appear related to therapeutic response, the determination of the status of *KRAS* gene plays a crucial role. The presence of mutations allows the protein of the *KRAS* to meet a constitutive activation and therefore to be active also when it is blocked the activity of EGFR. In CRC, *KRAS* mutations are found in 35%-45% of cases, and usually (> 90% of cases) are borne by the codons 12 and 13, more rarely codon 6^[41-43].

The role of *KRAS* mutations as a prognostic factor independent of treatment seems unlikely but it is still controversial.

Approximately 35% CRC tissues carry a mutation at codon 12 (25%) or 13 (10%) of *KRAS* that leads to the constitutive activation of EGFR downstream pathways^[44-48].

Information on the *KRAS/BRAF* genotype is also extremely useful when selecting systemic chemotherapy for advanced and recurrent patients with CRC, because it can help identify patients with poor prognoses. *KRAS* and *BRAF* are currently under focus as potential prognostic and predictive biomarkers in patients with metastatic diseases treated with anti-EGFR monoclonal antibodies (mAb), such as cetuximab and panitumumab^[49-53].

Several retrospective analyses revealed that cetuximab treatment is ineffective in patients with *KRAS* mutations, thereby suggesting that the *KRAS* genotype is a useful predictive biomarker for cetuximab or panitumumab therapy in CRC. It has also been suggested that wild-type *BRAF* is required for a successful response to panitumumab or cetuximab therapies in patients with mCRC. However, the prognostic relevance of the *KRAS* genotype in CRC remains controversial despite several multi-institutional investigations since the 1990s^[54-57].

The activation of EGFR signalling, such as Ras/Raf/MAP/MEK/ERK and/or phosphatase and tensin homologue deleted on chromosome 10/phosphoinositide-3-kinase/protein kinase B (PTEN/PI3K/Akt) pathways, constitutes a key step in tumourigenesis and the tumour progression of CRC^[58]. Two predominant

EGFR inhibitors have been developed including monoclonal antibodies that target the extracellular domain of EGFR and small molecule TKIs that target the receptor catalytic domain of EGFR. Although both classes of agents show clear anti-tumour activity, only the anti-EGFR mAb has been approved for clinical use in the treatment of patients with mCRC. Because the predictive value of alterations in *EGFR* expression level is unclear in the use of anti-EGFR mAb, the focus has shifted to alterations of key signalling pathways downstream of EGFR. In particular, *KRAS* and *BRAF* mutations have been studied as the activating mechanisms of the EGFR signalling pathway. Screening for *KRAS/BRAF* genotype is extremely important for identifying patients with shorter survival in response to systemic chemotherapy, regardless of the use of anti-EGFR mAb, and for predicting patients who would benefit from anti-EGFR mAb therapy. Therefore, the significance of *KRAS/BRAF* mutations as prognostic and/or predictive biomarkers in patients with CRC should be considered while selecting a method for *KRAS* genotyping. The *KRAS* genotype is a useful predictive biomarker for patients with metastatic CRC being treated with anti-EGFR mAb. Several studies have showed the possibility that *KRAS13* may have a specific phenotype different from other *KRAS* genotypes. Therefore, differences in *KRAS* mutations at codons 12 and 13 may result in different biological, biochemical, and functional consequences and clinical features, which may also influence the prognosis of CRC. In fact, a lot of retrospective analyses have suggested that *KRAS* mutations at codon 13, particularly *KRAS* p.G13D, as well as *BRAF* mutations are prognostic factors.

In particular, Tejpar *et al.*^[59], in pooled data from 1378 evaluable patients from the CRYSTAL and OPUS studies, have investigated the associations between tumour *KRAS* mutation status (wild-type, G13D, G12V, or other mutations) and PFS, OS, and response. Significant variations in treatment effects have been found for tumour response ($P = 0.005$) and PFS ($P = 0.046$) in patients with G13D-mutant tumours versus all other mutations (including G12V). Within *KRAS* mutation subgroups, cetuximab plus chemotherapy versus chemotherapy alone have significantly improved PFS [median, 7.4 mo *vs* 6.0 mo; hazard ratio (HR) = 0.47; $P = 0.039$] and tumour response (40.5% *vs* 22.0%; OR = 3.38; $P = 0.042$) but not OS (median, 15.4 mo *vs* 14.7 mo; HR = 0.89; $P = 0.68$) in patients with G13D-mutant tumours. Patients with G12V and other mutations did not benefit from this treatment combination. Patients with *KRAS* G13D-wild-type tumours receiving chemotherapy alone experienced worse outcomes (response, 22.0% *vs* 43.2%; OR = 0.40; $P = 0.032$) than those with other mutations. Effects were similar in the separate CRYSTAL and OPUS studies. The authors concluded that the addition of cetuximab to first-line chemotherapy confers a benefit to patients with *KRAS* G13D-mutant tumours. These findings also suggested that patients with CRC having *KRAS* mutations consti-

tute a heterogeneous population. Since the prognostic and/or predictive role of *KRAS13* mutations continues to remain controversial, further prospective clinical investigations are warranted. Also, *KRAS* wild-type status is an imperfect predictor of sensitivity to anti-EGFR monoclonal antibodies in CRC, motivating efforts to identify novel molecular aberrations driving RAS. The identification of *KRAS* mutations as markers of resistance to EGFR inhibitors has paved the way to the interrogation of numerous other markers of resistance to anti-EGFR therapy, such as *NRAS*, *BRAF*, and *PI3KCA* mutations. Other genomic and protein expression alterations have been recently identified as potential targets of treatment or as markers of chemotherapy or targeted-therapy resistance, including ERCC1 expression, c-Met expression, PTEN expression, HER2 amplification, HER3 expression, and rare *KRAS* mutations. As the number of distinct validated intra-tumour genomic assays increases, numerous molecular assays will need to be compiled into one multigene panel assay.

Mutations in *KRAS* account for about 85% of all RAS mutations in human tumours, *NRAS* for about 15%, and *HRAS* for less than 1%^[12]. Which particular RAS gene is mutated seems to be tumour specific; colonic, pancreatic and lung cancers have high frequencies of *KRAS* mutations. Nevertheless, there are only a few reports on *NRAS* mutations in CRC and none of these studies correlated RAS mutations with other molecular events. Irahara *et al*^[58] developed and validated a Pyrosequencing assay to detect *NRAS* mutations at codons 12, 13 and 61 and, utilizing a collection of 225 CRCs from two prospective cohort studies, the authors examined the relationship between *NRAS* mutations, clinical outcome, and other molecular features, including mutation of *KRAS*, *BRAF*, and *PIK3CA*, microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP). Finally, they examined whether *NRAS* mutation was associated with patient survival or prognosis. *NRAS* mutations were detected in 5 (2.2%) of the 225 CRCs and tended to occur in left-sided cancers arising in women, but did not appear to be associated with any of the molecular features that were examined^[58].

Several researches have suggested that tumours harbouring *BRAF* mutations have distinct clinic-pathological features compared with tumours harbouring *KRAS* mutations. Souglakos *et al*^[47] demonstrated that *BRAF* mutations in primary CRC mark patients with poor prognosis regardless of specific treatment regimen. Patients with *BRAF* mutation had significantly higher likelihood of disease progression ($P < 0.0001$) or death ($P < 0.0001$) with any treatment regimen. The *BRAF* V600E mutation predicted independently early relapse on first-line therapy and death. It was deduced that *BRAF* mutation does not simply substitute for *KRAS* activation in a linear signalling pathway but probably confers distinct impact on prognosis. It also suggests that *KRAS* mutation may bypass aberrant EGFR signalling. In the PETACC-3 study which included stage II and stage III cancers, *BRAF*

tumour mutation was found in 7.9% of cases and there was no significant variability with tumour stage. In a multivariate analysis, *BRAF* mutation was significantly associated with female, and highly significantly associated with right-sided tumours, older age, high grade, and MSI-high tumours. In univariate and multivariate analysis *BRAF* mutation was not prognostic for relapse free survival but was prognostic for OS, particularly in patients with MSI-L MSS tumours.

As a predictive marker, patients with *BRAF* mutant tumours treated with cetuximab had also lower PFS compared with those with *BRAF* wild type (0% *vs* 17%). In the study by Souglakos *et al*^[47] in 2009, a finding which could partly explain resistance to anti EGFR targeted therapy in a subset of patients with tumours harbouring *KRAS* wild type. This is in keeping with an earlier study by Di Nicolantonio *et al*^[60], where the response to panitumumab or cetuximab was found to be impeded by the presence of *BRAF* V600E mutation and restored (in a cellular model of CRC cells) by *BRAF* inhibitor sorafenib^[48,60]. They suggested that this experimental observation should encourage conceiving clinical trials using multiple therapies with EGFR and *BRAF*/MAPK inhibitors, considering that cetuximab, panitumumab, and sorafenib are already approved for clinical use.

Furthermore, *BRAF* mutations are significant negative prognostic biomarkers in patients with recurrent CRC across all disease stages. Besides, the prognostic value of *BRAF* mutations has been confirmed in patients with CRC treated with specific chemotherapy regimens in clinical trials evaluating a combination of cetuximab with chemotherapy. However, whether *BRAF* mutations are negative predictive biomarkers for anti-EGFR mAb has not been ascertained, because the controlled study, which directly compared the efficacy of adding anti-EGFR mAb to chemotherapy with that of chemotherapy alone, is lacking in a small population with *BRAF* mutations. The application of novel strategies targeting *BRAF* kinase is assured for the treatment of patients with CRC with *BRAF* mutations to improve their poor survival. However, clinical data suggest that the Ras/Raf/ERK pathway is insufficient for completely predicting the response to anti-EGFR mAbs. Thus, other factors, such as *PIK3CA*/*PTEN* deregulation and/or the expression status of epiregulin or amphiregulin, should also be studied on as possible predictive biomarkers for anti-EGFR mAb.

In line with these new evidence, Douillard *et al*^[61] have suggested that mutations in exons 3 and 4 *KRAS* and exons 2, 3 and 4 of *NRAS* represent factors of possible resistance to panitumumab. In particular, the population of patients with mCRC defined as “all ras wild type”, presented in the study PRIME a significant advantage in survival [(OS was 26.0 mo in the panitumumab-FOLFOX4 group *vs* 20.2 mo in the FOLFOX4-alone group (HR = 0.78; 95%CI: 0.62-0.99; $P = 0.04$)] with the use of panitumumab in combination with FOLFOX compared to chemotherapy alone. Also, the analysis of

the survival data showed a detrimental effect of this combination in the population of patients “all mutated RAS”. Finally, the PRIME study confirmed the strong negative prognostic role of *BRAF* mutations, although these have not shown a clear predictive effect related to anti EGFR therapies.

PTEN

PTEN negatively regulate the PI3K signalling pathway.

PI3KCA mutation and PTEN deletion could explain the resistance to anti EGFR therapy (for example to cetuximab or panitumumab).

Atreya *et al*^[62], analysed the frequency with which PTEN was lost, the degree of agreement by which PTEN was expressed in the primary tumour (70 human CRC) and metastatic sites (in particular LMs) and the possible prognostic significance of the expression of PTEN in the cases of CRC.

The results of this analysis showed a loss of PTEN expression in 12.3% of primary CRC and in 10.3% of liver metastases, with 98% of correlation between the expression of PTEN in primary tumour and in LMs.

In addition, the authors found a significant relationship between the lack of expression of PTEN and an increased risk of death, thus highlighting the possible role of PTEN loss as a marker of poor outcome in patients with CRC.

Currently, conflicting information exists regarding Her-2 over-expression and its clinic-pathological implications in CRC. Lim *et al*^[63], determined Her-2 over-expression in both serum and tumour tissue of ninety five CRC patients by chemiluminescent immunoassay and immunohistochemical staining. The results were confirmed using fluorescent in situ hybridization. Clinico-pathological parameters were analyzed according to Her-2 expression status. They founded that serum Her-2 levels were not significantly associated with prognostic parameters. They concluded that Her-2 expression analysis of CRC tissue, but not in serum, acts as a significant independent worse prognostic factor. Then, the assessment of Her-2 expression status may be valuable for the targeted therapeutic management of CRC.

Karagkounis *et al*^[64], studied the frequency and prognostic value of KRAS and BRAF mutations in subjects with CRC and LMs undergoing surgery for LMs. Therefore, the results that emerge from their analysis indicate that molecular markers such as KRAS may have a role in prognostic evaluation of patients undergoing surgery of LMs from CRC.

PREDICTIVE VALUE OF EARLY METABOLIC PET/CT RESPONSE

With the availability of many new drugs and molecular targeted becomes stronger and stronger the need for the medical oncologist to obtain information that can somehow predict the effectiveness of a treatment or giving

information on a possible response to the same.

Today, more than by the methods of traditional radiology, the nuclear medicine techniques such as 18 F - FDG seem meet part of these new needs of oncologist. Especially Lastoria *et al*^[65] showed as early changes in tumour metabolism measured by positron emission tomography/computed tomography (PET/CT) with 18 F-FDG could serve as prognostic indicators of a response to chemotherapy in an earlier and more accurate assessment can be obtained with the classical RECIST criteria.

In their experience, the authors analyzed 33 patients with resectable LM from CRC, within a phase 2 trials of preoperative FOLFIRI plus bevacizumab. A PET/CT evaluation was performed before and after one cycle of FOLFIRI plus bevacizumab. They concluded that, in patients with resectable LMs from CRC underwent preoperative chemotherapy, a good metabolic response obtained with PET/CT was predictive of improved long-term survival. Clearly, larger studies are needed to confirm these results.

Recently, Celik *et al*^[66], showed that in proteomics models of mCRC patients treated with bevacizumab, sTRAIL (TNF-related apoptosis-inducing ligand-) and CXCL8 could indicate tumour response and survival according to the metabolic responses obtained with FDG-PET/CT.

CONCLUSION

This report of prognostic and predictive factors of mCRC is by no means exhaustive, but wants to provide an overview of the topic to help guide the management of these patients.

In fact, at the current state of knowledge, it does not seem possible to precisely identify any bio - molecular - prognostic or predictive factor, with a clinical validity established and standardized. Despite this, the identification of several molecular factors that have prognostic significance in CRC will be essential in improving the treatment and outcome of the disease. It is possible to envisage that, rather than a single marker, identification a “molecular profile of risk,” resulting from the analysis of several molecular markers, should be developed and may have a more precisely clinical, prognostic and therapeutic value.

From the foregoing, it is clear how ongoing studies and strategies to identify prognostic and predictive markers of outcome of patients with CRC are always the most intriguing and the object of interest by many researchers.

Molecular techniques, studies and pharmacogenomics^[67-70] are helping develop a considerable number of new therapeutic strategies. This new knowledge will enrich and clarify the valuable information arising histological examination. Moreover, to better understand the interpretation of prognostic factors and predictive factors response to therapy, these results have been summarized and reported in Tables 1 and 2.

Table 1 Synopsis of major biomarkers derived from clinical studies for use with epidermal growth-factor receptor-targeted therapies in colorectal cancer, chemotherapy

Biomarkers	Prognostic	Predictive	Predictive efficacy	Methodology used	Clinical status
EGFR copy number ^[71]	Yes	Yes	Raised EGFR GCN and chromosome 7 polysomy associated with response rate (RR) of 30% <i>vs</i> 0% (PAN)	Fluorescence <i>in situ</i> hybridization	Awaiting further clinical validation
EGFR ligand expression (epiregulin and amphiregulin) ^[72,73]	Yes	Yes	Higher gene-expression profile of ligands in patients with disease control compared to non-responders to CET; OR for response 1.90 for epiregulin and 1.86 for amphiregulin	Gene-expression profiles using RNA and FFPE tumors	Awaiting further clinical validation
Activating KRAS mutations in codon 12 and 13 ^[48,74]	Yes	Predictive for lack of response	RR of 12%-17% for KRAS WT patients <i>vs</i> 0%-1% for KRAS mutations (PAN and CET)	PCR on DNA extracted from FFPE samples	FDA-approved clinical biomarker
KRAS G13D mutations ^[59,75]	Yes	Predictive for lack of response	No difference in response rates between G13D and activating KRAS mutations but, 3.6- and 2.1-mo improvement in OS and PFS ^[75] , improved RR, OR 3.38, 40.5% <i>vs</i> 22% ^[59] (CET + chemo)	PCR on DNA extracted from FFPE samples from multiple studies	Small patient numbers; awaiting results of prospective study (ICECREAM)
NRAS and BRAF mutations ^[49,76-78]	Yes	Predictive for lack of response	Lower RR for NRAS and BRAF mutations <i>vs</i> WT (7.7% and 0%-8.3% <i>vs</i> 38% and 17%-47%, respectively) (all KRAS WT patients treated with CET and PAN)	Mutation-frequency analysis using PCR and mass spectrometry (FFPE and fresh-frozen samples)	Evidence for significant negative association, but further clinical validation required
PIK3CA exon 20 mutations ^[77]	No	Predictive for lack of response	0% <i>vs</i> 36.8% RR for exon 20 mutations <i>vs</i> WT	Mutation-frequency analysis using PCR and mass spectrometry (FFPE and fresh-frozen samples)	Conflicting evidence when compared to other studies, further validation required
Serpin B5	Yes	No	No	HE	Awaiting further clinical validation
Mucinous histology	Yes	Yes	No	HE	Confirmed data

All figures shown are statistically significant ($P < 0.05$). PAN: Panitumumab; CET: Cetuximab; CRC: Colorectal cancer; Chemo: Chemotherapy; EGFR: Epidermal growth-factor receptor; GCN: Gene copy number; RR: Response rate; RNA: Ribonucleic acid; FFPE: Formalin-fixed paraffin-embedded; WT: Wild type; OS: Overall survival; PFS: Progression-free survival; PCR: Polymerase chain reaction; HE: Histology exam.

Table 2 Synopsis of major prognostic clinical factors derived from clinical studies on colorectal cancer, chemotherapy

Prognostic clinical factors	Positive	Negative	Methodology used	Predictive of response to therapy
Age:			CE	
Young	No	Yes		No
Elderly (according to CGA):				Some limitations to choose the T
Fit	Yes	No		
Unfit	No	Yes		
Frail	No	Yes		
PS-WHO:			CE	No
≤ 1	Yes	No		
≥ 2	No	Yes		
HIV+	No	Yes	LT, CE	Poor
Advanced clinical state	No	Yes	TNM, CE	No
Elevated CEA levels:			LT	No
Adjuvant	No	Yes		
Metastatic	No	Yes		
Elevated Ca19.9 levels	No	Yes	LT	No
Elevated ALP levels	No	Yes	LT	Poor
Skin rash ^[79,80]	Yes	Yes	HE	Further clinical validation required
Hypomagnesaemia ^[81,82]	Conflicting evidence	Conflicting evidence	Plasma magnesium levels	Further clinical validation required
Co-morbidities	No	Yes	ACE-27 ^[83] /CE	Some limitation to choose the T

CE: Clinical evaluation; LT: Laboratory test; HE: Histology exam; T: Treatment (including surgery, chemotherapy, radiation therapy); TNM: Tumor node metastasis.

Obviously, further studies are needed to better define the prognostic information allowing them to become important criteria to select patients who will benefit from the several drugs available.

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