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## Anti-EGFR Treatment in Patients with Colorectal Cancer

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### 1. Introduction

The survival of patients with colorectal cancer (CRC) has increased constantly for many years due to superior surgical techniques, improved postoperative care, regular follow-up and an increased use of effective systemic therapy in the adjuvant and the palliative setting [1,2]. All of these advancements are important, but the establishment of multidisciplinary teams which facilitate optimal selection of therapy for individual patients may have been the most important concept on its own.

In recent years a number of biologically active substances attacking specific signalling pathways in cancer cells (targeted therapy) have been developed and included in the treatment of patients with CRC. Three monoclonal antibodies (cetuximab, panitumumab, bevacizumab) have by now been approved for therapy in metastatic CRC (mCRC) [2,3].

Angiogenesis is necessary in tumour development and controlled in part by the vascular endothelial growth system which is inhibited by bevacizumab (Avastin®) and many other anti-angiogenic drugs.

Cetuximab (Erbix®) and panitumumab (Vectibix®) block the extracellular portion of the epidermal growth factor receptor (EGFR) and these two drugs will be discussed in detail in this chapter.

### 2. Targeted therapy - Inhibition of EGFR

EGFR is a trans-membrane glycoprotein that is involved in signaling pathways affecting cellular growth, differentiation, and proliferation and EGFR is expressed in many types of normal tissues. The EGFR is up regulated in a large number of cancers, in CRC in 60-80% of cases, and might be associated to a poor prognosis. Once a ligand binds to the extracellular domain of EGFR, receptor-dimerization occurs and down-stream signaling cascades are activated. Amongst the downstream effectors are the RAF/MEK/MAPK pathway and the PI3K/PTEN/AKT pathway.

Two anti-EGFR monoclonal antibodies are approved by US Food and Drug Administration and European Medicines Agency for the treatment of CRC – cetuximab and panitumumab. Both are directed against the ligand-binding site of EGFR and competitively inhibiting ligand-induced activation, and thereby inhibiting EGFR induced cell growth, survival, and

proliferation. In addition, cetuximab may act by inducing an antibody-dependent cell-mediated cytotoxicity reaction as cetuximab is an IgG1 antibody.

Cetuximab is a human-murine chimeric monoclonal antibody with terminal half-life around 4-5 days (range 3-7 days) whereas panitumumab is a fully humanized IgG2 monoclonal antibody with terminal half-life around 7 days (range 4-11 days).

### 3. Predicting efficacy of anti-EGFR therapy

Unfortunately only a fraction of patients will benefit from the EGFR inhibition and therefore much research is ongoing to identify predictive markers in order to tailor therapy for the individual patient.

Several studies have shown a clear correlation between the severity of skin rash and outcome of therapy of the anti-EGFR antibodies [4-7].

In addition, development of hypomagnesaemia may be a surrogate marker for outcome of therapy [8,9].

Until recently, the development of skin rash during therapy was the most promising predictive factor, but focus has now changed towards assessment of tumour tissue.

Predicting efficacy of anti-EGFR treatment is naturally focused on the EGFR and effectors in the down-stream-signaling pathways in the tumour. Even though EGFR is the target of the anti-EGFR antibodies there is no difference in efficacy in patients with EGFR positive and EGFR negative tumours as assessed by immunohistochemistry [10] and therapy is therefore not restricted to tumours overexpressing EGFR.

KRAS is a member of one of the intra-cellular signal-transduction cascades. If KRAS harbors a mutation (KRASmut), then the growth signal is constitutively activated independently of ligand binding to the extracellular part of the receptor.

KRASmut is found in approximately 40% of mCRC patients [11]. The KRAS mutation is an early event during the colorectal adenoma-carcinoma carcinogenic process [12] and thus there is a high concordance between KRAS mutations in the primary tumour and the metastasis [13]. Analyses of clinical trials with anti-EGFR antibodies in mCRC have demonstrated that the KRAS mutational status is central for the effect of anti-EGFR treatment. Patients with KRASmut do not or hardly ever respond to anti-EGFR therapy and progression-free survival (PFS) and survival is definitely shorter than in patients with KRAS wildtype tumours (KRASwt) [5,11,14-19]. However, recently it has been suggested that the different KRAS mutations might have different biological potentials, and that patients with codon 13 mutated tumours may be sensitive to therapy with cetuximab [20].

Normal expression and mutation status of other members of the down-stream signaling pathways (e.g. BRAF, PTEN and PI3K), are also needed for normal function of the EGFR pathway. In a recent study including more than 600 patients with mCRC treated with cetuximab and irinotecan in the third line setting response rates were as high as 41 % in the population of patients with wildtype KRAS, BRAF, NRAS, and PIK3CA exon 20 compared to 24% in the unselected population [11].

Furthermore many other attempts have been made in order to identify other predictive marker including of expression of ligands to the EGFR, mutations in the EGFR resulting in structural changes in the receptor, expression of other members of the EGFR-family; however currently the K-RAS gene mutational status is the only established marker of sensitivity to panitumumab and cetuximab, and the use of anti-EGFR antibodies should be restricted to patients with KRASwt tumours.

## 4. Adjuvant therapy

### 4.1 Adjuvant chemotherapy after radical resection for colon cancer

Adjuvant fluoropyrimidine-based chemotherapy for 6 months is standard of care in patients with radical resected stage III colon cancer, whereas it is more controversial in patients with stage II colon cancer. Modest but definite benefit of 4-5 % in 5-years survival has been demonstrated in pooled analyses and in the Quasar study [21-24].

Three large phase III trials have documented that addition of oxaliplatin to fluoropyrimidine (FOLFOX, FLOX, XELOX) are superior compared to single agent fluoropyrimidine in terms of disease-free survival and overall survival in stage III patients and probably also in high-risk stage II [25-27].

### 4.2 Adjuvant targeted therapy after radical resection for colon cancer

Cetuximab has been tested in the adjuvant setting. The US Intergroup N0147 study assessed the potential benefit of cetuximab added to adjuvant FOLFOX after resection in patients with colon cancer stage III. The primary end point was 3 year disease-free survival. The initial concept was to treat patients regardless of KRAS status, but when the impact of KRAS status in the metastatic setting was established NO147 was amended to include only patients with KRAS wild type tumours. In 717 patients with KRAS mutations included before amendment both 3-year disease-free survival (FOLFOX: 75.8% versus FOLFOX + cetuximab: 72.3%) and 3-year survival (88.0% versus 80.4%) favoured FOLFOX alone [28]. Surprisingly, the addition of cetuximab to FOLFOX in the KRAS wild-type population did not add any benefit as well, with a 3-year disease-free survival of 75.8% in the FOLFOX arm versus 72.3% in the FOLFOX-cetuximab arm [29].

The FOxTROT trial is presently evaluating a neo-adjuvant strategy with oxaliplatin-based chemotherapy with or without panitumumab in patients with high-risk but resectable colon cancer.

Data from ongoing or completed adjuvant trials are awaited, but currently cetuximab, panitumumab and other targeted therapies should not be used outside clinical trials.

## 5. Systemic treatment of metastatic colorectal cancer

Since the introduction of 5-fluorouracil in 1957, numerous well-conducted phase III studies have proven its efficacy and even nowadays fluoropyrimidine is the backbone of systemic therapy [30,31]. The era of modern combination therapy started when it was shown that irinotecan prolonged survival in patients with fluoropyrimidine-resistant disease. Since then irinotecan, oxaliplatin, and two oral formulations of 5-fluorouracil (capecitabine and uftoral) have been approved [32] and are used in the routine clinical practise.

Combination chemotherapy with fluoropyrimidine and irinotecan (e.g. FOLFIRI or XELIRI) or oxaliplatin (e.g. FOLFOX or XELOX) produces tumour regression in approximately half of patients with mCRC. PFS is prolonged from 6 to 9 months and the use of several sequential lines of chemotherapy has improved median survival from 6 months to more than 18 months.

When planning the treatment strategy for an individual patient in the daily clinic it is important to realize the goal of treatment – is there a possibility for cure or is the treatment of palliative character – which depends on the resectability of the metastases and on patient-related factors as performance status and co-morbidity.

Patients with mCRC may be grouped according to the resectability of their metastases: resectable at diagnosis and initially unresectable. Patients with initially unresectable mCRC can be further subdivided into two groups: potential resectable mCRC which may become resectable after tumour shrinkage and non-resectable which is defined as unresectable despite major tumour regression [33]. This classification has to be done in a close collaboration between surgeons, oncologists, radiologist and pathologist – in a multidisciplinary team. For patients with non-resectable mCRC therapy is primarily of palliative character.

In patients with potential resectable or symptomatic mCRC, tumour shrinkage is absolutely mandatory and therefore the most effective combination should be used as initial therapy. However, in patients with unresectable mCRC AND no tumour-related symptoms a sequential approach (single agent immediately followed by combination therapy upon progression) seems to be a safe strategy.

Targeted therapy enhance efficacy of chemotherapy but should be restricted to selected patients.

## 6. EGFR inhibition in patients with chemoresistent mCRC

There are no established cytotoxic drugs or combination in the third-line settings after progression to irinotecan, oxaliplatin and fluoropyrimidine, but this changed dramatically when efficacy of EGFR inhibition was proven in patients with chemo-resistant mCRC [2,3]. Data are summarized in Table 1.

The promising activity observed in phase I and II studies was first confirmed in the pivotal BOND study [34] where 329 patients with irinotecan-resistant mCRC were randomised to receive either weekly single agent cetuximab alone or cetuximab in combination with irinotecan. This combination significantly increased response rate from 11% to 23% and prolonged PFS from 1.5 months to 4.1 months. Survival was not significantly prolonged, perhaps due to cross-over and use of combination therapy as salvage therapy. As a result of the BOND study, cetuximab was approved for patients with irinotecan-resistant disease in US and Europe in 2004.

One of the criticisms of the BOND study was the lack of a control group and therefore NCIC-CO.17 was planned and completed [35]. Patients pre-treated with irinotecan and oxaliplatin were randomised to receive best supportive care (BSC – no crossover upon progression) or cetuximab monotherapy. Compared to BSC, cetuximab prolonged OS from 4.6 months to 6.1 months (Table 1).

In a parallel study, a similar benefit in terms of response and PFS was established for panitumumab [6]. In contrast to NCIC-CO.17, OS was not significantly prolonged perhaps due to the possibility of cross-over to panitumumab after progression in patients randomized to BSC. Based on these data, panitumumab was approved for monotherapy of refractory mCRC by the US Food and Drug Administration in September 2006 and conditionally approved in patients with tumours harbouring wild-type KRAS by the European Medicines Agency in December 2007. Presently there are more data on the combination of irinotecan and cetuximab as salvage therapy but it may be expected that efficacy of irinotecan and panitumumab will be comparable. Indirectly these data suggested that irinotecan with cetuximab (and perhaps irinotecan with panitumumab) increase response rate to more than 20%, prolong PFS from less than 2 months to more than 4

months and that OS is prolonged from around 5 months to 9 months, in patients treated unaided by KRAS status.

Author. year	Regimen	KRAS	No of patients	RR (%)	Median PFS (months)	Median OS (months)
Third line therapy						
Jonker et al NEJM 2007	BSC	?	285	0	1.8	4.6
	Cet	?	287	7*	1.9*	6.1*
Karapetis et al NEJM 2008	BSC	WT	113	0	1.9	4.8
	Cet	WT	117	13*	3.8*	9.5*
Van Cutsem JCO 2007	BSC	?	232	0	1.7	6.5
	Pan + BSC	?	231	10*	1.8*	6.5
Amado et al JCO 2008	BSC	WT	119	0	1.7	7.6
	Pan + BSC	WT	124	17*	2.8*	8.1
Cunningham et al NEJM 2004	Cet	?	111	11	1.5	6.9
	Cet + Iri	?	218	23*	4.1*	8.5
Di Fiore et al ASCO 2008	Weekly Cet + Iri	MUT	281	0	2.7	8.0
	Weekly Cet + Iri	WT		43*	5.5*	13.2*
Jensen et al ASCO 2010	Biweekly Cet + Iri	MUT	165	3	3.9	7.9
	Biweekly Cet + Iri	WT		23*	5.5*	12.1*
Second line therapy						
EPIC Sobrero et al JCO 2008	Iri	?	650	4	2.6	10.0
	Cet + Iri	?	648	16*	4.0*	10.7
181 Peeters et al JCO 2010	FOLFIRI	WT	294	10	3.9	12.5
	FOLFIRI + Pan	WT	303	35*	5.9*	14.5
	FOLFIRI	MUT	248	14	4.9	11.1
	FOLFIRI + Pan	MUT	238	13	5.9	11.8

Table 1. Selected studies evaluating efficacy of EGFR-inhibition (cetuximab or panitumumab) in patients with chemo-resistant mCRC.



In the second line setting, the EPIC and “181” studies (Tables 1) showed that irinotecan + cetuximab or FOLFIRI + panitumumab, respectively, significantly increased response rate. PFS was prolonged significantly in both studies but the higher response rate and longer PFS did not translate into an improvement in OS [36,37].

## 7. EGFR inhibition in patients with chemo-naïve mCRC

Excellent efficacy in patients with chemo-resistant mCRC started logically a number of phase II studies for chemotherapy-cetuximab or panitumumab combinations with response rates as high as 80%, high liver resection rates and long survival [38]. As a consequence of these promising data, phase III studies were planned and conducted (Table 2). All published randomized trials were initiated and started before the importance of KRAS was known and therefore these studies have included patients with both KRASwt and KRASmut. As described efficacy of EGFR monoclonal antibodies is restricted to patients with KRASwt however for comparison, data on patients with KRASmut are included in Table 2 but only data on KRASwt will be discussed.

Most trials combining anti-EGFR treatment with chemotherapy confirmed a much higher response rate (absolutely 10-20% difference) in the combination arm and most trials also showed that PFS was prolonged absolutely 1-2 months but this difference was not as long as anticipated or hoped. However, at this time only one phase III study could confirm that the benefit in response and PFS was translated to a significant and clinical meaningful improvement in survival [19].

In the CRYSTAL study more than 1200 patients with EGFR-expressing mCRC were randomised to FOLFIRI or FOLFIRI + cetuximab [19]. The investigators managed to collect tumour tissue and analyze KRAS status in an astonishing 89% of all patients. Response rate and resection rate was significantly higher and both median PFS (8.4 vs. 9.9 months) and median survival were significantly prolonged (20.0 vs. 23.5 months). A higher response rate and longer PFS were also observed in the OPUS [39] and PRIME [40] studies. In PRIME, median survival was non-significantly prolonged (19.7 vs. 23.9 months) at the same level as in the CRYSTAL trial. In the large COIN study only response rate was increased [41] and in the smaller NORDIC VII trial cetuximab did not improve efficacy of the Nordic bolus regimen [42].

Since addition of cetuximab or panitumumab improve response rate to combination chemotherapy, there has been a particular interest in the use of these agents in patients with potential resectable liver-only metastasis if it was anticipated that a major response could lead to potentially curative surgery. In the CELIM study, a randomized phase II trial with 111 patients with unresectable liver- metastasis, patients were randomized to FOLFOX + cetuximab or FOLFIRI + cetuximab [43]. In these selected patients the R0 resection rate was impressing 38% and 30%, respectively, which show the importance of selecting and evaluation patients at a multidisciplinary conference but also that the patients should receive the most effective systemic therapy to enhance the chance for curative surgery. In a retrospective analysis of response by KRAS status, a partial or complete response was noted in 70% of patients with KRASwt.

When cetuximab or panitumumab is chosen for patients with KRASwt, it must be concluded, that the chemotherapy combination should be carefully selected. A combination of fluoropyrimidine with oxaliplatin and cetuximab seem to have no or less additional

Author. year	Regimen	KRAS	No of patients	RR (%)	Median PFS (months)	Median OS (months)
First line therapy						
CRYSTAL van Cutsem et al NEJM 2009 & JCO 2011	FOLFIRI	WT	350	40	8.4	20.0
	FOLFIRI+Cet	WT	316	57*	9.9*	23.5*
	FOLFIRI	MUT	183	36	7.7	16.7
	FOLFIRI+Cet	MUT	214	31	7.4	16.2
PRIME Douillard et al JCO 2010	FOLFOX	WT	331	48	8.0	19.7
	FOLFOX+Pan	WT	325	55	9.6*	23.9
	FOLFOX	MUT	219	40	8.8*	19.3*
	FOLFOX+Pan	MUT	221	40	7.3	15.5
NORDIC 7 Tveit et al ASCO GI 2011	FLOX	WT	97	47	8.7	20.1
	FLOX + Cet	WT	97	46	7.9	22.0
	FLOX	MUT	58	40	7.8	20.4
	FLOX + Cet	MUT	72	49	9.2	21.1
COIN Maughan et al Lancet Oncol 2011	“Ox”	WT	367	50	8.6	17.9
	“Ox”+Cet	WT	362	59*	8.6	17.0
	“Ox”	MUT	268	41	6.9	14.8
	“Ox”+ Cet	MUT	297	40	6.5	13.6
OPUS Bokemeyer et al Ann Oncol 2011	FOLFOX	WT	97	34	7.2	18.5
	FOLFOX + Cet	WT	82	57*	8.3*	22.8
	FOLFOX	MUT	59	53*	8.6*	17.5
	FOLFOX + Cet	MUT	77	34	5.5	13.4
Second line therapy						
181 Peeters et al ECCO 2009	FOLFIRI	WT	294	10	3.9	12.5
	FOLFIRI+Pan	WT	303	35*	5.9*	14.5
	FOLFIRI	MUT	248	14	4.9	11.1
	FOLFIRI+Pan	MUT	238	13	5.9	11.8

Table 2. Recent studies evaluating EGFR-inhibition (cetuximab or panitumumab) as first line therapy according to KRAS-status.



benefit over chemotherapy alone [41,42] and presently capecitabine or bolus 5-fluorouracil in combination with oxaliplatin can not be recommended outside clinical trials (Table 2). Until otherwise proven, cetuximab or panitumumab should be combined with FOLFIRI or FOLFOX.

7.1 Combinations of targeted therapies

In vitro studies have shown that simultaneous inhibition of angiogenesis and EGFR systems have additive and perhaps even synergistic effect, but surprisingly this benefit could not be confirmed in first line randomised studies (Table 3).

In a small randomised phase II study, a triple-combination of cetuximab, irinotecan and bevacizumab was more effective than cetuximab + bevacizumab alone [44]. Even more interesting, PFS and survival for the triple-combination were considerably longer than the historical double-combination in the BOND1 trial [34]. It was therefore expected that a similar combination would increase efficacy also as first line therapy.

Author. year	Regimen	KRAS	No of patients	RR (%)	Median PFS (months)	Median OS (months)
CAIRO2 Tol et al NEJM 2009	CapOx+Bev	WT	156	50	10.6	22.4
	CapOx+Bev+Cet	WT	158	61	10.5	21.8
	CapOx+Bev	MUT	108	59*	12.5*	24.9*
	CapOx+Bev+Cet	MUT	98	46	8.3	17.2
PACCE Hecht et JCO 2009	“Ox”+Bev	WT	203	56	11.5*	24.5*
	“Ox”+Bev+Pan	WT	201	50	9.8	20.7
	“Ox”+Bev	MUT	125	44	11.0	19.3
	“Ox”+Bev+Pan	MUT	135	47	10.5	19.3
	“Ir”+Bev	WT	58	48	12.5	19.8
	“Ir”+Bev+Pan	WT	57	54	10.0	NR
	“Ir”+Bev	MUT	39	38	11.9	20.5
	“Ir”+Bev+Pan	MUT	47	30	8.3	17.8

Abbreviations in the tables:

RR = response rate, PFS = progression free survival, OS = overall survival, BSC = best supportive care, cet = cetuximab, pan = panitumumab, WT = wildtype, mut = mutant, iri = irinotecan, ox = oxaliplatin, bev = bevacizumab

Table 3. Recent studies evaluating double targeted therapy (inhibition of angiogenesis and EGFR) according to KRAS-status.

In the PACCE study more than 1000 patients were randomised to a combination of chemotherapy with bevacizumab (optional oxaliplatin-based regimen (n = 823) or irinotecan-based regimen (n = 230) with or without panitumumab [45]. The four-drug combination of oxaliplatin-based therapy with bevacizumab and panitumumab resulted in several serious adverse events and also a shorter PFS and survival, while there was no significant difference in efficacy data in the smaller group where therapy was based on irinotecan. Even in patients with KRAS wild-type there was evidence of a harmful effect of double targeted therapy.

In the CAIRO-2 study, 734 patients were randomised to XELOX + bevacizumab with or without cetuximab. Similar to PACCE study, PFS was significantly shorter in patients receiving double targeted therapy and subgroup analysis of patients with KRAS mutations showed that efficacy (response, PFS and survival) was significantly worse [46].

Double targeted therapy against angiogenesis and EGFR should not be used as first line treatment outside of controlled studies.

## 8. Weekly or biweekly cetuximab

Cetuximab is approved as weekly administration with an initial loading dose of 400 mg/m<sup>2</sup> followed by weekly administration of 250 mg/m<sup>2</sup>. However, as most cytotoxic regimens are administered in two-weeks (or longer) schedules it would be more convenient if cetuximab could be administered as a two-week schedule. Based on a study showing that there is no major differences in the pharmacokinetics and pharmacodynamics between the standard weekly cetuximab schedule and cetuximab 500 mg/m<sup>2</sup> given every second week [47,48] a simplified biweekly administration schedule of cetuximab has been developed [47-49]. The biweekly regimen has efficacy and safety profile similar to the weekly schedule [49-52] and ongoing studies will prospectively evaluate the biweekly regimen ([www.clinicaltrials.org](http://www.clinicaltrials.org) NCT00660582). In many institutions the biweekly schedule is used in the daily clinical setting based on the above-mentioned experiences.

Panitumumab is administered as an intravenous infusion at 6 mg/kg every 14 days or 9 mg/kg every 3 weeks. There is no loading dose.

## 9. Toxicity of anti-EGFR therapy

Toxicity of the anti-EGFR therapy is related to the blockade of the EGFR in the normal tissue. The most often reported side-effect is a papulo-pustular rash primarily in the seborrheic areas seen in up to 90% of patients [6]. The onset is usually within the first three weeks after start of therapy and with spontaneous improvement within the next 4-5 weeks [53]. Most cases are mild to moderate but severe in 5% to 20% of patients [6,7,34,35,54]. Prophylactic treatment with systemic tetracyclines reduces the severity of skin reactions but not the incidence of rash [55-57]. Other dermatological reactions are xerosis, fissures of palm and foot, paronychia and extensive growth of both eyelashes and eyebrows [53,54,58,59], but these side-effects are primarily seen after many months of exposure to anti-EGFR therapy.

Furthermore, cetuximab and panitumumab may induce severe hypomagnesaemia in as many as 25% of patients, but fortunately it is seldom symptomatic. Hypomagnesaemia results from inhibition of the EGFR in the kidneys - particularly in the ascending limb of the

loop of Henle. The hypomagnesaemia may be corrected by oral or IV supplements [60,61]. Anti-EGFR antibody therapy may as well cause nausea and diarrhea due to affection of the EFGR in the gastro-intestinal tract [34].

In addition, administration of chimeric antibodies also may give rise to severe allergic reactions in 1.4-4.5% [3]. The incidence of infusion reactions is reduced by the prophylactic use of antihistamines and corticosteroids as premedication [62]. No study has compared side effects of cetuximab and panitumumab, but cross-trial comparison shows that the spectrum of side effects is similar. However, as panitumumab is a human antibody anaphylactic reactions are rarely seen with panitumumab, and treatment with panitumumab does not require premedication [63]. A switch to panitumumab may be used after severe hypersensitivity reaction to cetuximab [64-66].

## 10. Conclusion

Optimal therapy of patients with CRC has increased in complexity with the introduction of targeted therapies, but unfortunately our expectations for these new drugs have not quite been settled. The largest benefits have been achieved with modern chemotherapy, which remains the backbone of treatment of patients with mCRC. However, targeted therapy has clinically significant effect, but we must learn to identify the correct regimes for the right patients. KRAS status is currently the most important predictive marker for efficacy of anti-EGFR therapy. To ensure the optimal treatment strategy, every patient with mCRC must be assessed by a multidisciplinary team.

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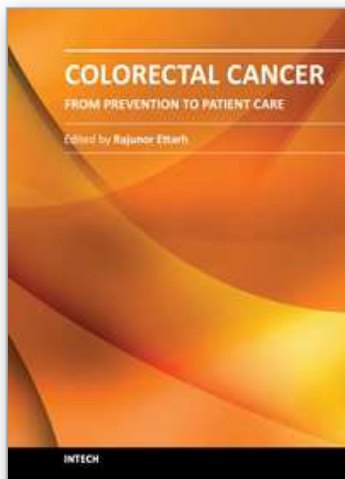
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## **Colorectal Cancer - From Prevention to Patient Care**

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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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