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Chapter 3

Treatment Strategies in Colorectal Cancer

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Abstract

Colorectal cancer is known to be one of the most commonly diagnosed cancers worldwide. It maintains a high mortality rate despite the newest methodological therapeutic approaches adopted in various academic establishments. The treatment modalities in colorectal cancer follow the degree of disease progression based on staging information. Earliest the cancer is diagnosed, the highest the possibility to be cured. Different strategies are being involved in treating colorectal cancer, starting from simple endoscopic polypectomy to remove a potential malignant polyp, to wider surgical intervention to get rid of a primary unmetastasized tumor, to other concomitant radio-chemotherapy combinations to reduce a bulky tumor rendering it operable, ending in more sophisticated chemotherapeutical regimens combined with targeted drugs to shrink the metastatic lesions and prolong survival rate. Different new treatments are being investigated with a sole aim to preserve the patient's quality of life and extend life span.

Keywords: colorectal cancer, colorectal polyps, chemotherapy, targeted therapy, immunotherapy, Lynch syndrome, familial adenomatous polyposis syndrome

1. Introduction

Colorectal cancers (CRC) are considered the third most commonly diagnosed cancers in the world. The incidence and mortality rates vary worldwide from lowest in Africa and Asia to highest in Australia, North America, and Europe. The etiology is mainly due to changes in dietary habits, from low-fiber ingestion to high-fat diet, increased body mass index (BMI), low physical activity, cigarette smoking, alcohol consumption, diabetes mellitus, ulcerative colitis, Crohn's disease, some inherited syndromes (familial adenomatous polyposis syndrome and nonpolyposis colorectal cancer or Lynch syndrome (LS), MUTYH-associated and Turcot-associated polyposis syndromes, Peutz-Jeghers syndrome, Juvenile polyposis syndrome, and Cowden syndrome), in addition to radiation therapy for another abdominal

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cancer [1–3]. Early diagnosis is necessary to get full remission, and screening has proved to be fundamental in decreasing the mortality rate. The treatment of CRC is multidisciplinary and implies a collaboration of many therapeutic teams including surgical, chemotherapy, as well as radiotherapy experts. In the following chapter, we will be studying the different treatment modalities and strategies approved and administered worldwide, according to CRC stages.

The staging classification of CRC has been conceived according to collaboration between the Union for International Cancer Control (UICC) and the seventh edition of the American Joint Committee on Cancer (AJCC-7), taking into consideration the Dukes' staging with its modifications by Astler-Coller (MAC) and Kirklin system (**Table 1**).

Stage	UICC/AJCC			Dukes	MAC
0	Tis	N0	M0	—	—
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
II A	T3	N0	M0	B	B2
B	T4a	N0	M0	B	B2
C	T4b	N0	M0	B	B3
III A	T1–T2	N1–N1c	M0	C	C1
	T1	N2a	M0	C	C1
B	T3–T4a	N1–N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1–C2
	T1–T2	N2b	M0	C	C1
C	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IV A	Any T	Any N	M1a	D	D
B	Any T	Any N	M1b	D	D

Tis, Tumor confined to the mucosa; T1, tumor invades the submucosa; T2, tumor invades the muscularis propria; T3, tumor invades subserosa or beyond, without invading other organs; T4, tumor invades nearby organs (T4a, without perforation of visceral peritoneum; T4b, with perforation of visceral peritoneum); N1, metastasis to one to three regional lymph nodes (RLNs) (N1a, metastasis to one RLN; N1b, metastasis to two to three RLNs; N1c, metastasis into areas of fat near lymph nodes but not the nodes themselves); N2, metastasis to four or more RLNs (N2a, metastasis to four to six RLNs; N2b, metastasis to seven or more RLNs); M1, distant metastases present (M1a, metastasis to distant organ, as the liver or lung, or distant set of lymph nodes; M1b, metastasis to distant organs, to distant set of lymph nodes, or to distant parts of the peritoneum as the lining of the abdominal cavity).

Table 1. Anatomic AJCC-7 staging for CRC.

2. Treatment of CRC by stage

2.1. Treatment of stage 0 CRC

In stage 0 colorectal cancer, the tumor is still confined to the inner lining of the colon (T in situ). A surgical removal of the cancer is all that is needed. A polypectomy or a colonoscopic local excision is usually sufficient. Partial colectomy is required in case of bigger tumors.

2.2. Treatment of malignant polyps

2.2.1. Definition, classification, and staging

Malignant polyps are adenomas that have been identified histologically, after endoscopic excision, to be adenocarcinomas which have invaded through the muscularis mucosa into the basic submucosa (pT1) [4]. They can occur sporadically or as part of a polyposis syndrome. They can be classified endoscopically by their size and morphology and histologically as favorable (low risk) and unfavorable (high risk). In 1985, Haggitt reconceived the Japanese society classification and the Paris endoscopic classification into a new one taking into consideration the level of invasion depth (**Table 2**).

Despite the big advantage and wide use of Haggitt's classification in assessing the quality of resection of endoscopic polypectomies, the sessile, flat, or depressed lesions yet were not successfully evaluated using this classification. In the early 1990s, Kikuchi succeeded in quantifying the grade of vertical and horizontal submucosal invasion, dividing the invasion into three levels (**Table 3**).

Morphologically, polyps are known to be either pedunculated or sessile. Pedunculated polyps are usually attached to the colonic mucosa via a stalk of variable length, while sessile polyps are devoid of stalk, are flattened in shape, and overlay the mucosa with less separation of the adenomatous epithelium part from the underlying layers of the colon [5].

Histologically, polyps can be divided into low-risk versus high-risk features (**Table 4**) [4].

Level	Location of carcinoma
0	Carcinoma in situ or confined to the mucosa. Not invasive
I	Carcinoma invading through the muscularis mucosa into the submucosa but limited to the head of the polyp
II	Carcinoma invading the level of the neck of the polyp
III	Carcinoma invading in any part of the stalk of the polyp
IV	Carcinoma invading into the submucosa of the bowel wall below the stalk of the polyp but above the muscularis propria

Table 2. Haggitt's classification according to the level of invasion.

Submucosal level	Submucosal invasion
Sm1*	Characterizes lesions that are limited to the upper third of the submucosal layer
Sm1a	Submucosal invasion under one fourth of tumoral width
Sm1b	Submucosal invasion between one fourth and a half of the tumoral width
Sm1c	Horizontal affection of the superior third of the submucosa over half of the tumoral width
Sm2	Characterizes lesions that are limited to the middle third of the submucosal layer
Sm3	Characterizes lesions that are limited to the lower third of the submucosal layer

*Sm1 lesions are further subdivided into three categories (a, b, and c) with regard to the degree of horizontal involvement of the upper submucosal layer (B), to the horizontal involvement of the total lesion (A). B/A ratios of 0.25, 0.25–0.5, and >0.5 correspond to a, b, and c, respectively.

Table 3. Kikuchi's classification according to submucosal invasion level.

Low-risk features (favorable)	High-risk features (unfavorable)
• Pedunculated (levels 1–3 according to Haggitt classification)	• Tumor budding
• Well-differentiated adenocarcinoma	• Poorly differentiated adenocarcinoma (grade 3)
• Free resection margin (2 mm)	• Positive, indeterminate, or <1 mm resection margin
• En bloc resection	• Piecemeal removal
• Neither lymphatic nor vascular invasion	• Presence of either lymphatic or vascular invasion
• Submucosal invasion Sm < 1 mm	• Submucosal invasion Sm* >1 mm

*While Sm1a + b lesions have a very low risk for metastasis, the malignant potential increases with depth of submucosal invasion [6].

Table 4. Polyp classification according to histological criteria.

2.2.2. Treatment

All of the aforementioned classifications are mandatory for accurate assessment of the degree of malignancy and aggressiveness of the resected polyp for rational clinical decision. Studies have shown polyps smaller than 5 mm in diameter, have negligible risk of malignancy, and are easily managed by standard techniques of endoscopic snare removal. Protruding polyps (Haggitt levels I, II, or III) with favorable histological features should be subjected to local excision or endoscopic polypectomy. Haggitt level IV lesions with favorable histology are considered low risk and can be favorably managed with endoscopic polypectomy provided margins are safe (>2 mm). Haggitt level IV protruding polyps and/or polyps exhibiting unfavorable features should be surgically excised due to the high incidence of lymph node metastasis. Excision can be performed either through traditional open approach or via more conservative laparoscopic techniques [7]. For sessile non-protruding polyps, a wider excision should be reconsidered requiring endoscopic mucosal resection (EMR) or endoscopic submucosal dissection

(ESD) [4]. Endoscopic mucosal resection is more specific for removal of sessile polyps limited to the mucosa and submucosa (Sm1a + b) and is typically used for complete excision of lesions up to 2 cm [8]. Endoscopic submucosal dissection is usually adopted for larger gastrointestinal lesions, where it more easily promotes the en bloc resection, yet it carries greater risk of perforation (31%) and late bleeding (15%) [9]. Lesions with a deep level of invasion (Sm1c, Sm2, or Sm3) or rectal lesions (specifically those of the distal third) showed higher incidence of lymph node metastasis 12–25% and should be treated by a definitive oncologic segmental resection due to the high risk of regional lymph node involvement.

2.2.3. Surveillance

Local recurrence is basically common in managed malignant polyps. Regular endoscopic follow-up is recommended to detect any disease recurrence; however, the duration of subsequent surveillance varies [10, 11]. In favorable histological criteria, protruding (levels I, II, or III), and noninvasive Sm1a + b polyps, it is recommended that a colonoscopy be carried out 3 months after the polypectomy [12, 13]. Further regular checkup is advised within 1, 3, and 5 years [14]. In malignant pedunculated polyps with unfavorable histological criteria, the risk of relapse or residual lesions reached 39% in treated patients. These patients are also found to have distant metastasis on follow-up, even 5 years after surgery [15]. Accordingly, in addition to the regular endoscopic surveillance, monitoring the serum level of carcinoembryonic antigen (CEA) and imaging techniques as computerized tomography or magnetic resonance imaging would enable early detection of disease recurrence. According to the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer's guidelines, shorter follow-up intervals are recommended in case of senility, positive family history, or hereditary nonpolyposis colorectal cancer (HNPCC). Furthermore, endoscopic ultrasound or flexible sigmoidoscopy at 3- to 6-month intervals for the first 2 years after polypectomy can be considered for detecting early curable recurrences.

2.3. Treatment of stage I CRC

Stage I CRC includes T1 and T2, where cancer is still limited to and has not yet invaded the layers of the colon into other nearby organs. T1 cancers are usually parts of polyps that were discussed hereinabove. For T2 cancers, the standard of care consists of partial colectomy with regional lymph node dissection. A laparoscopic-assisted colectomy can be an acceptable choice for patients who are not candidates for open colectomy.

Stage I adenocarcinoma of the rectum is relatively rare, and a surgical removal of the cancer is usually curable. For the low-risk stage I rectal cancer, both endoscopic resection and transanal excision can be used. Transanal endoscopic microsurgery (TEM) is a transanal operation suitable for small tumors and not too far from the anus. It involves wide excision of all layers of the invaded rectum with the surrounding tissue to secure negative margins. If the cancer is located in the upper part of the rectum, a low anterior resection (LAR) is recommended, where the incision takes part across the abdomen to remove the affected rectum along with some surrounding tissue and lymph nodes, and followed by anorectal anastomosis. If the cancer occupies the lower part of the rectum (alongside the anus), an abdominoperineal resection

(APR) with permanent colostomy is advised, when the distance between tumor and anus is too short to allow safe anastomosis. No additional therapy is needed after these operations, unless the surgeon finds the cancer with high-risk features. Then, an adjuvant concomitant chemoradiotherapy is appropriate with 5-fluorouracil (5-FU) or capecitabine [16].

2.3.1. Surveillance

Regular follow-up testing after the end of treatment aims at seizing any early disease recurrence. Colonoscopy should be repeated 1 year after therapy completion. In case of normal results, the next checkup should be after 3 years and then after 5 years. In case of finding any advanced adenoma (polyps with ruffled structure, larger than 1 cm, or with high-grade dysplasia), colonoscopy should be repeated within 1 year [17].

2.4. Treatment of stage II CRC

2.4.1. Assessing risk factors

The role of adjuvant chemotherapy remains undetermined in stage II CRC. Surgical intervention should aim at a wide resection of the tumor with the involved bowel segment, all together with cutting out of the lymphatic system draining that part. The resection should include at least 5 cm colon segment of either side of the resected tumor. For adequate tumor staging (II or III), and to determine and eliminate any possible lymph node metastases (pN), at least 12 lymph nodes should be excised and subjected to histological analysis. Partial colectomy may be the only needed treatment for low- and medium-risk stage II CRC patients. High-risk patients should be subjected to chemotherapy if one of the following risk factors was identified:

- High pT4 stage (T4 or tumor invading into adherent organs)
- Suboptimal lymph node resection (less than 12)
- Presence of lymphovascular or perineural invasion
- Bowel obstruction or perforation
- Poorly differentiated histology
- High carcinoembryonic antigen (CEA) marker level
- Positive margins

Various additional risk factors are being implied in assessing the additive benefit to the high-risk factors in stage II colorectal cancer using adjuvant chemotherapy.

One of the most promising risk factors is the microsatellite instability (MSI)/mismatch repair (MMR), which is regarded as a good prognostic factor. Microsatellites are short, tandemly repeated DNA sequences in the genome that are susceptible to errors of DNA replication in the presence of a defective mismatch repair (MMR) system. They are detected in about 15% of all colorectal cancers and can be used to determine stage II patients who are at very low risk of recurrence and with low benefit of adjuvant chemotherapy [18, 19]. Moreover, it has been

established in a multivariate analysis that microsatellite instability was significantly associated with survival advantage independently of any other prognostic factors (hazard ratio (HR) 0.42; 95% confidence interval 0.27–0.67; $p < 0.001$) [20].

Another potential predictive colorectal marker is the allelic deletion of chromosome 18q, or the loss of heterozygosity (LOH) of chromosome 18, which is considered as a bad prognostic factor. The 18q loci hold several genes that are highly related to apoptosis and carcinogenesis. Patients (stage II or III) presenting 18qLOH were found to have less disease-free survival and overall survival than those with retained chromosome 18 (DFS 44% versus 64%, $p = 0.002$; OS 50% versus 69%, $p = 0.005$) [21].

Another prognostic marker in CRC is the expression of guanylyl cyclase C (GCC) in resected lymph nodes. GCC is a protein that is usually expressed by intestinal cells but universally overexpressed in colorectal cancer. GCC is an intestinal tumor-suppressing receptor which regulates epithelial homeostasis. Silencing of GCC contributes to tumorigenesis by reflecting dysregulation of the cell cycle and DNA repair [22]. The presence of GCC in resected lymph nodes reflects the detection of prognostically important occult metastases [23].

The Kirsten rat sarcoma (*KRAS*) oncogene is a proto-oncogene involved in the normal tissue signaling pathways. *KRAS* mutation can occur via a single amino acid substitution or a single nucleotide substitution. The resulting protein is implicated in various malignancies, including colorectal cancer [24]. Even though the British QUASAR trial in 2007 did not succeed to show any significant difference in overall survival between fluorouracil-treated and folinic acid–treated observation groups in stage II CRC [25], the risk of disease recurrence was found significantly higher for *KRAS*-mutant than *KRAS* wild-type tumors (28% versus 21%), and the risk of recurrence appeared larger in *KRAS*-mutant rectal than colon tumors [26].

The tumor suppressor TP53, or genome guardian, is another important predictive prognostic factor in CRC. TP53 is the most commonly mutated gene in human cancers, and its prevalence in CRC comprises 34% of the proximal colon tumors where it is mostly related to lymphatic invasion and 45% of the distal colorectal tumors where it is majorly correlated with lymphovascular invasion [27]. Clinical studies have shown that CRC patients with mutant p53 are more 5-fluorouracil-based chemotherapy resistant and have poorer prognosis than those with wild-type p53 [28].

The transforming growth factor beta (TGF-β) signaling pathway plays a central but paradoxical role in the predisposition and progression of colorectal cancer. TGF-β acts as a potent tumor suppressor in normal intestinal epithelial cells by inhibiting cell proliferation and inducing apoptosis. However, mutations in the genes encoding for TGFB receptor 2 (TGFBR2), with high levels of microsatellite instability, promote colon tumorigenesis by perturbing the function of TGF-β signaling pathways and stimulating the proliferation and invasion of poorly differentiated and metastatic colon cancer cells [29, 30].

Thymidylate synthase (TS) is an enzyme implicated in the formation of thymidine, one of DNA nucleotides. It catalyzes the methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). This role in nucleotide metabolism has made TS an important target of many chemotherapeutic agents such as 5-FU and the new folate-based TS inhibitors

(raltitrexed and pemetrexed). Elevated intracellular TS levels have been implicated in emerging resistance to fluoropyrimidines and other TS inhibitors due to the increase in transcription and translation roles of TS. Therefore, high TS expression in early-stage CRC patients is correlated to a poorer overall survival in both chemotherapy-treated and chemotherapy-untreated patients following surgery [31].

2.4.2. Choice of chemotherapy

5-Fluorouracil remains the backbone chemotherapy in treating CRC. In MOSAIC study, patients with stage II or III disease were randomly assigned to receive adjuvant FOLFOX4 or 5-FU/leucovorin (LV). In stage II disease, no improvement in DFS or OS was noted in 899 patients upon adding oxaliplatin to 5-FU (DFS HR = 0.84, p = 0.258; OS HR = 1.00, p = 0.986). Moreover, in patients with high-risk stage II disease, the estimated 10-year overall survival was 75.4% in FOLFOX arm versus 71.7% in 5-FU/leucovorin arm (p = .058) [19]. Similar results were obtained with the NSABP C-07 trial, where patients were randomized to receive either bolus 5-FU/LV alone or with oxaliplatin. While the addition of oxaliplatin to 5-FU/LV improved DFS, no benefit in OS was observed at all [32]. Furthermore, the QUASAR study investigated the role of adjuvant 5-FU in disease recurrence in "average-risk" patients (patients without any high-risk feature). As a result, 5-FU decreased the risk of recurrence compared to observation alone (relative risk (RR) for colon cancer = 0.78, p = 0.004; RR for rectal cancer =0.68, p = 0.004). And, the risk of death was improved in treated patients (RR = 0.84; p = 0.046), with an absolute survival benefit of 3.6% [25]. A major predictive prognostic factor in stage II CRC is microsatellite instability. As known, microsatellites are repeated DNA sequences in the genome. They are very susceptible to errors in DNA replication and especially in case of a defective mismatch repair (MMR) system, where they really can substitute it [19]. In colon cancer, the high level of MSI is associated with mutations in the MMR system. Based on findings from over 7000 patients classified as MSI-high (MSI-H), MSI-low (MSI-L), or MSI-stable (MSS) colon cancers, those with MSI-H had a better prognosis compared to those with MSI-L or MSS tumors by 15% [33]. Another important predictive factor in stage II CRC is 18qLOH. Loss of heterozygosity of chromosome 18 is highly associated with decreased overall survival [21, 34, 35]. The ECOG 5202 trial aimed at stratifying patients according to the molecular prognostic factors, MSI and 18qLOH. The recommendations were for stage II patients with low-risk (MSI-H or with either MSS or MSI-L together with 18qLOH retention) observation without any treatment. However, for those with high-risk observation (either MSS or MSI-L with 18qLOH), chemotherapy with FOLFOX is suggested [19].

As a conclusion for stage II CRC adjuvant treatment, the following algorithm is reasonable (**Table 5**).

2.4.3. Access to radiotherapy

According to Johns Hopkins colorectal health team, radiotherapy can be used adjuvantly in case of pT4, where the lesion is fixed and adherent to the abdominal wall or bladder, as it provides a lower chance of recurrence. Similarly, in case of rectal cancer, neoadjuvant chemoradiotherapy is indicated in order to shrink the tumor size prior to surgery and to avoid colostomy if

Low risk (with MSI-H or with either MSS or MSI-L and retention of 18qLOH)	Observation
Average risk (with MSS)	Observation or fluoropyrimidine* as single agent (optional)
High risk**: • (with MSI-H and 18qLOH retention) • (with MSS or MSS-L and 18qLOH)	• Fluoropyrimidine as single agent • FOLFOX or CAPOX***

*Fluoropyrimidines are a class of antimetabolites that are converted in the body to 5-fluorouracil. These include 5-fluorouracil, capecitabine, doxifluridine, tegafur, and carmofur.

**The high-risk factors are mentioned hereinabove in the text.

***FOLFOX denotes folinic acid/5-FU/oxaliplatin; CAPOX denotes capecitabine/oxaliplatin.

Table 5. Stage II CRC adjuvant treatment algorithm.

possible. Radiotherapy is indicated when the rectal tumor has invaded the wall of the bowel or has spread into adjacent lymph nodes. 5-Fluorouracil or capecitabine are being used concomitantly with radiotherapy to sensitize tumor cells to radiation. In addition, concomitant chemoradiotherapy is indicated when the margins of resection are positive. However, no significant differences in overall survival were reported till now. EORTC 22921 was one randomized trial of 1011 patients that assessed the role of adjuvant 5-FU after preoperative chemoradiation for patients with T3 or T4 resectable tumor. Patients were divided in four arms including preoperative radiotherapy with or without chemotherapy and preoperative radiotherapy with or without chemotherapy followed by adjuvant chemotherapy. The OS for a median follow-up of 10.4 years was similar in the four groups (48.4–52.9%). There were no differences either in DFS rates or in the cumulative incidence of distant metastases [36]. A number of treatment strategies have been recently studied by various clinical trials, yet still no conclusive decisions have been taken. The major aim remains the patient's benefit from a better tumor resection with less side effects, longer survival, and minor recurrence rates.

2.4.4. Surveillance

Survivorship care is a follow-up that takes place after the end of treatment to provide a better disease control and a less recurrence morbidity. A thorough physical examination with a tumor marker CEA should be performed systematically every 3–6 months for 2 years. In case of normal results, the frequency can be reduced to 6 months for an additional 3 years. Radiological imaging including CT scans or MRIs is indicated once a year for a total of 5 years. Colonoscopy is also suggested at an interval of 1 year after treatment and then after 3 and 5 years if results are normal.

2.5. Treatment of stage III CRC

Stage III colon cancer is characterized by tumor of any size (T1–T4) with metastasis to regional lymph nodes. A partial colectomy to remove the involved part of the colon along with adjacent lymph nodes, followed by adjuvant chemotherapy (not beyond 8 weeks of surgery), is considered

the standard of care for this stage. However, in rectal cancer, tumor size (T3–T4, with invasion through intestinal muscular layer) with clinical positive lymph nodes is suggestive for neoadjuvant chemoradiotherapy and followed by adjuvant chemotherapy for a lower risk of recurrence rate. The European Society for Medical Oncology (ESMO) guidelines recommended in 2013 a stratification of the risk factors for disease recurrence of rectal cancer according to the following items identified by pretreatment MRI. These included the tumor invasion depth (T staging), the number of metastatic lymph nodes (N staging), the distance to anus, invasion of mesorectal fascia (MRF), and extramural vascular invasion (EMVI). Four risk groups were stratified (ultralow-, low-, medium-, and high-risk groups). Surgery alone was the choice for the ultralow-risk group, while neoadjuvant chemoradiotherapy with adjuvant chemotherapy was the best choice for the medium- and high-risk groups; the low-risk group showed a beneficial effect of adding chemoradiotherapy or chemotherapy [37]. These findings are compatible with the NCCN guidelines which recommended neoadjuvant chemoradiotherapy and adjuvant chemotherapy for those patients with high risk of local recurrence, including stage II (T3–T4, with tumor invading through the intestinal muscle layer) and stage III (positive lymph nodes) [17].

2.5.1. Choice of chemotherapy

After a wide surgical resection with anastomosis, the standard chemotherapy protocol is approved to be oxaliplatin and 5-FU/folinic acid (FOLFOX4 or FLOX). In the MOSAIC study, the addition of oxaliplatin to 5-FU/LV (FOLFOX) showed a significantly increased DFS at 6 years, with a reduction in the risk of recurrence of 23% compared with the control arm (5-FU/LV), with an OS absolute gain of 4.2%. Similar results were obtained in the NSABP C-07 study, either in DFS at 3 years or in terms of reduction in the risk of recurrence. As a result of these studies, FOLFOX has been adopted adjuvantly on a biweekly basis, for a period of 12 cycles. In case of contradiction to oxaliplatin, 5-FU/LV administered intravenously according to de Gramont, AIO, or Mayo Clinic regimen, or oral fluoropyrimidines (capecitabine) are comparable in benefit. Other drugs such as topoisomerase I inhibitor (irinotecan) or anti-VEGFR agent (bevacizumab) or *KRAS* wild-type drug (cetuximab) did not succeed in adding any advantage either in DFS or in OS in stage III colon cancer [38].

In neoadjuvant rectal treatment, 5-fluorouracil remains the standard chemotherapeutic agent to be administered concomitantly with radiation. In ASCO 2011, NASBP R-04 firstly randomly compared the effect of capecitabine (an oral fluoropyrimidine) and 5-FU in preoperative concurrent chemoradiotherapy of rectal cancer. The results showed neither significant difference in pathological complete response (pCR) rate nor in third and fourth degree of adverse reaction rate [39]. Recently, in Germany, a randomized clinical phase III multicenter non-inferiority study showed no statistical difference of 3 years of DFS and local recurrence rate between capecitabine and 5-FU, concluding that capecitabine can substitute 5-FU as adjuvant or neoadjuvant chemotherapy for locally advanced rectal cancer [40]. The role of oxaliplatin in radiotherapy has been thoroughly examined as in many randomized studies as STAR-01, ACCORD 12/0405, NSABP R-04, and PETACC 6. Unfortunately, neither study succeeded in showing any significant increase of the pCR rate or downstage rate comparing to single drug (5-FU or

capecitabine). In addition, ACCORD 12/0405 reported same OS (88%) in both combined two drugs (capecitabine with oxaliplatin) and single drug (capecitabine) [39, 41]. As a conclusion, single-agent fluoropyrimidine (5-FU or capecitabine) used concomitantly with pelvic radiotherapy remains the standard of care in stage III CRC.

2.5.2. Surveillance

Regular follow-up is highly advised in stage III CRC due to the high rate of recurrence. Detecting early relapse can be performed through a meticulous regular physical checkup with tumor marker CEA every 3 months for the first 2 years. A thoraco-abdomino-pelvic CT scan is required every 6 months for the first 2 years. A colonoscopy is advised in a 6-month period for the first year after treatment. The period of physical examination with CEA can be elongated for a 6-month period for the following 3 years in case of normal results. The CT scan period can be lengthened to 1 year for the following 5 years, and the colonoscopic evaluation can be further extended to once every 3 years in case of normal previous results.

2.6. Treatment of stage IV CRC

Almost 20–30% of the newly diagnosed CRC patients present with distant metastatic disease at the time of initial presentation. And, up to 50% of the early-stage CRC patients will eventually relapse with metastatic disease. Metastasis can occur in different organs and most commonly to the liver (50–60% of the cases). The lungs are less frequent (10–20%) and are more common in rectal than in colon cancer. Other less often places are the peritoneum, ovaries, adrenal glands, bones, and brain. In case of locally recurrent disease or with resectable metastases, the standard of care remains curative surgical intervention. Chemoradiotherapy or chemotherapy alone can also be considered an acceptable approach in case of rendering a tumor resectable. For non-resectable tumors and/or disseminated metastatic disease, systemic chemotherapy stays the main therapeutic approach. Fluoropyrimidines (5-FU and capecitabine) are the mainstay in all protocols used in metastatic colorectal cancer (mCRC). For nearly 40 years (mid-1950 to 1996), 5-FU was the only agent approved for mCRC treatment. Later on, different cytotoxic agents appeared, as the topoisomerase I inhibitor (irinotecan) and the third-generation platinum analog (oxaliplatin), which both led to considerable advances in mCRC treatment along with fluoropyrimidines. Targeted monoclonal antibodies, such as VEGF inhibitor (bevacizumab) and EGFR inhibitor wild-type *KRAS* (cetuximab and panitumumab), opened a new era in the management of mCRC. Many other promising targeted therapies include the anti-VEGF recombinant fusion protein (ziv-aflibercept), the dual targeting VEGFR2-TIE2 tyrosine kinase inhibitor (regorafenib), the human monoclonal antibody (IgG1) anti-VEGFR2 (ramucirumab), the anti-immune checkpoint programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) (nivolumab and pembrolizumab), and the combination of trifluridine, a nucleoside analog, with tipiracil, an inhibitor of the enzyme thymidine phosphorylase (trifluridine/tipiracil) which have been approved for combination treatment of mCRC, in addition to many other new drugs under investigations.

2.6.1. Choice of chemotherapy

Various randomized clinical trials have been designed to determine the efficacy of oxaliplatin versus irinotecan together with 5-FU/LV or capecitabine. The most well-known trial was the GERCOR C97-3 study conducted by Tournigand and coworkers [42] in France which investigated 5-FU/LV (46-hour infusion) and oxaliplatin (FOLFOX6) compared with 5-FU/LV and irinotecan (FOLFIRI) in mCRC. A similar efficacy was observed in both arms with respect to overall response rate (ORR, 56% versus 54%, respectively), median time to tumor progression (8.5 versus 8.1 months), and median OS (20.6 versus 21.5 months). Similar results were obtained by CALGB Cooperative Group (CALGB 80203) and the Hellenic Cooperative Oncology Group in Greece. Based on these results, both FOLFOX and FOLFIRI have been approved for first-line treatment in mCRC. A meta-analysis of six clinical studies was conducted by Guo et al. [43] to investigate the clinical efficacy of the oral capecitabine (Xeloda) plus irinotecan (XELIRI) versus FOLFIRI regimen in the first-line treatment of mCRC. The results showed no significant differences in terms of ORR, PFS, or OS between the two arms. Another important randomized study to compare XELOX non-inferiority with respect to FOLFOX6 in the first-line treatment of mCRC was conducted by Ducreux and coworkers [44]. No differences were observed between both arms in terms of the clinical efficacy endpoints of ORR (42% versus 46%, respectively), PFS (8.8 versus 9.3 months, respectively), and OS (19.9 versus 20.5 months, respectively). Based on these and many other studies, it has been established that both protocols FOLFOX and FOLFIRI can be safely substituted by oral XELOX and XELIRI in terms of clinical efficacy (PFS and OS).

It is has been proven that doublet chemotherapy has superior clinical efficacy over single-agent fluoropyrimidine chemotherapy. However, a new question emerged: is triplet chemotherapy with 5-FU, oxaliplatin, and irinotecan can provide improved clinical efficacy over doublet chemotherapy? To answer this question, the Gruppo Oncologico Nord Ovest (GONO) of Italy conducted the first randomized phase III study to compare 5-FU/LV, oxaliplatin, and irinotecan (FOLFOXIRI) with FOLFIRI in the front-line setting [45]. After a median follow-up of 5 years, the final analysis confirmed the superiority of the FOLFOXIRI regimen over FOLFIRI, in terms of improved ORR, PFS, and median OS [46]. However, there was significantly higher grade 2/grade 3 neurotoxicity (19% versus 0%) and grade 3/grade 4 neutropenia (50% versus 28%) compared with FOLFIRI, the matter that limits the use of this regimen to relatively more fit patient population (ECOG performance status 0–1).

2.6.2. Chemotherapy in association with targeted therapy

In order to understand the role of targeted therapy in treating mCRC, we should first perceive their mode of action on a molecular level. Bevacizumab (Avastin®) is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A), which stimulates angiogenesis in a variety of diseases, including cancer [47]. In 2004, bevacizumab has been approved in the United States for use in combination with standard chemotherapy for metastatic colon cancer. The CALGB/SWOG 80405 phase III randomized study compared the potential benefit of cetuximab and bevacizumab added to conventional chemotherapy (FOLFOX or FOLFIRI) [48]. In contrast to the FIRE study that showed identical ORR and PFS, but a 3.7-month improvement in OS toward the cetuximab arm, CALGB/SWOG 80405

study showed no significant difference at all either in PFS (10.4 versus 10.8 months) or in OS (29.9 versus 29.0 months) in patients treated with cetuximab compared with bevacizumab. Recently, Venook and coworkers investigated the potential effect of primary tumor location on the clinical efficacy of patients treated on CALGB/SWOG 80405 study. It was strange to report that there was a significant improvement in OS ($p < .0001$) for patients with left-sided tumors compared with right-sided tumors (33.3 versus 19.4 months). For the bevacizumab arms, the OS was maintained high in both groups (left-sided tumors versus right-sided tumors) and significantly higher for left-sided primary tumors (31.4 versus 24.2 months). However, in the cetuximab arms, the OS in left-sided tumors was 19.3 months (which was 36.0 months) and only 16.7 months for right-sided tumors. These findings highlighted the importance of sidedness as an important predictive marker and in determining response to anti-EGFR antibody in mCRC [49].

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are both monoclonal antibodies that inhibit the epidermal growth factor receptor (EGFR). Both drugs were approved by the FDA to treat mCRC that exhibit *KRAS* wild-type genes in 2009. However, due to high rate of cetuximab resistance (45%), further studies identified the role of *NRAS* and *BRAF V600E* in treatment response [50]. The *KRAS*, *NRAS*, and *BRAF* are oncogenes that encode proteins involved in the mitogen-activated protein kinase (MAPK) signaling pathway, which regulates cell proliferation and survival. Mutations in these genes are found in about 45%, 4%, and 8% of mCRC, respectively [51], and this is responsible for activating excess proteins, whose activation does not require EGFR upstream signaling, leading to negative feedback loops that limit EGFR activation, the fact that limits the role of anti-EGFR drugs. Therefore, only the wild type of *KRAS* and *NRAS* is indicated for the treatment of EGFR inhibitors. Mutation in *BRAF V600E* was also considered as bad indicator in response to EGFR inhibitors and a strong negative prognostic marker in mCRC. Data from the randomized phase III Medical Research Council COIN trial in mCRC showed an OS of 8.8 versus 14.4 versus 20.1 months, respectively, for patients with *BRAF*-mutant, *KRAS* exon 2-mutant, and *KRAS* exon 2 wild type [52]. Moreover, the presence of *BRAF* mutation in mCRC has been associated with big primary tumors (T4), poor histologic differentiation, and peritoneal carcinomatosis [53–55].

Due to the poor prognosis factor of the BRAF V600E-mutated gene, many trials tried to establish a standard treatment for BRAF-mutated mCRC. Vemurafenib is a BRAF enzyme inhibitor, which interrupts the B-Raf/MEK step on the B-Raf/MEK/ERK pathway, in case where BRAF possesses V600E mutation. In 2017, it has been approved by the FDA for the treatment of late-stage melanoma with BRAF V600E-mutated gene. In 2010, a phase I trial for solid tumors including colorectal cancer was launched to study the effect of vemurafenib (PLX4032) on mCRC patients with mutant BRAF. Unfortunately, the results were not as promising as they were in malignant melanoma, with median PFS of 3.7 months [56]. Loupakis and coworkers studied in a retrospective exploratory analysis of a phase II trial the effect of FOLFOXIRI regimen with bevacizumab on BRAF-mutated mCRC patients. Data found PFS and OS of 11.8 and 24.1 months, respectively [57]. Two limitations were reported in the study: the first was that only patients older than 70 were included, or those who fit (ECOG PS 0) 71–75 old patients, and the second was the rarity of BRAF-mutant patients (8% of the population). In TRIBE phase III study, FOLFOXIRI regimen was studied either with bevacizumab or alone as first-line treatment mCRC, and the median OS was 31 versus 25.8 months in favor of the combination.

However, in the mutant BRAF subgroup, the median OS was 13.4 months [58, 59]. According to ASCO recommendations in 2017, FOLFOXIRI with or without bevacizumab should be considered in patients with a BRAF mutation and good performance status.

The programmed death-ligand 1 (PD-L1) with its receptor programmed cell death protein 1 (PD-1) is T-cell surface checkpoint protein that plays a major role in suppressing the immune system, promoting self-tolerance by downregulating T-cell inflammatory activity, and leading to carcinogenesis [60]. In the recently updated 2017 NCCN guideline, two novel anti-PD-1 antibodies, nivolumab (Opdivo®) and pembrolizumab (Keytruda®), have been indicated as treatment options for patients with unresectable MSI-H- or MMR-deficient CRC, although not yet FDA approved for mCRC [17]. This was based on the interim results of two ongoing studies: KEYNOTE-016, a phase II study of pembrolizumab as monotherapy in MSI-H-/MMR-deficient tumors, and CheckMate 142, a study of nivolumab versus nivolumab combination with ipilimumab, another monoclonal antibody, in recurrent or mCRC. This decision has been taken into account due to the impressive durable response in both studies [61, 62].

Ziv-aflibercept (Zaltrap®), a novel anti-VEGF, is a recombinant fusion protein that consists of vascular endothelial growth factor (VEGF)-binding portions from the extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of the human immunoglobulin (IgG) 1 [63]. In 2012, it has been approved by the FDA for use in combination with FOLFIRI for the treatment of patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen treatment. A randomized double-blind placebo-controlled global multicenter phase III VELOUR trial randomized two groups: one to receive FOLFIRI with ziv-aflibercept and the other FOLFIRI with placebo. A statistically significant improvement in OS was observed in patients in the FOLFIRI plus ziv-aflibercept group compared with the FOLFIRI plus placebo group [HR 0.82 (95% CI, 0.71–0.94), p = 0.0032, stratified log-rank test]. The median OS was 13.5 versus 12.06 months, and the median PFS was 6.9 versus 4.7 months, respectively, in the ziv-aflibercept group compared with the placebo group [64].

Regorafenib (Stivarga®), a new oral anti-angiogenic drug, is an oral multi-kinase inhibitor which targets angiogenic, stromal, and oncogenic receptor tyrosine kinase (RTK). It inhibits many membrane-bound and intracellular kinases that are involved in normal cellular functions and pathologic processes, mainly the VEGFR2-TIE2 tyrosine kinase receptors. In 2012, it has been approved by FDA for the treatment of mCRC patients which have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and with the anti-VEGF therapy bevacizumab and, if KRAS wild type, with an anti-EGFR therapy. The approval was based on the results of an international randomized (2:1), double-blind, placebo-controlled CORRECT trial. The patients were randomized to get either oral regorafenib or placebo. A statistically significant prolongation in overall survival was observed in regorafenib arm [hazard ratio (HR) 0.77 (95% CI 0.64–0.94), p = 0.0102]. The median survival time was 6.4 versus 5 months in favor of the regorafenib group (phase III, 2011; FDA, 2012) [65].

Ramucirumab (Cyramza®) is a fully human monoclonal antibody (IgG1), which works by blocking the binding of VEGF to its receptor VEGFR2, hence preventing the downstream effect of VEGF in angiogenesis. Recently, it has been approved by FDA for use in combination with

FOLFIRI for the treatment of patients with mCRC whose disease has progressed on a first-line regimen containing bevacizumab, oxaliplatin, and fluoropyrimidine [66]. A randomized double-blind multinational trial divided patients into FOLFIRI plus ramucirumab-receiving group and FOLFIRI plus placebo. A statistically significant improvement in OS was observed in patients who received FOLFIRI plus ramucirumab compared with those who received FOLFIRI plus placebo [median overall survival 13.3 versus 11.7 months; HR 0.85 (95% CI 0.73–0.98), p = 0.023, stratified log-rank test]. The DFS was also in favor of ramucirumab arm (5.7 versus 4.5 months) [67].

Trifluridine/tipiracil (TFD/TPI) (Lonsurf®) is a new combination drug approved in 2015 for the treatment of mCRC. It is a combination of two active components: trifluridine, a nucleoside analog, and tipiracil, a thymidine phosphorylase inhibitor, which prevents trifluridine rapid metabolism, hence increasing its bioavailability. In 2015, it has been approved by the FDA for use in patients with mCRC who have been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) biological therapy and an anti-epidermal growth factor receptor (EGFR) therapy, if RAS wild type [68]. Based on a pivotal phase III study (RECOURSE) to assess the efficacy and safety of TFD/TPI compared with that of placebo in a large international population, the outcomes were in favor of TFD/TPI arm, in terms of median OS (7.1 versus 5.3 months) and median PFS (2.0 versus 1.7 months) [69].

2.6.3. Disease recurrence

In case of recurrence, surgical option for liver or lung metastases should be considered in the first place followed by adjuvant chemotherapy, albeit others prefer to administer neoadjuvant chemotherapy for 2–3 months before any metastasectomy. In non-resectable tumors and disseminated metastasis, chemotherapy remains the mainstay in treating disease recurrence. It should be based on non-previously used protocols, i.e., if FOLFOX was used in previous treatment modalities, FOLFIRI should be the right option, and if both FOLFOX and FOLFIRI have been used, the choice shifts toward XELOX or XELIRI. Another alternative is to use infusional 5-FU or oral capecitabine as monotherapies. Other possibilities are the use of newly approved drugs as ziv-aflibercept with FOLOIRI, ramucirumab plus FOLFIRI, oral regorafenib, trifluridine/tipiracil, and nivolumab or pembrolizumab in case of MSI-H or dMMR. According to the last NCCN guideline in 2017, adjuvant Stereotactic Body Radiation Therapy (SBRT) should be considered in some localized lung or liver lesions. Moreover, the hepatic arterial infusion (HAI) pump therapy can be used as a substitute to systemic chemotherapy in unresectable CRC liver metastases, where it demonstrated significant tumor response rates [70]. Chemoembolization or embolization via radioactive beads is another way to treat liver metastases through the hepatic artery in chemorefractory colorectal tumors [71]. In case of peritoneal carcinomatosis, a novel strategy has emerged combining cytoreductive peritonectomy with hyperthermic intraperitoneal chemoperfusion (HIPEC), with a median survival of 3 years [72]. Many other options are being studied to be used as palliative treatment in advanced metastatic disease, such as external-beam radiotherapy, photodynamic therapy, cryotherapy, and radiofrequency ablation, in addition to oncothermia and many others under trials to palliate and manage the disease burden (**Table 6**).

Locally recurrent disease, with resectable metastases	Colectomy + metastasectomy	
Locally recurrent disease (T4)	Chemoradiotherapy or chemotherapy alone followed by colectomy	
Non-resectable tumors and/or disseminated metastatic disease	Chemotherapy	FOLFOX or FOLFIRI (substitutable by XELOX or XELIRI)
		FOLFOXIRI (ECOG good performance status and BRAF V600E mutation)
	Targeted therapy*	Bevacizumab (for right-sided tumors)
		bevacizumab or cetuximab, or panitumumab (for left-sided tumors and wild-type *KRAS* and *NRAS* genes)
		Bevacizumab (for left-sided tumors and mutant-type KRAS and NRAS genes)
Disease recurrence		Nivolumab or pembrolizumab as monotherapy (for MSI-H or dMMR)
		FOLFIRI + ziv-aflibercept
		FOLFIRI + ramucirumab
		Regorafenib as monotherapy
		Trifluridine/tipiracil as monotherapy
		Clinical trials

*Targeted therapy should be added to chemotherapy, unless otherwise mentioned.

Table 6. Metastatic CRC treatment algorithm.

2.7. Miscellaneous

2.7.1. Lynch syndrome and familial adenomatous polyposis syndrome

Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant disorder that increases the risk of many types of cancer, including endometrial, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, skin, and particularly colon cancer [73]. It is considered the most common hereditary colorectal diseases and accounts for 1–3% of all CRC. It is associated with inherited mutation in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2. This defect in MMR genes leads to tumor DNA microsatellite instability (MSI) and promotes carcinogenesis [74]. For this reason MSI profiling with immunohistochemistry testing for DNA mismatch repair has been considered essential in diagnosing Lynch syndrome (LS). The revised Bethesda guidelines have endorsed the testing for MSI, for families at high risk, in any of the following situations in CRC diagnosed in patients <50 years of age, the presence of Lynch-associated tumors, and MSI-H identified in patients <60 years old, identifying Lynch-related tumors in one or more first-degree relative and in patients <50 years of age and identifying Lynch-related tumors in two or more second-degree relatives regardless

of age [75, 76]. The mainstay in the treatment of Lynch syndrome is colectomy. However, due to the risk of developing synchronous or metachronous secondary tumors, subtotal colectomy with ileorectal anastomosis should be considered in young patients [76]. Recently, three kinds of chemotherapy have been investigated for the treatment of LS: 5-FU with leucovorin, oxaliplatin, and irinotecan. Most studies showed no benefit of chemotherapy in such patients, just one small study on stage IV CRC reported one complete response and three partial responses with MSI-H tumors compared to MSI-L/MSS tumors [77]. The use of acetylsalicylic acid (aspirin) as chemoprevention by patients with LS is highly supported to reduce the risk of CRC [78]. The Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) trial was conducted to study aspirin chemoprevention that has colorectal cancer as the primary endpoint. The initial findings did not show any significant difference in colorectal adenoma or cancer formation up to 4 years. In 2010, after a longer follow-up (56 months), the results showed a significant decrease in the incidence of CRC and LS-related cancers between the aspirin (600 mg) and placebo groups. Prescription of aspirin for people at high risk was recommended, but the optimum dose and duration of treatment remain to be established, hopefully in CAPP3 [79]. The colonoscopic surveillance in Lynch syndrome is recommended from the age of 20–25 years and repeated at 1–2 years of interval.

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder caused by a germline mutation in the adenomatous polyposis coli (APC) gene, on chromosome 5q21, and characterized by the presence of numerous adenomatous polyps in the colon and rectum. It is responsible for about 1% of all CRC cases, and, often, extracolonic manifestations can take place as in Gardner syndrome (sebaceous cysts, epidermoid cysts, fibromas, desmoid tumors, osteomas, dental anomalies and congenital hypertrophy of the retinal pigment epithelium (CHRPE)), Turcot syndrome (brain tumors), gastric and duodenum polyps, soft tissue tumors, and thyroid cancers. FAP can be subdivided into classical FAP, attenuated FAP (AFAP), and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) [80]. Clinical diagnosis can be based on the number of polyposis, where more than 100 adenomas can be counted in case of FAP, from 10 to 99 in case of AFAP, and gastric polyps restricted to the body and fundus of the stomach (gastric fundic gland polyposis) in case of GAPPS [81]. Identification of a heterozygous germline pathogenic variant in APC should be confirmed by a molecular genetic testing for a definitive diagnosis. Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is recommended in case of diffuse spreading out of the polyps with severe familial phenotype presence. Total colectomy with ileorectal anastomosis (IRA) is advised in case of scarce adenomas with a mild familial phenotype presence. In AFAP, endoscopic polypectomy can be considered in case of reduced polyposis number. In GAPPS, gastrectomy is recommended since gastric carcinoma is detected in 13% of GAPPS. Regular yearly endoscopic surveillance should be taken into account to detect any disease recurrence. In families with classic FAP, endoscopic evaluation should begin at age of 12–14 years and be continued lifelong in mutation carriers. Regular physical examination and screening via CT scans or MRI for extracolonic manifestations should also start early in life or as soon as colorectal polyposis is diagnosed [82].

MUTYH-associated polyposis (MAP) is another inheritable form of FAP that is caused by autosomal recessive mutations of the MUTYH gene [83]. It accounts for about 10–20% of all polyposis patients [2]. Clinically, in MAP patients, between 20 and 99 adenomas should be present upon endoscopy [84]; however, a molecular genetic testing is necessary to differentiate between APC

and MUTYH mutations [85]. In case of reduce polyposis number, endoscopic polypectomy can be sufficient. In case of polyp dissemination all around the colic frame, IPAA is the treatment of choice, and if the rectum is intact, IRA can be used to conserve it [85, 86]. Regular annual checkup by endoscopy should be maintained in all families presenting MAP disorder [87].

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