Colorectal cancer is the second leading cause of cancer death. Approximately 26,000 new cases are diagnosed yearly in France, resulting in more than 10,000 deaths, and 5-year survival remains low, at 40%.

This poor prognosis is partly due to the fact that, in 30% of cases, colorectal cancer is metastatic or at a locally advanced stage when discovered. Moreover, visceral metastases complicate the development of the cancer after resection of the primary tumour in 40% to 50% of cases. The liver is the most frequently involved, followed by the abdominal lymph nodes, the peritoneum, the lungs, and far more rarely, the bones, adrenal glands or brain. Metastasis, whether synchronous or metachronous, most frequently occurs in the liver (around 40% of cases), thus exacerbating mortality [1, 2].

The prognosis is poor for patients with visceral metastasis, and depends on such factors as the patient’s general condition and the number and sites of metastatic disease. Nevertheless, several studies have shown that the prognosis for metastatic disease can be improved if treatment is aimed at ‘curing’ patients. Surgical resection of metastases, which is the first treatment option, is feasible, either immediately or after chemotherapy in only 10% of cases. The other cases are often candidates for systemic or locoregional chemotherapy treatment.

The metastatic potential of colorectal carcinoma seems to correlate with the expression of certain oncoproteins involved in regulating apoptosis and the cell cycle. The presence of the p53 protein in the primary tumour is an indicator of liver and lymph node metastases. Also, overexpression of c-erb B2 in the primary tumour may be an indicator of potential metastasis, particularly in the liver [3].

Once the recently acquired knowledge in the molecular biology of colorectal cancer has been formally recognised as a factor for prognosis/prediction of natural history and/or tumoural response, this will lead to great changes in medical practice.

During the last few decades, steady progress has been made in cancer treatment in terms of curability, survival duration and quality of life. This progress has varied according to the type of cancer. Major advances were made in the 1970s in the treatment of breast, testicular and childhood cancer; the end of the century will probably see advances in colorectal cancer treatment also.

Improved diagnostic techniques, such as MRI (magnetic resonance imaging), PET (positron emission tomography), and CEA (Carcino-Embryonic Antigen) scanning, and the introduction of new chemotherapeutic agents, are no less important than improved knowledge about the disease. As a result of such innovations, a new multidisciplinary approach to colorectal cancer treatment has emerged, with new goals that replace those associated with standard treatment.

Local disease (adjuvant setting)

Who will be able to benefit from adjuvant treatment after complete resection of the primary tumour?

Prognosis will mainly depend on the stage of the disease [4]. For most patients with early stage disease (A and B1 according to the Astler-Coller modification of Duke’s staging [5, 6]) surgery alone is curative. However, once the tumour has invaded the muscularis propria (stage B2-B3), 5-year survival decreases to 70%. For stages C1, C2 and C3, 5-year survival is between 25% and 60%. The decreased survival correlates with an increase in the number of invaded proximal lymph nodes [4, 7]. Other anatomical factors that are predictive of relapse include perforation, obstruction and adhesions to and/or invasion of adjacent organs [8].

Some studies have reported the predictive value of elevated CEA serum levels in preoperative patients with negative lymph nodes [9-14]. Other factors that have been proposed as predictive of relapse include cell cycle (ploidy), DNA synthesising activity (S phase), and cell proliferation [15-18].

Thymidylate synthase (TS), a key target enzyme of 5-FU, has treatment-related prognostic value. In a recent study, Johnston et al. [19] reported a 5-year survival rate of 60% for patients with metastatic disease and low TS levels, compared to 40% for patients with high TS levels.

P53 acts as a tumour suppressor gene, located in 17 p13. Under normal conditions, it encodes for a 'wild-type' p53 protein which has a very short half-life and is undetectable by immunohistochemistry. Where there is gene mutation, p53 protein is non-functional, has a much longer half-life and becomes detectable by immunohistochemistry. The identification of mutated p53 protein is an independent factor that is
predictive of poor prognosis in some types of colon carcinoma [21-23].

Lenz et al. [24] reported a > 90% risk of relapse in patients with stage II (B2-B3) colon cancer who had both mutated p53 protein and elevated TS levels.

Choosing the adjuvant treatment

**Systemic treatment:**

5-FU alone:

In the meta-analysis carried out by Buyse in 1988, out of 17 randomised trials comprising 6791 colorectal cancer patients, only treatments with 5-FU-based chemotherapy showed a slight improvement in survival, of around 3% to 5% [23]. This meta-analysis did not consider either administration schedules or 5-FU doses.

Biochemical modulation of 5-FU:

The modulation of 5-FU by folinic acid (FA) has proven its efficacy in the palliative treatment of metastatic colorectal carcinoma, leading to several controlled trials in the adjuvant setting. A complete analysis of 1526 patients (1493 eligible), of whom 841 (56%) had stage B disease at diagnosis, showed a 3-year disease-free survival of 71%, which compares favourably with 5-FU alone, compared with 62% in the untreated control group (p = < 0.0001), with a relative reduction in risk of relapse of 35 ± 9% and a 3-year survival of 83% versus 78% (p = 0.03) [26].

A trial by the NSABP (C04) comparing 5-FU/Levamisole, 5-FU/FA (high dose) and 5-FU/Levamisole/FA (high dose) in 2151 patients with stage B and C colon cancers demonstrated no significant difference in disease-free survival (p = 0.12) or in overall survival (p = 0.14) among the three arms [27].

5-FU in continuous infusion (CI):

5-FU in continuous infusion may be a feasible alternative to biochemical modulation. Phase III trials have demonstrated improved response rates for CI 5-FU compared to bolus 5-FU in advanced colorectal cancer [28].

**Novel agents:**

Recently acquired knowledge about the molecular biology of colorectal carcinoma, including the role of p53 protein in the cell cycle and apoptosis [29, 30], the role of deficient mismatch repair [31, 32], and the role of thymidylate synthase activity in 5-FU resistance [33], has encouraged the development of treatment strategies using new agents with novel mechanisms of action.

These new anticancer agents include oxaliplatin, a cisplatin analogue of the DACH (diaminocyclohexane) family of platinums, the new thymidylate synthase inhibitors (ralitrexed, Tegafur (UFT), and capecitabine); irinotecan; and immunotherapeutic agents, in particular the monoclonal antibody anti-17-1A. The activity demonstrated by these new chemotherapeutic agents in advanced colorectal carcinoma, pretreated or not by 5-FU, has opened new avenues for their application in the adjuvant setting, with or without 5-FU.

As concerns postoperative immunotherapy by the antibody anti-17-1A (Panorex), Riethmuller et al. reported in a randomised trial of 166 patients that overall and disease-free survival were significantly better in the group treated by the antibody, with a reduction in mortality risk of 30% (p = 0.04) and a risk of relapse of 27% (p = 0.027) [34].

Advanced or metastatic disease

The term ‘advanced’ colorectal cancer denotes very different clinical and prognostic situations which require an adaptive, multidisciplinary approach to their treatment according to the specific clinical settings.

Despite progress made in treatment modalities, the prognosis for advanced colorectal cancer remains ominous. Better results could be obtained by targeting patients likely to benefit from a particular treatment modality, by using screening techniques such MRI, PET and CEA scanning, and by improving the identification of prognostic factors, particularly via molecular biology.

**Advanced disease may be divided into two categories:**

1. Potentially ‘curable’ disease
2. Very advanced disease (purely palliative situation)

**1. Potentially ‘curable’ disease**

Improvements in the treatment of advanced disease, due to the biochemical modulation of 5-FU and the introduction of
new combination agents should produce a higher rate of quicker and better responses. In addition, the multidisciplinary approach combining surgical resection of liver metastases with chemotherapy could provide hope of a cure to some patients with metastatic disease. One of the main goals of future studies should be to distinguish those patients with advanced disease who are potential subjects for curative treatment from those who are not immediate candidates for curative surgery.

Surgery provides the only hope of a cure in advanced colorectal cancer. Liver metastasis resection can increase 5-year survival by 30% [41-43]. Similarly, lung metastases resection can be curative and increase survival [44].

Many patients present with liver metastases that are considered inoperable because of their size, site and/or number, or have extrahepatic metastatic invasion.

One recent technique, cryosurgery, reduces liver metastases that are often considered inoperable, thus increasing the number of patients with potentially 'curable' metastatic disease [45]. A recent randomised trial involving 123 patients demonstrated a better 5-year survival rate in patients treated by liver cryosurgery (44%) than in patients treated by standard metastatic surgery (36%) [46].

For patients with inoperable metastatic disease, the treatment option is often chemotherapy that is referred to as 'palliative.' The goals of this chemotherapeutic option should be two-fold: adequate tumour control and acceptable safety. Tumour control is assessed by response rate and disease-free survival. An optimal response rate increases tumour operability and facilitates curative surgery.

The experience of randomised trials in metastatic colorectal carcinoma has given cause to doubt the value of bolus 5-FU/FA as standard treatment. All the schedules including 5-FU as continuous infusion have shown superior tumour control, and, for the most part, less toxicity [47].

Although 5-FU remains the reference chemotherapy treatment for colorectal cancer, its efficacy is limited by resistance that is either spontaneous (in over 50% of cases) or secondary (in almost all cases). This resistance is partly related to an overexpression or a modification in thymidylate synthase activity.

Several new anticancer agents with novel mechanisms of action (oxaliplatin, irinotecan, raltitrexed and other thymidylate synthase inhibitors) have opened avenues that were, until now, unimaginable – it is now possible to propose second-line treatment to patients progressing under 5-FU, and to envisage chemotherapy treatment combining several cytotoxic agents [48-50].

One interesting approach is the sequential treatment of advanced colorectal carcinoma by intrahepatic chemotherapy combined with systemic chemotherapy. In one published trial, the Mayo Clinic team reported 62% of objective responses with a median survival of 18 months but there was no impact on median time to progression in 40 patients with inoperable liver metastases, treated by hepatic intra-arterial fluorodeoxyuridine (FUDR) combined with systemic chemotherapy by bolus 5-FU/FA [52]. Should this approach be optimised by using new agents in systemic treatment? Should the approach be extended to the postoperative setting? (After resection of liver metastases?)

One advantage of these new strategies for advanced colorectal cancer patients is that they result in improved response rates which enable more patients to receive curative surgery [51, 53]. Even in first line treatment, the improved knowledge of molecular targets permits the identification of patients who might benefit from the new strategies.

2. Very advanced disease (palliative setting)

The treatment consists of optimising treatment choices in first line as well as in second line after failure with standard treatment. 5-FU has been the reference treatment since the 1950s. However, response rates rarely reach 15% with single agent 5-FU [54, 55] and a consensus has not yet been reached regarding dose, schedule and mode of administration.

The 5-FU/FA combination has been shown to be more active in terms of objective response rates [56, 57], but is barely superior in terms of survival [57, 58].

Although continuous infusion 5-FU has demonstrated a statistically significant survival advantage of about one month over short infusion [47], this finding has no major clinical relevance. As a result, clinical research efforts have focussed on the development of other anticancer agents, to be used as single agents or in combination with 5-FU or its analogues. The introduction of new agents has led to a redefinition of the whole approach to the treatment of metastatic colorectal cancer allowing the optimisation of combinations, schedules and sequences of administration.

Raltitrexed, irinotecan and oxaliplatin have been intensively developed in the last few years.

Thymidylate synthase inhibitors

- Raltitrexed (Tomudex) has been tested in phase II trials at the recommended dose of 3 mg/m² in the United States, Europe and Australia [58], in 177 patients with non pretreated advanced colorectal carcinoma. The response rate was 26% with a median survival of 9.6 months. In a randomised phase III European trial of raltitrexed versus weekly 5-Fu/FA bolus 5D q4w (Mayo clinic), there was no statistically significant difference in objective response and median survival [60].
- Other thymidylate synthase inhibitors are currently being developed: LY 231514, BW 18431189, Thymitaq.

New 5-FU analogues

- Orally administered tegafur (UFT) showed a response rate of 25%, with a median survival of 7.5 months in 56 patients evaluable in first and second line in a multicentric phase II trial in Japan [60]. Another similar trial in the United Kingdom showed a response rate of 16.6%, with a median survival of 7.8 months in 36 patients [62]. Three American trials testing the combination of UFT with folinic acid per os showed response rates of 25%, 30% and 42.2% [63-65].
Capecitabine (Xeloda), a promising oral analogue already registered in the United States for breast cancer treatment, has been tested in phase II randomised trials in a two weeks out of three schedule, with or without folic acid. The latter regimen, having obtained objective responses of 28%, was used in later phase III trials [66]. It will soon be available for colorectal cancer patients.

Other 5-FU analogues, such as S1, BOF A2, and 776C85 (dihydropyrimidine dehydrogenase inhibitor) are currently undergoing clinical development.

Platinum analogues: Oxaliplatin

The efficacy of single agent oxaliplatin has been proven in first line treatment, with a 27% of objective response rate in 38 treated patients [67].

The recent combination of oxaliplatin with 5-FU/FA has shown objective response rates exceeding 40%, even after treatment failure with 5-FU [68, 69].

Extensive research with the chronomodulated combination of oxaliplatin/5-FU-FA has been carried out by Lévi et al., treating more than 500 patients with a 5 day q3w, or 4 day q2w schedule. This combination obtained response rates of about 50%, including second line, with median survival exceeding one year and reaching 17 months in first line [69–71].

De Gramont also administered oxaliplatin in combination with his biweekly FU/FA schedule and obtained objective responses of 45% and a median survival of 17 months in 46 pretreated patients [68].

Topoisomerase I inhibitors: Irinotecan (CPT-11)

Like oxaliplatin, the most interesting property of CPT-11 is its lack of cross-resistance with 5-FU. Phase II studies have reported response rates of 18.8% to 29% in non pretreated patients, and 17% in those progressing under 5-FU [72, 73]. Other agents belonging to the metalloprotein family are currently undergoing preclinical and clinical development.

Conclusion

Treatment regimens which combine new agents with novel mechanisms of action will probably result in an improved prognosis for colorectal cancer. Several possibilities are feasible in the 'palliative' setting: tritherapy consisting of three active agents, (oxaliplatin/irinotecan/5-FU; capecitabine/oxaliplatin/irinotecan), alternated chemotherapy allowing several agents to be administered, and, possibly, sequential treatments combining systemic and locoregional chemotherapy treatment. Some details still require clarification, such as optimal dose, route of administration and administration schedule.

The potential role of these new agents needs to be assessed in adjuvant and palliative settings. Recently acquired knowledge in the molecular biology of colorectal carcinoma may enable patients who could benefit from these new agents in adjuvant and palliative settings to be identified [74, 75].

These new treatment approaches are based on two phenomena: the development of a multidisciplinary strategy in which chemotherapy is combined with tumour resection, either before or after chemotherapy, and the appearance of adjuvant treatments.

Colorectal cancer should no longer be considered a homogenous, infrequently curable disease, and it is difficult, and possibly unnecessary, to propose any kind of inflexible 'decision-making tree,' to guide oncologists in their choice of treatment. It is important, however, to be very familiar with the treatment options based on recently acquired knowledge in the biological, diagnostic and therapeutic fields, which can be adapted to every clinical situation and which should be prospectively validated (see Figures 1 and 2).

Under the guidance or 'dictation' of the pharmaceutical industry, progress in the clinical development of new agents in France, particularly for advanced colorectal carcinoma, has led to the registration and marketing of major anticancer agents such as oxaliplatin and irinotecan. This progress is likely to be applied to the postoperative phase. Two randomised trials are currently ongoing in France using standard 5-FU/FA versus 5-FU/FA combined with the new agents (5-FU/FA + irinotecan and 5-FU/FA + oxaliplatin) in localised colorectal cancer with a high risk of relapse. The new thymidylate synthase inhibitors are among the agents that could feasibly be used in the adjuvant setting.

![Figure 1. Treatment algorithm for localised colorectal cancers.](image-url)
Several trials are presently ongoing in metastatic disease, assessing combinations of new agents with or without 5-FU ± FA in first line after failure with fluoropyrimidines. The goal of these trials is to optimise the treatment of advanced colorectal carcinoma, by using new combinations (bidual tritherapy), and new administration schedules (alternating, chronomodulation).

Future trials should incorporate not only new anticancer agents, but also new treatment modalities, such as sequential chemotherapy (systemic or locoregional), where the operability of metastases is a criterion of evaluation, and, also, prognostic factors, including molecular biological parameters.

The means at our disposal could enable us to radically influence the natural history of colorectal cancer within the next few years. It is our responsibility to ensure that these cells reach their full potential.

Acknowledgements

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Table 1. Ongoing trials in France—end anticancer agents for colorectal carcinoma

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<tr>
<th>Indication</th>
<th>Phase</th>
<th>Treatments</th>
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<tbody>
<tr>
<td>Local disease (adjuvant)</td>
<td>III</td>
<td>CPT-11</td>
</tr>
<tr>
<td>Advance disease</td>
<td>II</td>
<td>CPT-11</td>
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<td>Non pretreated</td>
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<tr>
<td>Pretreated</td>
<td>II</td>
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<td>III</td>
<td>5-FU/F</td>
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Abbreviations: CPT-11, irinotecan; 5-FU, L-OHP, oxaliplatin.
* The list is not exhaustive.
References


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