CHAPTER 14
Neoadjuvant treatment in colon cancer

Surgical treatment is essential for a good prognosis of the disease, since local recurrence is low if surgery is effective. This should be oncologically adequate, which implies en bloc resection, central vascular ligation, extensive lymphadenectomy and complete excision of the mesocolon. Oncological results are directly related to surgical results. The main form of recurrence is systemic.

The 5-year DFS ranges from 35 to 88% with adjuvant therapy and from 14% to 79.6% with surgery alone. The absolute benefit of adjuvant chemotherapy ranges from 8.7 to 22%.[1]

Indications for neoadjuvant therapy

According to NCCN, neoadjuvant therapy is indicated for bulky T4b and N+ tumors, which define at-risk patients.[2] The latest ESMO guidelines do not clarify the indication.[3]

Published trials include patients with bulky or extensive T3-T4 tumors, with or without N, right colon tumors, and patients too frail for initial surgery.

Fundamentals of adjuvant therapy

These concepts are extensively developed in the chapter on adjuvant treatment, but in summary:

- The 2009 MOSAIC study demonstrated a 5-year DFS of 73.3% and a 6-year OS of 72.9% with FOLFOX.[4]
- The NSABP R04 study reported a 5-year DFS of 66-67% and a 5-year OS of 80-81%. Overall recurrence was 11.2-12.1% and in R0 resections 3.1-5.1%.[5]
- Survival is related to distant micrometastases for which chemotherapy is the only treatment. Since survival is related to systemic relapse, it is worth asking why not starting neoadjuvant therapy earlier.

In patients with locally advanced colon tumors, neoadjuvant chemotherapy or radiotherapy may produce tumor regression and facilitate resection with negative margins. Evidence IIB.[6]

Neoadjuvant chemotherapy may facilitate complete resection of locally advanced colon cancer.[7–9] Current NCCN guidelines consider the use of neoadjuvant oxaliplatin (OXA) in patients with T4b colon tumors.[2] A comparative analysis of the oncologic outcome of surgery with or without neoadjuvant therapy is shown in Table 14.1.

In a 2020 systematic review of six studies, neoadjuvant chemotherapy resulted in tumor volume reduction in two-thirds of patients and major pathologic regression in 4 to 37% ($p = 0.005$). It also resulted in improved 3-year DFS in patients who responded to treatment compared with non-responders (94 vs. 63%) and a 23% lower 3-year mortality rate in patients with cT4b tumors, but no benefit in those with cT3 and cT4a tumors.[9]

The potential advantages of neoadjuvant therapy are:

- Effective and well-established strategy in other tumors of the digestive tract and other organs.
- Opportunity for early systemic treatment.
- Improving surgery through downstaging and downsizing.
- Lower risk of incomplete resection or higher rate of R0 resection.
- Lower risk of tumor cell spread.
- Early treatment of micrometastatic disease.
- Improve tolerance and compliance with less treatment loss.
- In vivo sensitivity test of pathological response, assessing regression as a factor for better prognosis.
- Rehabilitation: preparation period for surgery to improve the risk of morbidity and mortality with treatment.
- Potential and theoretical non-surgical management of colon cancer.

Obviously, there is controversy about this approach due to what could be considered disadvantages:

- Local and distant progression (15-20% of patients progress in the first 3 months of systemic treatment).
- Overtreatment (low-stage, non-responder patients).
- Toxicity that potentially affects surgery.
- Potentially higher rate of postoperative complications.
- Lower rate of complete surgery due to potential disease progression.

Key findings from the major published studies are detailed below.

The FOxTROT trial,[10] a prospective randomized study of 1053 patients from the UK, Denmark, and Sweden, compared patients with non-metastatic T3-T4 tumors, not at risk of obstruction, treated with 6 weeks of FOLFOX followed by surgery to those treated with surgery plus adjuvant therapy. The primary endpoint was the absence of recurrent or persistent disease after 2 years. Secondary endpoints included safety, histologic stage, completeness of resection, and OS.

Neoadjuvant therapy was feasible in 90% of patients, with a higher proportion of patients receiving adjuvant therapy than in the control group. Data related to surgery, especially morbidity and mortality, were similar to those of the control group. Patients receiving neoadjuvant chemotherapy had a significant reduction in T and N tumor stage, a 3.8% complete pathologic response, and a tendency to present less recurrence and persistence of the disease at 2 years (14 vs. 17.5%).

The 2-year recurrence decreased by 28%, there was a higher rate of R0 resection (94 vs. 81%), less incomplete surgery due to the presence of R2 or residual metastasis (5.1 vs. 10.3%) and less findings of T4 (21 vs. 31%), N0-1-2 (59, 25 and 15% vs. 48.8, 25 and 25.9%) and apical N + (3.8 vs. 7.5%), all with significant difference.

Patients with tumor regression or better histopathological response had fewer recurrences, with an obviously better prognosis. Patients with dMMR did not respond to chemotherapy and had a worse prognosis. MMR status would seem to predict resistance to chemotherapy, since the response in patients with dMMR, as measured by tumor regression, is lower than in the MMR proficient group (7 vs. 23%; $p < 0.001$). This also supports MSI testing before starting neoadjuvant therapy in colon cancer.

According to the FOxTROT trial, neoadjuvant therapy is safe, well tolerated, does not increase perioperative morbidity, and has a trend toward a lower rate of serious complications. Evidence of histopathologic regression was observed in 59%, including complete pathologic response. There was a clear reduction in histologic staging and a reduction in incomplete resections (94 vs. 89%). Less residual or recurrent disease was demonstrated at 2 years (16.9 vs. 21.5%). Tumor regression was strongly associated with lower recurrence. Panitumumab did not demonstrate benefit in neoadjuvant therapy. In addition, there was little benefit in dMMR tumors. They conclude that neoadjuvant therapy improves oncologic and surgical outcomes and should be considered as a treatment for colon cancer.[1,11]

Table 14.1. Comparison of oncological outcome of surgery with and without neoadjuvant therapy.

Oncological outcome	Neoadj + Sx + Adj	Sx + Adj	P value
R0 resection (%)	90.6	85.9	0.001
3-year DFS (%)	81.2	76.3	0.001
3-year OS (%)	83.8	79.4	0.001

Neoadj: Neoadjuvant therapy. Sx: Surgery. Adj: Adjuvant therapy. DFS:Disease-free survival. OS: Overall survival.

The PRODIGE 22 trial, a French multicenter randomized study of 104 patients with T3-T4, N0-2 tumors treated with perioperative FOLFOX versus surgery plus adjuvant therapy, showed that patients in the neoadjuvant group were more likely to have tumor regression (44 vs. 8%) and significant downstaging of pTNM.[12,13] However, there was no difference in 3-year OS (90.3 vs. 90.4%) or DFS (76.8 vs. 69.2%). A limitation of this study was clinical upstaging in one-third of patients, indicating possible overtreatment in the experimental group.[12]

Along with FOxTROT, both studies randomized a control group with surgery and adjuvant chemotherapy vs. the experimental group with neoadjuvant therapy followed by surgery and adjuvant chemotherapy. While neither found an OS advantage, a 2018 retrospective analysis of the National Cancer Database found a 3-year OS advantage (74 vs. 66%; $p < 0.001$) in cT4b patients treated with neoadjuvant therapy compared with adjuvant chemotherapy. In this subgroup, OS was 23% higher.[14]

In the OPTICAL study conducted in China, patients with T3-T4, N1-2 tumors were randomized to receive FOLFOX or CAPOX followed by surgery and adjuvant chemotherapy for 3 months versus surgery and optional chemotherapy. Results, presented but not published, showed that 26% of patients in the control group had low-risk stage II, indicating overtreatment. As in FOxTROT, 94% of patients received 6 weeks of neoadjuvant therapy, but only 69% completed it. There were no differences in rates of laparoscopic surgery, R0 resection, and postoperative morbidity.[15] In the study group, there was a significant improvement in 3-year OS (94.9 vs 88.5%). At 20 months, the survival curve separated and was maintained at 5 years. However, the 2% (78.7 vs 76.6%) improvement in 3-year DFS was not significant, except in women (84.2 vs 74.7%). The neoadjuvant group had a 7% complete pathologic response. There was a 10% reduction in pT4 and a 5% reduction in pN2. Patients with dMMR were more resistant to chemotherapy with 51% poor or no response.[15]

The Scandinavian NeoCol study included 250 nonmetastatic patients with T3-T4, N0-2 tumors randomly assigned to 4 cycles of FOLFOX or 3 cycles of CAPOX followed by surgery with adjuvant chemotherapy for 3 months vs upfront surgery with adjuvant chemotherapy. There was no difference in 5-year DFS (85%) or OS (90%). Complete response was 3%. There was little reduction in pT4 with 3 cycles, but node-negative disease was more common with neoadjuvant therapy (59 vs 48%), as was lymphovascular invasion (25 vs. 39%). R0 resection was higher in the study group (93 vs. 90%), which also had more laparoscopy and less anastomotic dehiscence.[16]

In summary, three randomized controlled trials demonstrated the safety of preoperative chemotherapy, with excellent 6-week compliance. It is not applicable to dMMR tumors due to lack of response. Efficacy varies between trials. FOxTROT demonstrated improvement in recurrent or residual disease, OPTICAL demonstrated benefit in OS, while NeoCol found no difference at 5 years in OS or DFS. Unlike NeoCol, FOxTROT and OPTICAL demonstrated downstaging (Table 14.2).

Table 14.2. Analysis of tumor regression and survival achieved with neoadjuvant therapy.

Trial	T	N	TR (%)	3-year DFS (%)
FOXTROX	+	+	93 vs. 88	80.7 vs. 75.8
PRODIGE 22	+	+	94 vs. 98	76.8 vs. 69.2
OPTICAL	+	+	97 vs. 95	78.7 vs. 76.6
NeoCol	+	+	93 vs. 90	p = NS

TR: Tumor regression. DFS: Disease-free survival. NS: Not significant.

An analysis of the period 2003–2023, with 2729 patients in 8 studies (4 randomized controlled trials and 4 retrospective studies) of neoadjuvant surgery in colon cancer, demonstrated a complete pathological response of 4.6% and proved that surgery can be performed with good oncologic principles, obtaining better R0, DFS, and OS rates. It was concluded that it is a practical approach supported by evidence in the literature.[17] Table 14.3 summarizes the results of neoadjuvant treatment studies in colon cancer.

Table 14.3. Results of published trials on neoadjuvant therapy in colon cancer.

Trial	N	Age	rT4	rN+ (%)	Neoadj (%)	Safe Sx	Endpoint
FOXTROX	1052	65	25.5	75.3	90	+	R2 2-year recurrence
PRODIGE 22	104	63	11.5	76.9	96	+	TRG
OPTICAL	738	56	75.4	77.2	93.5	+	3-year DFS
NeoCol	250	66	26%			+	3-year DFS

Radiotherapy

Neoadjuvant radiotherapy is not widely used. A single-center study and a National Cancer Database study concluded that neoadjuvant radiotherapy may be associated with greater tumor downstaging, higher R0 resection rate, and improved OS.[18,19]

Neoadjuvant immunotherapy according to MMR status

Immunotherapy in pMMR tumors

The mismatch repair (MMR) system is responsible for repairing small sequence errors (1 to 4 base pairs) produced during DNA replication. The state of this system can be proficient (pMMR) or deficient (dMMR) and this has therapeutic implications.

The NICHE 1 study suggests a potential role for neoadjuvant immunotherapy in non-metastatic patients with locally advanced or potentially resectable tumors. Thirty-one pMMR patients treated with neoadjuvant ipilimumab plus nivolumab were studied versus a control group treated with 2 doses of celecoxib (cyclooxygenase and PGE2 inhibitor). Mild toxicity was observed in 13%. The results were impressive in 9 patients, with 4 complete responses, 3 major responses with less than 10% viable tumor, and 2 partial responses with less than 50% remaining tumor. The remaining 22 patients did not respond to treatment with more than 50% viability. There were only 2 patients with recurrence, classified as non-responders. Considering that metastatic pMMR patients have a poor response to checkpoint inhibitors, the efficacy achieved by immunotherapy in NICHE 1 has unprecedented results and suggests that the immunological context in the early stages of the primary tumor is more sensitive to immunotherapy than in the metastatic context. The presence of CD8 and PD1 expressing T cells improved the response, resulting in a predictive biomarker of response to immunotherapy to be validated.[20]

The NEST1 trial (NCT05571293) evaluated neoadjuvant immunotherapy with botensilimab (anti-CTLA4 enhanced agent) plus balstilimab (anti-PD1) in stage I-III in proficient tumors. A dramatic pathologic response was reported in 2 patients.[21] A similar situation occurred in the NICOLE study with the use of antiPD1, where 2 of the 18 patients had a major pathologic response and 1 of them a complete response.[22]

Neoadjuvant therapy is ideal for evaluating the efficacy of therapies targeting early-stage disease with mutated BRAF V600E or amplified HER2.

Immunotherapy in dMMR tumors

Metastatic dMMR tumors are rare (5%) and are more commonly seen in patients with earlier stages (15-18% in stage II and 11% in stage III). They have a more favorable prognosis but are less sensitive to chemotherapy, so adjuvant chemotherapy is not recommended for stage II dMMR tumors. Both FOxTROT and OPTICAL demonstrated a lack of response or resistance to neoadjuvant chemotherapy in these cases.[11,15]

In the NICHE1 study, the dMMR group (47% T4 and 78% N+) had excellent clinical and pathological response. After a 32-month follow-up, recurrence-free survival was 100%.[20] The NICHE2 study included 113 patients with non-metastatic resectable dMMR tumors, treated with the same neoadjuvant regimen. Most patients were high risk (63% T4, 62% N2, and 48% T4N2). Major pathological response was observed in 95% with 67% complete pathological response. One-hundred percent had R0, with no impact on oncological surgical outcome. With a 13-month follow-up, recurrence-free survival was 100%. Immunotherapy was extremely well tolerated with no related mortality.[23]

The PICC trial conducted in China, studied a group with neoadjuvant therapy with immune checkpoint inhibitors compared to a control group with celecoxib. Thirty-four patients were included, 17 with toripalimab (anti-PD1) for 3 months and 17 with celecoxib. All had R0 and complete response was 88 vs. 65%, respectively. After a 15-month follow-up, OS and DFS were 100%.[24]

The NICHE3 study, recently presented at the European Congress of Oncology, evaluated the treatment of resectable patients with dMMR tumors with 2 doses of nivolumab with relatlimab (anti-LAG3 antibody). Tolerance was excellent and the outcome was impressive, with a major pathological response of 89% and a complete pathological response of 79%. It included unstable T4N2 patients who did not require emergency surgery, who received 2 applications of nivolumab (antiPD1) and ipilimumab (antiCTLA4). All were resected and were R0. Toxicity was minor, with only 4% serious adverse events. Complete pathological response was 100% in dMMR and 27% in pMMR.[25]

Between the NICHE1 and NICHE2 studies, a 67% tumor disappearance and 95% regression were observed, with no recurrence.

The evidence for neoadjuvant immunotherapy in non-metastatic colon tumors is compelling. Only the NICOLE study did not find a complete pathological response. Therefore, according to the NICHE study, it is recommended that patients with cT4b,
antiPD1 could be used if the approach is nonsurgical. Monotherapy is less toxic, but the combination would seem to be more effective.

Final comments

Despite the existing evidence, neoadjuvant therapy should not be considered as standard therapy for colon tumors. However:
- Six-week chemotherapy treatment has been shown to be safe with a reduction in the recurrence rate at 2 years.
- It may be considered, particularly for locally advanced tumors (T4 or N2), with a higher risk of surgery or incomplete resection.
- In the case of MSI, do not consider the application of chemotherapy without associated immunotherapy.

Neoadjuvant therapy in locally unresectable tumors

Neoadjuvant therapy is recommended in some situations of advanced tumors. The described regimens are FOLFOX and CAPOX. When a locally advanced tumor is initially unresectable, it is suggested to evaluate its conversion to resectable by using preoperative chemotherapy and radiotherapy (conversion neoadjuvant therapy). A 23% decrease in the risk of death at 3 years was reported in patients with T4b who received neoadjuvant therapy.[9,24]

A prospective randomized study of patients with T3-T4, N0-N2 treated with preoperative FOLFOX found a 59% histopathologic regression and a 3.5% complete pathological response. In addition, a lower rate of incomplete resection, a higher rate of R0 resection, and a lower 2-year recurrence were observed, although there was no significant difference in 2-year DFS.[11]

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