Cancer Treatment Reviews 96 (2021) 102177

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Hot Topic

Total neoadjuvant therapy for rectal cancer: Making sense of the results from the RAPIDO and PRODIGE 23 trials

E.F. Giunta [a], G. Bregni [b], A. Pretta [b], A. Deleporte [b], G. Liberale [c], A.M. Bali [d], L. Moretti [e], T. Troiani [a], F. Ciardiello [a], A. Hendlisz [b], F. Sclafani [b,*]

[a] Medical Oncology Unit, Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[b] Department of Medical Oncology, Institut Jules Bordet – Université Libre de Bruxelles (ULB), Brussels, Belgium
[c] Department of Surgery, Institut Jules Bordet – Université Libre de Bruxelles (ULB), Brussels, Belgium
[d] Department of Radiology, Institut Jules Bordet – Université Libre de Bruxelles (ULB), Brussels, Belgium
[e] Department of Radiotherapy, Institut Jules Bordet – Université Libre de Bruxelles (ULB), Brussels, Belgium

ARTICLE INFO

Keywords:
Rectal cancer
Total neoadjuvant therapy
RAPIDO
PRODIGE 23
Induction chemotherapy
Consolidation chemotherapy

ABSTRACT

A few months ago, results from two randomised phase III trials of total neoadjuvant therapy (TNT) in locally advanced rectal cancer were presented (RAPIDO and PRODIGE 23), consistently showing better short- and long-term outcomes with TNT as compared with standard neoadjuvant long-course chemoradiotherapy (CRT) or short-course radiotherapy (SCRT). These results represent corroborating evidence in support of a practice that many centres had already implemented based on promising preliminary data. Also, they provide new, high-level evidence to endorse TNT as a new management option in the treatment algorithm of stage II-III rectal cancer in those centres where CRT and SCRT have long remained the only accepted standard neoadjuvant treatments. Having two consistently positive trials is certainly reassuring regarding the potential of TNT as a general treatment approach. Nevertheless, substantial differences between these trials pose important challenges in relation to the generalisability and applicability of their results, and translation of the same into practical clinical recommendations. In this article, we address a number of key questions that the RAPIDO and PRODIGE 23 trials have raised among the broad community of gastrointestinal oncologists, proposing an interpretation of the data that may help the decision making, and highlighting grey areas that warrant further investigation.

Introduction

For many years, long-course chemoradiotherapy (CRT) and short-course radiotherapy (SCRT) have represented standard neoadjuvant treatments for stage II-III rectal cancer. CRT generally consists of 28–30 fractions of 1.8 Gy with concurrent fluorouracil or capecitabine followed by surgery after an interval of ≥6 weeks, while SCRT involves the delivery of 5 fractions of 5 Gy followed by surgery either 1 or up to 8 weeks later [1–3]. These therapeutic approaches are equivalent in terms of survival, toxicity and patient-reported outcomes [4–6]. Therefore, in clinical practice and international guidelines, CRT and SCRT are considered interchangeable, with a preference for the former when substantial tumour downsizing is needed to achieve clear resection margins or allow sphincter-sparing surgery [7,8].

Since a few years ago, this paradigm has increasingly been challenged by the notion of total neoadjuvant therapy (TNT), an alternative multimodal strategy meaning to intensify pre-operative treatment by delivering both radiotherapy and systemic dose chemotherapy [9]. The historical bases of TNT lie on a number of factors. First, despite many advances over time and the routine adoption of a multidisciplinary approach by specialised teams, a substantial proportion of non-metastatic rectal cancer patients (especially among those with high-risk features) suffer tumour recurrence [10]. Second, while adjuvant chemotherapy is still offered in many cases, this has never been shown to be beneficial if neoadjuvant radiotherapy and high-quality surgery are carried out, with the only exception of a randomised phase II trial [11–16]; by contrast, it has long been hypothesised that moving systemic chemotherapy from the adjuvant to the neoadjuvant setting could ensure better compliance and an early and more efficient targeting of micrometastases, which now outperform local residual disease as the leading cause of recurrence [17]. Third, emerging data suggesting a time-dependent radiotherapy effect on tumour regression have

* Corresponding author.
E-mail address: francesco.sclafani@bordet.be (F. Sclafani).

https://doi.org/10.1016/j.ctrv.2021.102177
Received 18 January 2021; Received in revised form 27 February 2021; Accepted 1 March 2021
Available online 16 March 2021

Table 1
Main randomised trials of TNT before RAPIDO and PRODIGE 23.

Trial	N	Eligibility	Treatment	Primary endpoint	Primary outcome	pCR	DFS	OS
Maréchal et al. [31]	57	cT2-T4/N+	CRT FOLFOX x2 → CRT	ypT0-1 N0	34%† 32%†	28%† 25%†	NR	NR
GCR 3 [27,28]	108	≥cT3, N+, EMVI+, MRF + or distal	CRT* → CAPOX x4 CAPOX x4 → CRT*	pCR	13%† 14%†	NR	 64%†□ 62%†□	78%†□ 75%†□
WAIT [33]	49	cT3-T4 or N+	 CRT CRT → 5FU x3	pCR	25%† 16%†	NR	NR	NR
KCSG CO 14-03 [32]	110	cT3-T4	CRT CRT → CAPOX x2	ypT0-2 N0	21%‡ 36%‡	 6%† 14%†	NR	NR
POLISH II [29,30]	515	Fixed cT3 or cT4	CRT* RT → FOLFOX x3	R0 resection	71%† 77%†	12%† 16%†	41%†□ 43%†□	49%†□ 49%†□
KIR [34]	180	cT2/3 and N+, EMVI+, or MRF+	HDRBT FOLFOX x6 → HDRBT	Chemo compliance	53%‡ 80%‡	28%† 31%†	68%†□ 72%†□	82%†□ 84%†□

* Oxaliplatin-based chemoradiotherapy.
□Survival estimates at 5 years.
□Survival estimates at 8 years.
†Non statistically significant.
‡Statistically significant.
Abbreviations: DFS: disease-free survival; pCR: pathological complete response; OS: overall survival; CRT: chemoradiotherapy; EMVI: extramural venous invasion; MRF: mesorectal fascia; HDRBT: high-dose rate endorectal brachytherapy; NR: not reported.

gradually led physicians to stretch the radiotherapy-to-surgery interval, this opening an opportunity window that encouraged the delivery of sequential, preoperative chemotherapy [18]. Finally, intensification of neoadjuvant therapy has the potential to increase the proportion of patients who achieve clinical complete response (cCR), and could therefore become eligible for watch & wait, an approach that has gained more and more traction over the last few years given the excellent survival data and positive implications in terms of long-term functional outcome and quality of life [19].

Until recently, the only available data on the use of TNT in rectal cancer were from relatively large retrospective or prospective series (generally showing promising results) [9,20–26], and small randomised trials (often failing to meet their primary endpoints) (Table 1) [27–34]. Not surprisingly, the lack of strong and unequivocal evidence generated substantial heterogeneity in terms of recommendations from international guidelines and treatment patterns across centres [68]. The NCCN guidelines fully endorsed TNT back in 2016, and this rapidly became common practice in many US centres [8]. By contrast, the latest version of the ESMO guidelines from 2017 considered TNT only as a potential alternative to CRT for the so-called "ugly" tumours, and the majority of European centres continued adopting conventional CRT or SCRT in most cases [7].

A few months ago, however, preliminary results from the randomised phase III RAPIDO and PRODIGE 23 trials were presented, ultimately tipping the balance towards TNT, and setting a new standard of care [35,36]. Nevertheless, many questions remain, especially concerning the selection of patients who are most likely to benefit from neoadjuvant treatment intensification and the choice of the most appropriate TNT regimen to adopt. By thoroughly analysing and comparing these trials and interpreting their results in light of the

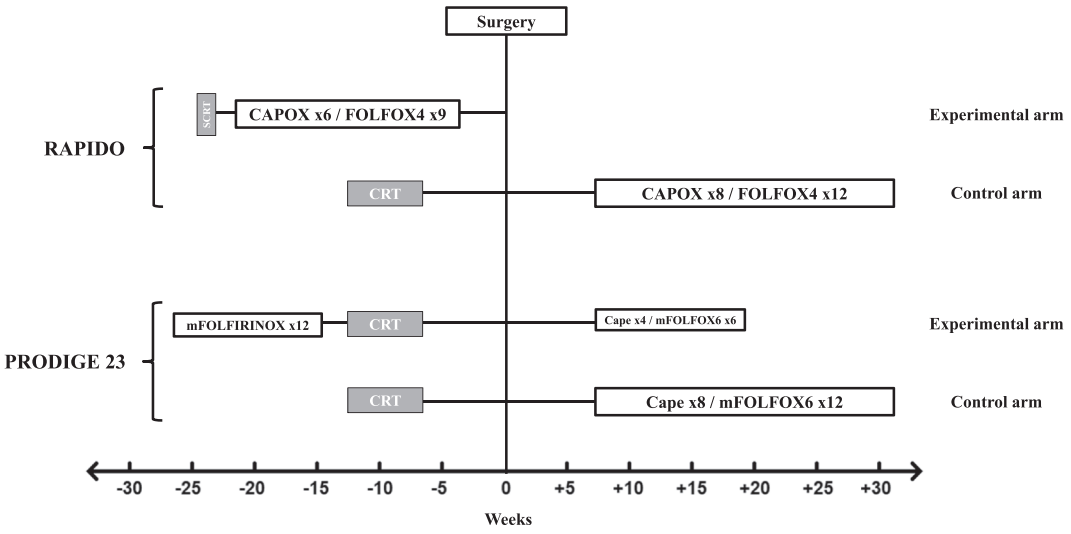


Fig. 1. Study design of the RAPIDO and PRODIGE 23 trials.

Table 2
Efficacy data from RAPIDO and PRODIGE 23 trials.

	RAPIDO	PRODIGE 23
Primary endpoint	(DRTF) 30.4% (vs 23.7%) HR 0.75, p = 0.019	(DFS) 75.5% (vs 68.5%) HR 0.69, p = 0.034
pCR rate	28.4% (vs 14.3%) OR 2.37, p < 0.0001	27.8% (vs 12.1%) p < 0.001
Locoregional failure (at 3 years)	8.3% (vs 6.0%) HR 1.42, p = 0.12	NR
Distant metastases (at 3 years)	(Cumulative probability) 20.0% (vs 26.8%) HR 0.69, p = 0.0048	(Metastasis-free survival) 78.8% (vs 71.7%) HR 0.64, p = 0.017
OS (at 3 years)	89.1% (vs 88.8%) HR 0.92, p = 0.59	90.8% (vs 87.7%) HR 0.65, p = 0.07

Abbreviations: DRTF: disease-related treatment failure; DFS: disease-free survival; pCR: pathological complete response; NR: not reported; OS: overall survival.

existing evidence and unmet needs, we seek to answer to these questions, and provide both physicians and patients with some guidance to follow in the decision-making process.

RAPIDO AND PRODIGE 23: Two high-quality and consistently positive trials

Data presented at the 2020 ASCO Annual Meeting have been considered by many as major breakthroughs in the management of non-metastatic rectal cancer. For the first time after decades, a new multimodal neoadjuvant strategy consistently led to better short- and long-term outcomes, as shown by two large and well-conducted academic phase III trials.

Both RAPIDO and PRODIGE 23 trials were run by expert investigators under the auspices of prestigious cooperative groups [35,36]. The former was an international collaboration driven by the Dutch Colorectal Cancer Group (DCCG) and the Nordic Gastrointestinal Tumour Adjuvant Therapy Group (NGTATG), the latter was a French national study supported by the Unicancer Gastrointestinal, Fédération Francophone de Cancérologie Digestive (FFCD), Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR), and Groupe Francais Chirurgie du Rectum (GRECCAR). In both cases, TNT was compared against standard control arms (CRTfollowed by surgery ± adjuvant chemotherapy) and pre-planned target recruitment completed (n = 912 and 461, respectively) (Fig. 1).

Most importantly, both studies met the respective primary endpoints with statistically significant HRs translating into clinically meaningful outcome improvements. In the RAPIDO trial, disease-related treatment failure (DRTF, an outcome measure including progression, R2 resection, recurrence, new primary colorectal cancer, cancer- or treatment-related death) occurred at 3 years in 23.7% of patients treated with TNT and 30.4% of those who had received standard therapy (HR 0.75, p = 0.019). Of note, in this study the original primary outcome measure was disease-free survival (DFS), and the pre-defined target difference was reduced from 10% to 7.5% in due course, following a lower-than-expected number of events [35]. The PRODIGE 23 trial used the more conventional endpoint of 3-year DFS, relative and absolute advantages of similar magnitude being reported in favour of the investigational group (ie, 75.7% versus 68.5%, HR 0.69, p = 0.034) [36]. Notably and further confirming the positive results, consistency between the two trials was also observed for secondary endpoints. In either study, the pathological complete response (pCR) rate in the TNT arm was doubled as compared with the control arm (ie, 28.4% versus 14.3% in RAPIDO, 27.8% versus 12.1% in PRODIGE 23), and use of TNT led to an absolute 7% reduction (or 25% relative reduction) in the risk of distant metastases at 3 years (Table 2) [35,36].

Table 3
Patient characteristics from RAPIDO and PRODIGE 23 trials.

	RAPIDO	PRODIGE 23
No. of patients	912	461
Median age (yrs)	62	61
Elderly patients	40% (≥65 yrs)	13% (≥70 yrs)
Males	67.1%	66.4%
Performance status	(ECOG)	(WHO)
0	80.5%	79.1%
1	19.5%	20.9%
Distance from anal verge		
< 5 cm	25.7%	36.9%
5–10 cm	39.3%	50.3%
10–15 cm	35.0%	12.8%
Clinical T stage		
T2	3%	1.1%
T3	65.8%	82.2%
T4	31.1%	12.8%
Clinical N stage		
cN0	8.4%	10.4%
cN1	26.1%	N+: 89.6%
cN2	65.5%	
Other high-risk features		
EMVI +	29.9%	NR
MRF +	61%	27%
Lateral N+	14.8%	NR

Abbreviations: EMVI: extramural venous invasion; MRF: mesorectal fascia; NR: not reported.

While still preliminary, these data appear robust and compelling enough to justify routine adoption of TNT in clinical practice. Similar effect estimates across studies are one of the hallmarks of evidence-based medicine, and having two consistently positive trials should reassure regarding the actual performance of the investigational treatments. The lack of statistically significant improvements in overall survival (OS) with TNT should not be seen as a major limitation, as data are not mature yet, and neither trial was powered to address this question. Furthermore, although DFS and (even less) DRTF are not validated surrogates for OS in rectal cancer, previous evidence suggests that 2-year DFS may be a stronger predictor of OS than pCR, which is still used as a common primary endpoint for phase II studies [37,38]. Finally, it is interesting to note that improvements in DFS and DRTF were achieved mostly due to better distant tumour control, a task we failed to accomplish for many years.

Nevertheless, there are substantial differences between these two trials (especially in terms of eligibility criteria and TNT regimens) that make interpretation of the results and translation of these into everyday clinical recommendations quite challenging.

Selection of patients suitable for TNT

Having established that TNT should be regarded as a new standard of care, the first question that arises is about the patients who are most likely to benefit from such approach. It has long been thought that intensification of neoadjuvant treatment with pre-operative delivery of systemic dose chemotherapy could be a reasonable option for patients with most advanced tumours, who especially bear the risk of metastatic dissemination and distant recurrence [17]. Eligibility for many of the pivotal trials of TNT was based on the presence of high-risk features, this decision reflecting also the intent to avoid over-treatment of patients with good prognosis tumours [20–22]. Considering indeed the relatively high curative rate of standard neoadjuvant CRT or SCRT followed by high-quality surgery, and the marginal impact (if any) of adjuvant chemotherapy, moving systemic dose chemotherapy from the adjuvant to the neoadjuvant setting in unselected patients could still carry an unacceptably high risk of unnecessary toxicity [39].

In line with these considerations, the RAPIDO trial recruited only patients with at least one of the five following high-risk features as detected by baseline pelvic MRI: T4, N2, extramural venous invasion (EMVI), mesorectal fascia (MRF) involvement/threatening, and enlarged lateral pelvic lymph nodes. Enrichment for poor prognosis patients in this study is confirmed by the high proportion of those who had at least two risk factors (up to almost 65%) [35]. The contention that TNT should be indicated only for high-risk locally advanced rectal cancers, however, is challenged by the eligibility criteria of the PRODIGE 23 trial. In this study, recruitment was extended to all stage II-III patients (as revealed by MRI +/- endorectal ultrasound) regardless of the presence of high-risk features. Notably, while approximately 90% of patients had N + tumours at baseline, the proportion of those with T4 stage (17% vs 31%) and MRF involvement/threatening (27% vs 61%) was substantially lower than in RAPIDO (Table 3) [36]. Based on these data, it is reasonable to propose TNT to patients with stage III tumours and to those with stage II tumours bearing at least one of the above-mentioned high-risk factors. Adopting such practice would mitigate concerns about the general risk of over-treatment, as patients who are considered here as suitable candidates for TNT are currently the most likely to be offered adjuvant chemotherapy following a non-TNT-based pre-operative strategy [8]. More data, however, are needed to support the routine adoption of TNT in patients with low-risk stage II tumours. Also, information regarding the quality assurance of MRI and the impact of endorectal ultrasound on patient eligibility in the PRODIGE 23 trial is awaited.

Table 4
Safety data from RAPIDO and PRODIGE 23 trials.

	RAPIDO	PRODIGE 23
Compliance to (chemo)radiotherapy	100% RT (vs 93% CRT)	98% CRT (vs 99% CRT)
Compliance to neoadjuvant chemotherapy	85% (vs 67% adj chemo)	92% (vs 75% adj chemo)
Grade ≥ 3 AEs during neoadjuvant therapy	48% (vs 25%)	NR
Grade ≥ 3 AEs during adjuvant chemotherapy	NA (vs 35%)	44% − 3 months (vs 74% − 6 months)
Post-operative complications	50% (vs 47%)	29% (vs 31%)
Treatment-related deaths	3% (vs 3%)	NR

Abbreviations: RT: radiotherapy; CRT: chemoradiotherapy; adj: adjuvant; Aes; adverse events; NA: not applicable; NR; not reported.

In addition to tumour stage and MRI-based high-risk features, patient-related characteristics should also be taken into account in the treatment selection process. In this regard, it is worth noting that the vast majority of patients included in the RAPIDO and PRODIGE 23 trials (ie, approximately 80%) had an ECOG/WHO performance status of 0 [35,36]. Also, the median age in either trial was 61 years (which appears slightly lower than that from previously reported studies of standard (C)RT) [1,3] and, as a result of more stringent eligibility criteria (ie, age ≤ 75 years), only about 12% of patients in the PRODIGE 23 trial had ≥ 70 years (Table 3). Therefore TNT appears especially indicated for younger/fitter patients, while it is unknown to which extent the RAPIDO and PRODIGE 23 study results could be generalised to an older/less fit, real-world population. For patients aged >75 years, TNT may still be considered, but it should not include induction triplet chemotherapy.

While subject to inherent limitations, subgroup analyses have the potential to shed some light into the patient selection process. In the RAPIDO trial the TNT effect was consistent across all patient subgroups [35]. Unfortunately, data from the PRODIGE 23 trial are awaited, but once available these could provide further insights into the role of the abovementioned high-risk features, and clarify whether the study positive results are largely driven by specific risk categories.

Selection of the optimal TNT schema

While the consistently positive results of the RAPIDO and PRODIGE 23 trials strongly support the superiority of TNT over standard neoadjuvant therapy in stage III and high-risk stage II patients, they do not reveal the optimal TNT schema to use in routine practice. In fact, they have generated some uncertainty among oncologists who now have to choose between two similarly effective treatment options. This uncertainty is enhanced by the fact that the RAPIDO and PRODIGE 23 trials adopted two diametrically opposed strategies. In the former, the investigational arm consisted of upfront SCRT followed by 18 weeks of doublet oxaliplatin-based chemotherapy (ie, 6 cycles of CAPOX or 9 cycles of FOLFOX4) and surgery. No adjuvant chemotherapy was administered [35]. In the latter, TNT included 12 weeks of upfront triplet chemotherapy (ie, mFOLFIRINOX) followed by CRT, surgery and 12 weeks of adjuvant chemotherapy (fluoropyrimidines with or without oxaliplatin) (Fig. 1) [36].

If we stuck to the study eligibility criteria, the PRODIGE 23 schema could be considered for all patients with stage II-III tumours, while the RAPIDO strategy should be restricted to those with high-risk tumours only. Such a rigorous interpretation of the data would make treatment allocation easier, limiting the proportion of patients who could be candidates for either TNT regimen. Nevertheless, if we rather considered the results from these trials as supporting evidence of the superiority of a TNT strategy (however structured) over standard neoadjuvant therapy across all study patients, it is legitimate to infer that the benefit of the RAPIDO approach could hold for low-risk stage III tumours. While potentially hazardous, this conclusion would also conciliate what is considered to be a paradoxical mismatch between the two trials in terms of the anticipated recurrence risk of the study population (ie, higher in RAPIDO, lower in PRODIGE 23) and the intensity of the TNT schema (ie, lower in RAPIDO, higher in PRODIGE 23).

Bearing in mind the differences between the RAPIDO and PRODIGE 23 trials in terms of study design, and the inherent limitations of any inter-trial comparison, efficacy data appear very similar, as above noted, and not useful to settle the question about the best TNT to use in routine practice. As far as safety is concerned, this does not appear to be a key decisional factor either. In general, as previously shown by the pivotal Spanish GRC-3 trial, toxicity is lower and compliance is higher when systemic chemotherapy is moved from the adjuvant to the neoadjuvant

setting [27]. Safety findings from the RAPIDO and PRODIGE 23 trials are in line with this contention, and they do not seem to be substantially influenced by the chemotherapy regimen, the radiotherapy schema, or the order in which chemotherapy and radiotherapy are administered. In the RAPIDO trial, the rate of grade $\geq$ 3 adverse events during the pre-operative phase was higher in the investigational than in the control arm (ie, 48% vs 25%), but this difference was balanced by the additional toxicity of adjuvant therapy in the latter (ie, 35% of grade $\geq$ 3 adverse events); furthermore, treatment-related toxicity did not affect compliance to neoadjuvant chemotherapy, which remained higher than adjuvant chemotherapy in the control arm (ie, 85% vs 67%) [35,40]. Unfortunately, information on the overall rate of grade $\geq$ 3 adverse events during the pre-operative phase in the PRODIGE 23 trial is not yet available. Nevertheless, the safety profile of induction mFOLFIRINOX was better overall than what was previously shown by studies with triplet chemotherapy in the metastatic setting [41]. The feasibility of this treatment is also confirmed by the high proportion of patients (92%) who completed 6 cycles of induction chemotherapy as per study protocol. Notably, no major differences between the RAPIDO and PRODIGE 23 trial are apparent in terms of compliance to radiotherapy (100% and 98%, respectively), and the investigational TNT treatment in neither trial was reported to be associated with a higher rate of post-operative complications or a negative impact on quality of life (Table 4) [35,36,40].

Given these data and the lack of a direct comparison between the RAPIDO and PRODIGE 23 investigational treatments, no definitive conclusion can be drawn regarding the optimal TNT schema to use in routine practice. As is often the case, the decision to adopt one approach over the other will likely be influenced by pre-existing treatment patterns (at the country or institution level), physicians' general attitude and familiarity with one particular TNT schema or some components of the same. It should be noted though, that the RAPIDO and PRODIGE TNT strategies are not entirely interchangeable, and there are some nuances that could be factored in the decision making, ultimately informing treatment choice.

When the RAPIDO or PRODIGE 23 TNT strategies may be the preferred option

Induction versus consolidation chemotherapy

For many years, the debate about the use of systemic chemotherapy before (C)RT has largely focused on radiobiological considerations. While delivering induction systemic chemotherapy has long been viewed as an appealing option, concerns remained about the potential risk that chemotherapy-driven accelerated repopulation of resistant tumour clones could reduce the tumoricidal effects of sequential radiotherapy [42]. Over time, these concerns have been mitigated by the promising oncological outcomes of many retrospective and non-randomised prospective studies [9,20–26], and now finally swept away by the results of the PRODIGE 23 trial [36]. Nevertheless, the timing of systemic chemotherapy may still matter, or at least have some important practical implications.

CAO/ARO/AIO-12 and OPRA were the first randomised phase II trials to address the question about the optimal sequence of systemic chemotherapy and radiotherapy within the context of a TNT strategy [43,44]. In the CAO/ARO/AIO-12 study, 306 stage II-III rectal cancer patients were randomised to oxaliplatin-based chemotherapy (3 cycles of FOLFOX) given before or after oxaliplatin-based CRT. While the study had a non-comparative pick-the-winner design, a higher proportion of patients (25% vs 17%) achieved pCR in the consolidation chemotherapy arm, which was the only one to fulfil the pre-defined statistical hypothesis [43]. In the OPRA trial, 306 patients with distal tumours were randomised between 4 months of oxaliplatin-based chemotherapy (FOLFOX or CAPOX) before or after fluoropyrimidine-based CRT, followed by surgery or watch & wait. Bearing in mind the non-comparative design, no difference was observed between the two arms in term of 3-year DFS (77% vs 78%, both survival estimates being in line with historical control data) and pCR rate (10% vs 8%). According to preliminary analyses, however, the proportion of patients who were able to preserve their sphincter following cCR and the adoption of a watch & wait strategy was substantially higher in the consolidation arm (59% vs 43%) [44].

Again, drawing firm conclusions based on inter-trial comparison and inference should be generally discouraged. Nevertheless, the available data suggest that survival outcomes are unlikely to be influenced by the timing of systemic chemotherapy. As long as this treatment is delivered before surgery (and therefore not too long delayed), the effective targeting of micro-metastases is preserved. In contrast, despite identical pCR rates were reported in the RAPIDO and PRODIGE 23 trials, a TNT strategy including consolidation chemotherapy may lead to deeper responses of the primary tumour, and therefore could represent the preferred approach at least for those patients who are interested in pursuing non-operative management in the case of a confirmed cCR. Of course, more data are needed to confirm this hypothesis. Also, one question that remains unanswered is whether the increased pCR/cCR rate observed with consolidation chemotherapy is exclusively attributable to the sequential strategy *per se* or somewhat influenced (and if so, to which extent) by the longer interval between radiotherapy and surgery or the first imaging reassessment time point, that at least to a certain limit may increase the chances of tumour regression [45–48]. For instance, in the CAO/ARO/AIO-12 trial, the median CRT-to-surgery interval was doubled in the consolidation arm (90 vs 45 days) [21].

Assuming that a RAPIDO-like strategy could be preferred over a PRODIGE-like approach based on the above considerations (ie, deeper tumour responses and comparable safety), the question arises whether there are any advantages of delivering systemic chemotherapy before radiotherapy. In fact, in some clinical circumstances induction chemotherapy may represent the optimal choice. This is for instance the case of patients with bulky cancers at baseline. Systemic chemotherapy elicits tumour response much more quickly than CRT or SCRT [49] and, as shown in previous studies, the tumour shrinkage effect achieved with induction chemotherapy may result in a rapid symptomatic relief [50]. Also, upfront administration of chemotherapy may provide a pragmatic solution for those patients who do not have rapid access to the radiotherapy facilities or for whom delays in the start of radiotherapy are anticipated due to internal logistical issues. Finally yet importantly, induction chemotherapy may provide an opportunity window to assess in vivo tumour sensitivity/response and to decide on the next course of action, including proceeding with surgery without pre-operative radiotherapy [51]. In this regard, substantial interest has recently emerged for radiotherapy-free neoadjuvant strategies to reduce the risk of long-term toxicity and poor functional outcomes. For instance, the FOWARC trial showed the feasibility of delivering neoadjuvant FOLFOX chemotherapy without radiotherapy in stage II-III rectal cancer patients [52,53]. While this was formally a negative study in view of its superiority design and the results should be interpreted with caution given a number of limitations, it is notable noting that the reduction in pCR rate with the omission of radiotherapy did not translate into a difference in either local recurrence rate, DFS or OS. Upon availability of confirmatory data [such as those from the ongoing PROSPECT/NCCTG N1048/Alliance trial (NCT01515787)], induction chemotherapy with selective use of radiotherapy may become standard practice for many patients, especially those with high and/or MRF- tumours.

Long-course chemoradiotherapy versus short-course radiotherapy

It is well established that CRT and SCRT are largely equivalent in terms of long-term toxicity, local recurrence rates, and survival outcomes [4–6]. Even the pCR rate, which has historically been higher with CRT, appears similar if SCRT is followed by delayed surgery (ie, after an interval of 4 to 8 weeks), as shown by the Stockholm III trial [3,18]. Also, there are no compelling data suggesting potential synergistic effects between either radiotherapy regimen and induction versus

consolidation chemotherapy. Therefore, it is unlikely that clinical or radiobiological considerations linked to the radiotherapy schedule may drive the decision to adopt one TNT schema over the other. On the other hand, there are some practical implications of using SCRT or CRT within the context of a TNT strategy, that may ultimately count in the decision making.

While the overall duration of the neoadjuvant treatment (ie, from treatment start to surgery) in the RAPIDO and PRODIGE 23 trial is quite similar (ie, theoretically 23–26 weeks and 26–27 weeks, respectively), the latter is burdened by a substantially higher number of in-hospital treatment days (ie, theoretically 11–14 days versus 34 days) [35,36] (Fig. 1). This difference is mostly attributable to the use of CRT instead of SCRT, and it increases further if the additional 12 weeks of adjuvant chemotherapy from the PRODIGE 23 trial are considered (ie, theoretically, 11 to 14 days versus 38–40 days). In a general context where treatment cost saving and cautious use of healthcare resources are paramount, an SCRT-including TNT strategy such as that investigated in the RAPIDO trial is by far more convenient than a CRT-based TNT approach as proposed in the PRODIGE 23 trial. This point is especially valid at the present time, with healthcare systems being under massive pressure for the COVID-19 pandemic crisis [54,55]. Also, it is very likely that for the same reason, the RAPIDO TNT strategy may be the preferred option for patients and their caretakers, especially if these happen to live a long distance from the healthcare facilities.

As outlined above, however, rapid access to the radiotherapy treatment is not always possible especially in developing countries, and opting for CRT after 12 weeks of induction chemotherapy can avoid substantial delays in treatment start. What is not known, however, is whether, regardless of the preferences or circumstances driving the decision about CRT versus SCRT, the type and timing of radiotherapy should mirror either the RAPIDO or PRODIGE 23 strategy. Only limited, non-randomised data are available for upfront CRT followed by consolidation chemotherapy or induction chemotherapy followed by SCRT [25,32,33,43].

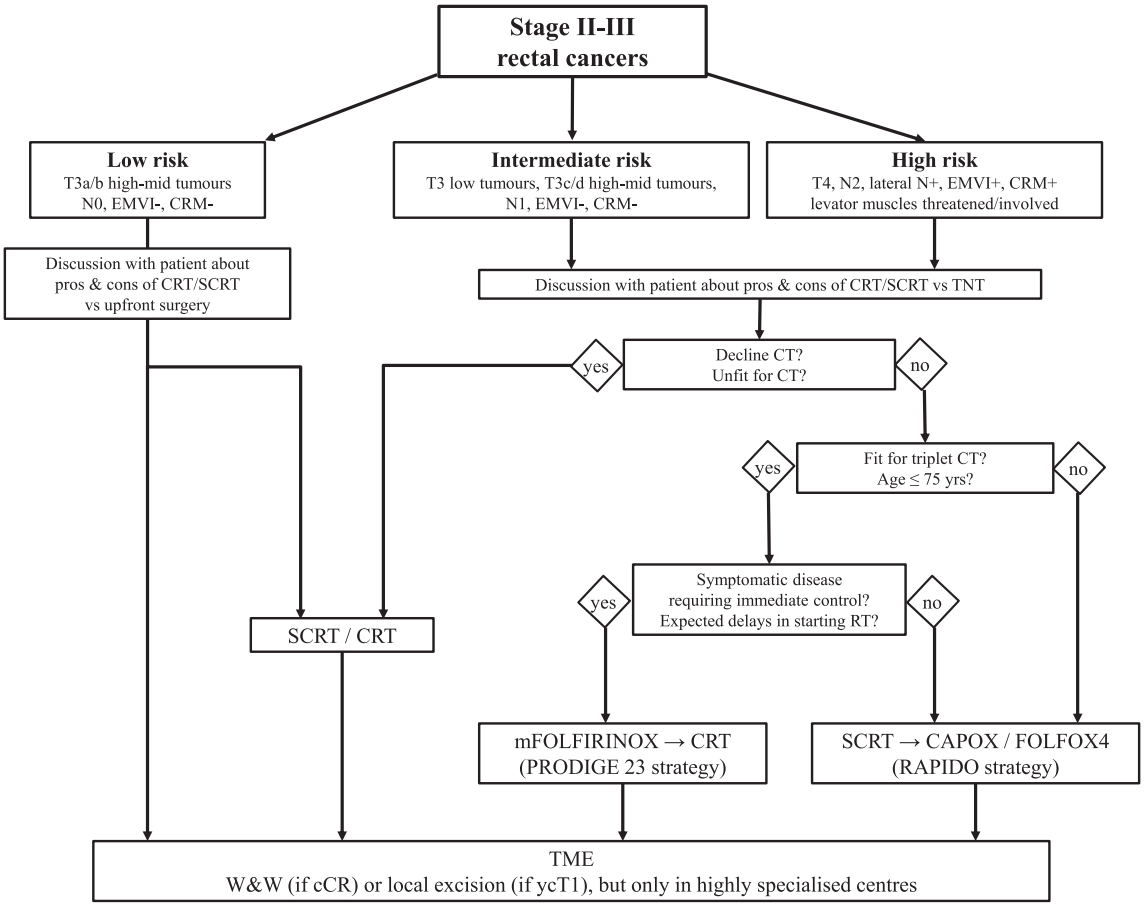
Open questions regarding the RAPIDO and PRODIGE 23 TNT regimens

In addition to the above-discussed points regarding the optimal patient selection and the choice of the most appropriate TNT schema to propose to our patients, a number of other questions remain about specific treatment components of the RAPIDO and PRODIGE 23 TNT strategies.

The first question concerns the optimal duration of consolidation chemotherapy if the RAPIDO approach is used. Should this be continued for 18 weeks (ie, 9 cycles of FOLFOX or 6 cycles of CAPOX), or a shorter duration could be equally effective? This is a legitimate question, especially considering that in the adjuvant setting of colon cancer (where the value of systemic chemotherapy is by far higher than in rectal cancer) 12 weeks of oxaliplatin-based chemotherapy were shown to be non-inferior to 24 weeks of the same treatment at least for patients with low-risk tumours [56]. Although no randomised data are available, results from previous studies help to shed some light into this topic. In the MSKCC 12-201 trial, 259 patients with stage II-III rectal cancer were prospectively enrolled into four sequential treatment arms, three of which had a RAPIDO-like treatment strategy with SCRT followed by 2, 4 or 6 cycles of consolidation FOLFOX chemotherapy [57]. Notably, the pCR rate was directly proportional to the number of chemotherapy cycles, increasing from 25% when 2 cycles were given to up to 38% among patients who had received 6 cycles. Of course, and as abovementioned, these results might have been largely influenced by the longer radiotherapy-to-surgery interval (median values increasing with the number of cycles and ranging from 11 to 19 weeks), and could not be entirely reflective of the benefit deriving from a longer duration of the consolidation chemotherapy. Also, the study did not test the impact of extending consolidation chemotherapy up to 9 cycles (i.e., 18 weeks). Indirect confirmation of the potential value of a longer duration of consolidation chemotherapy (or simply a longer radiotherapy-to-surgery interval) comes from the negative results of the POLISH II trial. No significant difference was observed for any of the outcome measures of this study, where 515 patients with fixed cT3 or cT4 tumours were randomised between oxaliplatin-based CRT followed by surgery and SCRT followed by "only" 3 cycles of FOLFOX and surgery [29,30]. Overall, in the absence of tolerability issues and until new evidence becomes available, it is not advisable to administer less than 18 weeks of consolidation chemotherapy if the RAPIDO-based TNT strategy is used. The true impact of the duration of consolidation chemotherapy on survival is unknown, and it cannot be ruled out that a shorter chemotherapy treatment may have a detrimental effect on long-term outcomes.

The second question is about the induction chemotherapy regimen used in the PRODIGE 23 trial. Is triplet chemotherapy necessary, or similar results could be achieved with oxaliplatin-based doublet chemotherapy? Historically, treatment intensification in the metastatic setting has not been very popular among oncologists, and it took several years and follow-up/confirmatory studies after the pivotal TRIBE trial for FOLFOXIRI (or its variant FOLFIRINOX) to become a universally accepted, routinely used, first-line regimen [40,58,59]. Not surprisingly, concerns have already risen by many who consider 12 weeks of induction mFOLFIRINOX as a disproportionate measure for patients with relatively early-stage rectal tumours. Furthermore, irinotecan has never been shown to play a role in the peri-operative setting of colorectal cancer [60,61], and the risk of overtreatment in a population that mostly remains free of recurrence even with conventional neoadjuvant CRT or SCRT is very high. Deciphering the added value of irinotecan in this setting is impossible at this stage. Randomised data on TNT with intensified induction treatments in non-metastatic rectal cancer are available only for the combination of chemotherapy plus monoclonal antibodies: while higher radiological response rates were observed in favour of the intensive arm at the end of the induction phase, overall results were disappointing (possibly influenced by suboptimal patient selection criteria) [22,62]. On the other hand, at least two randomised phase II trials failed to demonstrate the superiority of a PRODIGE-like strategy including induction oxaliplatin-based doublet chemotherapy over standard therapy [27,28,31]. What we know from the metastatic setting is that intensification of chemotherapy increases response rates, progression-free survival and OS at the price of increased toxicity [40,58,59,63]. Assuming that this notion holds true for early-stage patients, the advantage of administrating mFOLFIRINOX upfront lies in the rapid and deep tumour downsizing, thus improving tumour-related symptoms and widening the proportion of patients who could potentially be spared from sequential radiotherapy within the context of an adaptive treatment strategy [51]. Of note, the potential of mFOLFIRINOX in this setting is being addressed in the ongoing NORAD01 trial [64]. As far as the risk of increased toxicity is concerned, data from the PRODIGE 23 trial appear reassuring overall, and they suggest that safety is less of an issue in this setting, this conclusion being likely influenced by the early-stage population. Overall, in the absence of specific contraindications to triplet chemotherapy, oncologists should not be reluctant to deliver 12 weeks of mFOLFIRINOX if a PRODIGE-based TNT strategy with induction chemotherapy is considered.

The last question is about the actual value in the PRODIGE 23 trial of adjuvant chemotherapy, a treatment component that has not generally been included in classical TNT studies. All phase III trials of adjuvant chemotherapy in rectal cancer patients who had received neoadjuvant radiotherapy and high-quality surgery failed to show any survival improvement [11–15,65]. It is then legitimate to hypothesise that, if patients are treated with an intensified neoadjuvant therapy including systemic chemotherapy, there are no chances whatsoever that adjuvant chemotherapy may be beneficial. Also, it should be noted that in the investigational arm of the PRODIGE 23 trial, 29% of patients never started adjuvant chemotherapy, and only 57% completed the assigned treatment [36]. These figures are in line with those from the



Abbreviations: *CRT: chemoradiotherapy; SCRT: short-course radiotherapy; RT: radiotherapy; TNT: total neoadjuvant therapy; CT: chemotherapy; EMVI: extramural venous invasion; CRM: circumferential resection margin; W&W: watch and wait; cCR: clinical complete response.*

Fig. 2. Proposed neoadjuvant treatment algorithm for stage II-III rectal cancers.

abovementioned negative phase III trials, and further limit the value of adjuvant chemotherapy in the setting of TNT [11–14]. Of course, these assumptions should be confirmed by randomised data. Meanwhile, if the decision is made to adopt the PRODIGE 23 schema, patient suitability for adjuvant chemotherapy after surgery should be carefully assessed, and in the absence of specific contraindications an open discussion should take place with the patient regarding pros and cons of each management option (the decision to use either mFOLFOX or capecitabine in the trial was left to the discretion of the investigator). Moving forward, a TNT strategy whereby adjuvant chemotherapy is replaced by systemic chemotherapy delivered before and after CRT according to a "sandwich" treatment appears more interesting and worth testing in future clinical trials [66,67].

Conclusions

For decades, outcome improvements for locally advanced rectal cancer have mostly resulted from technical advances (especially in imaging, surgery, and pathology), and routine use of multimodal approaches as proposed by specialised multidisciplinary teams. For the first time since the standardisation of TME, we have two randomised phase III trials consistently showing better short- and long-term outcomes with a new multimodal treatment. We believe that results from these trials should be considered as practice-changing, and TNT be rapidly included as a management option in the treatment algorithm of patients with stage II-III tumours (Fig. 2). Of course, full peer-reviewed data from the PRODIGE 23 trial are eagerly awaited to confirm interpretations and recommendations outlined in this article. Also, many questions about TNT remain unanswered, and these should represent the subject of future studies.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Emilio Francesco Giunta – Honoraria: Novartis
Amelie Deleporte – Travel grants: Amgen, Ipsen.
Teresa Troiani – Consultancy, advisory board: Amgen, Bayer, Merck, Novartis, Roche, Sanofi. Research funding: Bayer, Merck, Novartis, Roche, Sanofi, Servier.
Fortunato Ciardiello – Consultancy, advisory board: Amgen, Bayer, BMS, Cellgene, Lilly, Merck, Pfizer, Roche, Sanofi, Servier, Symphogen. Research funding: Amgen, AstraZeneca, Bayer, Ipsen, Merck, Roche, Takeda.
Alain Hendlisz – Consultancy, advisory board: Amgen, Bayer, Eli Lilly, Merck, Pierre Fabre, Servier, Sirtex. Research funding: Amgen, AstraZeneca, Ipsen, Leo Pharma, Merck, Roche, Sanofi, Teva Pharma. Travel grant: Merck, Roche, Sirtex.
Francesco Sclafani – Consultancy, advisory board: Bayer. Research funding: AstraZeneca, Bayer, BMS, Roche. Travel grants: Bayer, Lilly.

All other authors do not have any conflicts of interests.

Acknowledgments

Giacomo Bregni is supported by an ESMO Research Fellowship. Any views, opinions, findings, conclusions ore recommendations expressed in this material are those solely of the authors and do not necessarily reflect those of ESMO.

References

[1] Van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12(6):575–82. https://doi.org/10.1016/S1470-2045(11)70097-3.

[2] Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926–33. https://doi.org/10.1200/JCO.2011.40.1836.

[3] Erlandsson J, Holm T, Pettersson D, Berglund Å, Cedermark B, Radu C, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, noninferiority trial. Lancet Oncol 2017;18(3):336–46. https://doi.org/10.1016/S1470-2045(17)30086-4.

[4] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudełko M, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004;72(1):15–24. https://doi.org/10.1016/j.radonc.2003.12.006.

[5] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93(10):1215–23. https://doi.org/10.1002/bjs.5506.

[6] Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30(31):3827–33. https://doi.org/10.1200/JCO.2012.42.9597.

[7] Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. ESMO Guidelines Committee. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl_4):iv22–40. https://doi.org/10.1093/annonc/mdx224.

[8] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Rectal Cancer Version 6.2020 - June 25, 2020. https://www.nccn.org.

[9] Cercek A, Roxburgh CSD, Strombom P, Smith JJ, Temple LKF, Nash GM, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol 2018;4(6):e180071. https://doi.org/10.1001/jamaoncol.2018.0071.

[10] Brouwer NPM, Bos ACRK, Lemmens VEPP, Tanis PJ, Hugen N, Nagtegaal ID, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer 2018;143(11):2758–66. https://doi.org/10.1002/ijc.31785.

[11] Sainato A, Cernusco LNV, Valentini V, De Paoli A, Maurizi ER, Lupattelli M, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). Radiother Oncol 2014;113(2):223–9. https://doi.org/10.1016/j.radonc.2014.10.006.

[12] Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. Ann Oncol 2014;25(7):1356–62. https://doi.org/10.1093/annonc/mdu147.

[13] Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15(2):184–90. https://doi.org/10.1016/S1470-2045(13)70599-0.

[14] Breugom AJ, van Gijn W, Muller EW, Berglund Å, van den Broek CBM, Fokstuen T, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol 2015;26(4):696–701. https://doi.org/10.1093/annonc/mdu560.

[15] Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16(2):200–7. https://doi.org/10.1016/S1470-2045(14)71199-4.

[16] Hong YS, Kim SY, Lee JS, Nam BH, Kim KP, Kim JE, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. J Clin Oncol 2019;37(33):3111–3. https://doi.org/10.1200/JCO.19.00016.

[17] Glynne-Jones R, Anyamene N, Moran B, Harrison M. Neoadjuvant chemotherapy in MRI-staged high-risk rectal cancer in addition to or as an alternative to preoperative chemoradiation? Ann Oncol 2012;23(10):2517–26. https://doi.org/10.1093/annonc/mds010.

[18] Erlandsson J, Lörinc E, Ahlberg M, Pettersson D, Holm T, Glimelius B, et al. Tumour regression after radiotherapy for rectal cancer - results from the randomised Stockholm III trial. Radiother Oncol 2019;135(Jun):178–86. https://doi.org/10.1016/j.radonc.2019.03.016.

[19] van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018;391(10139):2537–45. https://doi.org/10.1016/S0140-6736(18)31078-X.

[20] Chau I, Allen M, Cunningham D, Tait D, Brown G, Hill M, et al. Neoadjuvant systemic fluorouracil and mitomycin C prior to synchronous chemoradiation is an effective strategy in locally advanced rectal cancer. Br J Cancer 2003;88(7):1017–24. https://doi.org/10.1038/sj.bjc.6600822.

[21] Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 2010;11(3):241–8. https://doi.org/10.1016/S1470-2045(09)70381-X.

[22] Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, et al. Multicenter randomized phase II clinicaltrial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapywith or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30(14):1620–7. https://doi.org/10.1200/JCO.2011.39.6036.

[23] Sclafani F, Brown G, Cunningham D, Wotherspoon A, Tait D, Peckitt C, et al. PANEX: a pooled analysis of two trials of neoadjuvant chemotherapy followed by chemoradiotherapy in MRI-defined, locally advanced rectal cancer. Ann Oncol 2016;27(8):1557–65. https://doi.org/10.1093/annonc/mdw215.

[24] Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12(4):513–9. https://doi.org/10.6004/jnccn.2014.0056.

[25] Gollins S, West N, Sebag-Montefiore D, Susnerwala S, Falk S, Brown N, et al. A prospective phase II study of pre-operative chemotherapy then short-course radiotherapy for high risk rectal cancer: COPERNICUS. Br J Cancer 2018;119(6):697–706. https://doi.org/10.1038/s41416-018-0209-4.

[26] Schou JV, Larsen FO, Rasch L, Linnemann D, Langhoff J, Høgdall E, et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. Ann Oncol 2012;23(10):2627–33. https://doi.org/10.1093/annonc/mds056.

[27] Fernández-Martos C, Pericay C, Aparicio J, Salud A, Safont M, Massuti B, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28(5):859–65. https://doi.org/10.1200/JCO.2009.25.8541.

[28] Fernandez-Martos C, Garcia-Albeniz X, Pericay C, Maurel J, Aparicio J, Montagut C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial. Ann Oncol 2015;26(8):1722–8. https://doi.org/10.1093/annonc/mdv223.

[29] Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryński J, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 2016;27(5):834–42. https://doi.org/10.1093/annonc/mdw062.

[30] Ciseł B, Pietrzak L, Michalski W, Wyrwicz L, Rutkowski A, Kosakowska E, et al. Long-course preoperative chemoradiation vs. 5 x 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. Ann Oncol 2019;30(8):1298–1303. https://doi.org/10.1093/annonc/mdz186.

[31] Maréchal R, Vos B, Polus M, Delaunoit T, Peeters M, Demetter P, et al. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. Ann Oncol 2012;23(6):1525–30. https://doi.org/10.1093/annonc/mdr473.

[32] Kim SY, Joo J, Kim TW, Hong YS, Kim JE, Hwang IG, et al. A randomized phase 2 trial of consolidation chemotherapy after preoperative chemoradiation therapy versus chemoradiation therapy alone for locally advanced rectal cancer: KCSG CO 14–03. Int J Radiat Oncol Biol Phys 2018;101(4):889–899. https://doi.org/10.1016/j.ijrobp.2018.04.013.

[33] Moore J, Price T, Carruthers S, Selva-Nayagam S, Luck A, Thomas M, et al. Prospective randomized trial of neoadjuvant chemotherapy during the 'wait period' following preoperative chemoradiotherapy for rectal cancer: results of the WAIT trial. Colorectal Dis 2017;19(11):973–9. https://doi.org/10.1111/codi.13724.

[34] Garant A, Kavan P, Martin AG, Azoulay L, Vendrely V, Lavoie C, et al. Optimizing treatment sequencing of chemotherapy for patients with rectal cancer: The KIR randomized phase II trial. Radiother Oncol 2020;155:237–45. https://doi.org/10.1016/j.radonc.2020.11.008.

[35] Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, et al. RAPIDO collaborative investigators. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally

advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22(1):29–42. https://doi.org/10.1016/S1470-2045(20)30555-6.
[36] Conroy T, Lamfichekh N, Etienne P, Rio E, Francois E, Mesgouez-Nebout N, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: final results of PRODIGE 23 phase III trial, a UNICANCER GI trial. J Clin Oncol 2020;38(15 Suppl.):4007. https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4007.
[37] Fokas E, Glynne-Jones R, Appelt A, Beets-Tan R, Beets G, Haustermans K, et al. Outcome measures in multimodal rectal cancer trials. Lancet Oncol 2020;21(5):e252–64. https://doi.org/10.1016/S1470-2045(20)30024-3.
[38] Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, et al. Selection of appropriate end-points (pCR vs 2yDFS) for tailoring treatments with prediction models in locally advanced rectal cancer. Radiother Oncol 2015;114(3):302–9. https://doi.org/10.1016/j.radonc.2015.02.001.
[39] Hong TS, Ryan DP. Total neoadjuvant therapy for locally advanced rectal cancer-the new standard of care? JAMA Oncol 2018;4(6):e180070. https://doi.org/10.1001/jamaoncol.2018.0070.
[40] van der Valk MJM, Marijnen CAM, van Etten B, Dijkstra EA, Hilling DE, Kranenbarg EM, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - RESULTS of the international randomized RAPIDO-trial. Radiother Oncol 2020;147:75–83. https://doi.org/10.1016/j.radonc.2020.03.011.
[41] Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007;25(13):1670–6. https://doi.org/10.1200/JCO.2006.09.0928.
[42] Glynne-Jones R, Grainger J, Harrison M, Ostler P, Makris A. Neoadjuvant chemotherapy prior to preoperative chemoradiation or radiation in rectal cancer: should we be more cautious? Br J Cancer 2006;94(3):363–71. https://doi.org/10.1038/sj.bjc.6602960.
[43] Fokas E, Allgäuer M, Polat B, Klautke G, Grabenbauer GG, Fietkau R, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. J Clin Oncol 2019;37(34):3212–22. https://doi.org/10.1200/JCO.19.00308.
[44] Garcia-Aguilar J, Patil S, Kim JK, Yuval JB, Thompson H, Verheij F, et al. Preliminary results of the organ preservation of rectal adenocarcinoma (OPRA) trial. J Clin Oncol 2020;38(15_suppl):4008. https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4008.
[45] Sloothaak DA, Geijsen DE, van Leersum NJ, Punt CJA, Buskens CJ, Bemelman WA, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 2013;100(7):933–9. https://doi.org/10.1002/bjs.9112.
[46] Probst CP, Becerra AZ, Aquina CT, Tejani MA, Wexner SD, Garcia-Aguilar J, et al. Extended intervals after neoadjuvant therapy in locally advanced rectal cancer: the key to improved tumor response and potential organ preservation. J Am Coll Surg 2015;221(2):430–40. https://doi.org/10.1016/j.jamcollsurg.2015.04.010.
[47] Akgun E, Caliskan C, Bozbiyik O, Yoldas T, Sezak M, Ozkok S, et al. Randomized clinical trial of short or long interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 2018;105(11):1417–25. https://doi.org/10.1002/bjs.10984.
[48] Evans J, Bhoday J, Sizer B, Tekkis P, Swift R, Perez R, et al. Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy? Ann Oncol 2016;27(6):149–206. https://doi.org/10.1093/annonc/mdw370.
[49] Dhadda AS, Zaitoun AM, Bessell EM. Regression of rectal cancer with radiotherapy with or without concurrent capecitabine–optimising the timing of surgical resection. Clin Oncol (R Coll Radiol) 2009;21(1):23–31. https://doi.org/10.1016/j.clon.2008.10.011.
[50] Sclafani F, Peckitt C, Cunningham D, Tait D, Giralt J, Glimelius B, et al. Short- and long-term quality of life and bowel function in patients with MRI-defined, high-risk, locally advanced rectal cancer treated with an intensified neoadjuvant strategy in the randomized phase 2 EXPERT-C trial. Int J Radiat Oncol Biol Phys 2015;93(2):303–12. https://doi.org/10.1016/j.ijrobp.2015.03.038.
[51] Sclafani F, Cunningham D. Neoadjuvant chemotherapy without radiotherapy for locally advanced rectal cancer. Future Oncol 2014;10(14):2243–57. https://doi.org/10.2217/fon.14.127.
[52] Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Modified FOLFOX6 with or without radiation versus fluorouracil and leucovorin with radiation in neoadjuvant treatment of locally advanced rectal cancer: initial results of the Chinese FOWARC multicenter, open-label, randomized three-arm phase III trial. J Clin Oncol 2016;34(27):3300–7. https://doi.org/10.1200/JCO.2016.66.6198.
[53] Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Neoadjuvant modified FOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: final results of the Chinese FOWARC trial. J Clin Oncol 2019;37(34):3223–33. https://doi.org/10.1200/JCO.18.02309.
[54] Vecchione L, Stintzing S, Pentheroudakis G, Douillard JY, Lordick F. ESMO management and treatment adapted recommendations in the COVID-19 era: colorectal cancer. ESMO Open 2020;5(Suppl 3):e000826. https://doi.org/10.1136/esmoopen-2020-000826.
[55] Marshall JL, Yarden RI, Weinberg BA. Colorectal cancer care in the age of coronavirus: strategies to reduce risk and maintain benefit. Colorectal. Cancer 2020;9(1). https://doi.org/10.2217/crc-2020-0010.
[56] André T, Meyerhardt J, Iveson T, Sobrero A, Yoshino T, Souglakos I, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol 2020;21(12):1620–9. https://doi.org/10.1016/S1470-2045(20)30527-1.
[57] Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Timing of rectal cancer response to chemoradiation consortium. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol 2015;16(8):957–66. https://doi.org/10.1016/S1470-2045(15)00004-2.
[58] Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015;16(13):1306–15. https://doi.org/10.1016/S1470-2045(15)00122-9.
[59] Cremolini C, Antoniotti C, Rossini D, Lonardi S, Loupakis F, Pietrantonio F, et al. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 2020;21(4):497–507. https://doi.org/10.1016/S1470-2045(19)30862-9.
[60] Van Cutsem E, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol 2009;27(19):3117–25. https://doi.org/10.1200/JCO.2008.21.6663.
[61] Ychou M, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol 2009;20(12):1964–70. https://doi.org/10.1093/annonc/mdp236.
[62] Fernández-Martos C, Pericay C, Losa F, García-Carbonero R, Layos L, Rodríguez-Salas N, et al. Effect of aflibercept plus modified FOLFOX6 induction chemotherapy before standard chemoradiotherapy and surgery in patients with high-risk rectal adenocarcinoma: the GEMCAD 1402 randomized clinical trial. JAMA Oncol 2019;5(11):1566–73. https://doi.org/10.1001/jamaoncol.2019.2294.
[63] Cremolini C, Antoniotti C, Stein A, Bendell J, Gruenberger T, Rossini D, et al. Individual patient data meta-analysis of FOLFOXIRI plus bevacizumab versus doublets plus bevacizumab as initial therapy of unresectable metastatic colorectal cancer. J Clin Oncol 2020. https://doi.org/10.1200/JCO.20.01225.
[64] Brouquet A, Bachet JB, Huguet F, Karoui M, Artru P, Sabbagh C, et al. NORAD01-GRECCAR16 multicenter phase III non-inferiority randomized trial comparing preoperative modified FOLFIRINOX without irradiation to radiochemotherapy for resectable locally advanced rectal cancer (intergroup FRENCH-GRECCAR-PRODIGE trial). BMC Cancer 2020;20(1):485. https://doi.org/10.1186/s12885-020-06968-1.
[65] Bregni G, Akin Telli T, Camera S, Deleporte A, Moretti L, Bali AM, et al. Adjuvant chemotherapy for rectal cancer: Current evidence and recommendations for clinical practice. Cancer Treat Rev 2020;83:101948. https://doi.org/10.1016/j.ctrv.2019.101948.
[66] Gao YH, Lin JZ, An X, Luo JL, Cai MY, Cai PQ, et al. Neoadjuvant sandwich treatment with oxaliplatin and capecitabine administered prior to, concurrently with, and following radiation therapy in locally advanced rectal cancer: a prospective phase 2 trial. Int J Radiat Oncol Biol Phys 2014;90(5):1153–60. https://doi.org/10.1016/j.ijrobp.2014.07.021.
[67] Golo D, But-Hadzic J, Anderluh F, Brecelj E, Edhemovic I, Jeromen A, et al. Induction chemotherapy, chemoradiotherapy and consolidation chemotherapy in preoperative treatment of rectal cancer - long-term results of phase II OIGIT-01 trial. Radiol Oncol 2018;52(3):267–74. https://doi.org/10.2478/raon-2018-0028.
[68] Bregni G, Akin Telli T, Camera S, Baratelli C, Shaza L, Deleporte A, et al. Grey areas and evidence gaps in the management of rectal cancer as revealed by comparing recommendations from clinical guidelines. Cancer Treat Rev 2020;82:101930. https://doi.org/10.1016/j.ctrv.2019.101930.