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Incorporating neoadjuvant chemotherapy into locally advanced colon cancer treatment pathways: real life experience of implementing FOxTROT

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What does this paper add to the literature?

Translating the findings of the FOXTROT trial into improved patient outcomes is dependent on implementation of new neoadjuvant chemotherapy (NAC) pathways in colorectal cancer. This paper provides practical guidance for the whole MDT on how NAC be implemented with minimal impact on service capacity and budget while protecting patient safety and confidence.

Introduction

The international FOxTROT trial, recently published in the *Journal of Clinical Oncology*, (ref awaited) is the first randomised controlled trial testing neoadjuvant chemotherapy (NAC) with oxaliplatin and 5-fluorouracil in locally advanced but operable colon cancer. 1053 patients with operable, radiologically staged T3-T4, N1-2, M0 colon cancer were recruited from over 100 sites in the UK, Sweden and Denmark. Patients were randomised to 6 weeks of planned chemotherapy before resectional surgery, followed by adjuvant chemotherapy; or upfront surgery followed by adjuvant chemotherapy (total 18 weeks in both arms). NAC was safe and, compared with standard treatment, there was no increase in surgical complications, a higher R0 rate (95% vs 89%, $p<0.001$), and significant primary and nodal pathological downstaging. The trial met its primary endpoint with fewer patients experiencing recurrent or residual disease at 2 years with NAC compared with control: (16.8% vs 21.2%, risk ratio=0.74, $p=0.042$).

Rapid translation of these results into patient benefit is expected, particularly as the chemotherapeutic agents are already used routinely and do not incur any additional cost or toxicity. However, offering NAC as standard care for advanced colon cancer requires adaptations to current treatment pathways so presents organisational challenges.

To date, the Leeds Cancer Centre, St James's University Hospital, UK has commenced 64 patients on the novel pathway following presentation and adoption of the FOxTROT results. Here, we describe our experience and share strategies developed across the MDT to

minimise impact on person hours, service capacity and budget, whilst building patient safety and confidence.

The multidisciplinary team (MDT)

Key lesson: Involve the whole colon cancer MDT

Engagement and buy-in from all local MDT (tumour board) members is key to delivering NAC. Collaborative working involving the surgeon, oncologist, radiologist, pathologist and specialist nurse is critical for the success of the patient pathway.

Key lesson: Specialist colorectal radiology expertise is critical

An important determinant of patient eligibility for NAC is radiological staging, so specialist radiologist input is key. Radiologists should be confident that patients considered for NAC have a cT3 or cT4 tumour and be empowered to highlight the suitability of these patients for NAC at MDT. There is no evidence base for treating borderline cT2/3, cN0 disease with NAC. These patients should proceed directly to surgery.

Key lesson: Access to rapid mismatch repair (MMR) testing should not be a deal-breaker

Consistent with studies of adjuvant chemotherapy,[1] a subgroup analysis within FOxTROT suggested a lack of survival benefit—but no harm—from NAC in patients with MMR deficient (dMMR) tumours. MMR (or microsatellite instability) testing is recommended for all patients with colorectal cancer at the point of diagnosis,[2] and is increasingly accessible to clinicians and patients – although results are not universally available in time to influence decision making at the first MDT meeting. Rapid turnaround of MMR testing provides greater precision in patient selection and is recommended. However, as NAC resulted in recurrence-free survival benefit in the unselected FOxTROT population, lack of rapid MMR testing

should not impede access to NAC, particularly for patients with disease distal to the splenic flexure, where the dMMR rate is only 5%.

Key lesson: Clinical Nurse Specialist (CNS) oversight is key to a smooth and efficient patient journey

In addition to their existing roles as a primary point of contact and support for the patient, the CNS coordinates the activities of the rest of the multidisciplinary team to optimise progression along the treatment pathway, tracking pending results of investigations (such as MMR testing), and communicating projected operation dates to expedite decision making and planning.

Patient flow and first clinic review

Key lesson: Be flexible and respond to patient feedback when implementing pathway changes

Conventionally, the first clinic review for patients with operable colon cancer is with the colorectal surgeon and CNS, where diagnosis and planned surgical resection are discussed. Oncology review has previously been indicated only for consideration of post-operative adjuvant chemotherapy.

Several models for consultations on the NAC pathway have been utilised in Leeds – each with advantages and disadvantages. It is important to reduce delays to ensure that patients receive NAC promptly. Initial oncology review is efficient but requires physician confidence in assessing symptoms of potential bowel obstruction and addressing patient queries about the likely operative plan. Additionally, patient distress can arise through receipt of an unexpected oncology clinic appointment – avoided through post-MDT communication from the CNS team.

As confidence has grown among the oncology and CNS teams, patients are now frequently reviewed first by oncology. That being the case, patient feedback indicates early discussion

of the planned operation with their surgeon provides reassurance. Additionally, where there is evidence of impending obstruction, flexibility in surgical clinics and lists is required to enable defunctioning surgery prior to commencing NAC (as per the FOxTROT protocol) or stenting. Early review by both teams has been found to improve the patient experience and best facilitate surgical prehabilitation. However, the order of oncology and surgical reviews will depend upon patient needs and local working practices.

Neoadjuvant chemotherapy

Key lesson: Clear communication between oncology and surgery minimises delays

Where NAC is commenced, high priority is given to early provision of treatment to minimise delay. The oncologist is responsible for communicating the ideal time window for definitive surgery, including any alterations to this arising from chemotherapy toxicities.

Proceeding to surgery

Key lesson: Additional post-neoadjuvant chemotherapy imaging may not be necessary; NAC does not place significant additional demands on surgical clinics

Initially, a post-NAC CT scan was routinely requested in all patients but this was subsequently stopped as post-NAC CT findings did not result in changes to the planned operative approach. Post-NAC imaging can be requested if required based on the specifics of an individual case, keeping additional demands on radiology resources to a minimum. However, particularly during the early stages of NAC delivery by an MDT, a second pre-operative MDT review with updated imaging may provide reassurance and facilitate learning opportunities.

Following uncomplicated completion of NAC, and where the surgical plan has been discussed at the start of the pathway, patients can safely proceed directly to surgery without increased demands on surgical clinics.

Histopathology

Key lesson: Surgeons must complete NAC details on the resection pathology request form

Assessment of tumour regression grade (TRG) following chemotherapy is essential to gauge treatment response and inform subsequent discussions regarding adjuvant chemotherapy – particularly without a post-NAC CT scan. Full clinical details of NAC are therefore required on the histopathology request, usually completed by the surgical team.

Follow-up

The post-operative pathway is not altered. Postoperative MDT discussion (with additional assessment of the TRG) and surgical outpatient review are arranged as usual, followed by oncology review to discuss the merits of adjuvant treatment.

Future developments and patient stratification

Service developments under consideration include the provision of a joint surgical and oncological colon cancer clinic to streamline the pathway. The CNS role could be expanded, for example to initiate investigations to determine suitability for NAC (such as DPD deficiency testing) prior to initial clinic review.

FOxTROT-2 is currently recruiting at UK centres to determine whether dose modified neoadjuvant chemotherapy may be beneficial for older, frailer patients who were under-represented in the original trial. FOxTROT-3 is also open to recruitment to explore whether escalation of neoadjuvant chemotherapy to triple agent 5-fluorouracil, irinotecan and oxaliplatin is of benefit to younger, fitter patients (ISRCTN83842641).

The strength of recently presented data from the NICHE-2 single-arm phase II trial of neoadjuvant nivolumab and ipilimumab for stage II-III dMMR colon cancer, where 102 of 106 patients (95%) exhibited a major pathological response (≤10% residual viable tumour cells)[3], indicate neoadjuvant immunotherapy is likely to become standard of care for this patient subgroup in coming years. The NICHE-2 trial findings reinforce the need for rapid MMR testing to be made available at the point of diagnosis in all centres.

At present, *RAS* and *BRAF* mutation testing is frequently only performed in circumstances where palliative anti-EGFR therapy is being considered. A subset of *RAS* wild-type patients who were randomised to receive neoadjuvant chemotherapy with anti-EGFR therapy (panitumumab) within FOxTROT did not benefit from this regimen. Whether *RAS* and *BRAF* mutant subgroups benefitted equally from NAC in FOxTROT is currently being explored. The current evidence therefore does not mandate bringing forward *RAS* and *BRAF* testing in the treatment pathway. However, this may change in future and the FOxTROT-4 trial, currently in set-up, will examine the role of BRAF targeted therapy (encorafenib plus cetuximab) in the neoadjuvant setting.

Multigene testing such as the 500 gene panel is increasingly available, however such multigene panels are not yet feasible within the narrow window for neoadjuvant therapy in most centres, and at present there are no widely available targeted therapies that can take advantage of additional genetic profiling. Translational work using the FOxTROT biobank is being conducted with the aim of identifying additional molecular markers to improve patient selection and outputs from this work may soon become of more practical use in the neoadjuvant setting as access and turnaround for multigene panels improves. Additionally, as subgroups of patients with MMR proficient disease are being found to benefit from neoadjuvant immunotherapy,[4,5] rapid assessment of novel predictive biomarkers developed from this work will soon become integral to the provision of quality care.

Conclusion

NAC for locally advanced colon cancer has been shown to improve surgical outcomes and longer-term cancer outcomes. Provision of NAC requires some modifications to current treatment pathways but can be delivered with team working and without the requirement for additional resources.

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Figures and Legends

Figure 1. Leeds resectable colon cancer pathway. To minimise delays to chemotherapy, *DPYD* gene testing should be conducted as early in the pathway as feasible.
CT=computed tomography; MMR=mismatch repair testing; MDT=multidisciplinary team meeting; pMMR=proficient mismatch repair; NAC=neoadjuvant chemotherapy; CNS=clinical nurse specialist; chemo=chemotherapy.