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Do clinical trials change practice? A longitudinal, international assessment of colorectal cancer prescribing practices

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ABSTRACT

Introduction: Over half of the 1.5 million individuals globally who are diagnosed with colorectal cancer (CRC) present with stage II-III disease. Understanding clinician attitudes towards treatment for this group is paramount to contextualise real-world outcomes and plan future trials. The aim of this study was to assess clinician awareness of trials assessing the optimal duration of CRC adjuvant therapy, their attitudes towards shorter treatment and their self-reported practice.

Methods: A survey was developed using OnlineSurveys® and distributed to clinicians in April 2019, with a follow-up survey disseminated to a subset of respondents in August 2020. Microsoft Excel® and Stata® were used for analysis.

Results: 265 clinicians replied to the first survey, with the majority aware of findings from the International Duration Evaluation of Adjuvant Therapy collaboration and contributory trials. Practice change was greatest for patients under 70 with low-risk stage III CRC, with most uncertainty around using 3-months of doublet chemotherapy for high-risk stage II disease. In August 2020, clinicians (n = 106) were more likely to use 3-months of FOLFOX for low-risk stage III disease and 3-months of CAPOX for stage II disease compared to April 2019. There was no indication that the COVID-19 pandemic had enduring changes on treatment decisions beyond those made in response to trial evidence.

Discussion: Clinicians use a risk-stratified approach to treat CRC the adjuvant setting. Lower utilisation of doublet chemotherapy for older and stage II patients has affected the extent of trial implementation. Active dialogue regarding how trial results apply to these groups may improve consensus.

Introduction

The findings from six clinical trials comparing 3 months of fluoropyrimidine-oxaliplatin chemotherapy to the standard duration of 6 months of treatment in the adjuvant setting for stage II and/or stage III colon cancer have been reported since June 2017. Results from these trials were pooled within the International Duration of Adjuvant Chemotherapy (IDEA) stage II[1] and stage III [2] collaborations. Stage III results were initially disseminated at the American Society of Clinical Oncology (ASCO) conference in June 2017, published in full in March 2018 [2], and updated in June 2020 [3].' [4] The stage II collaboration findings were disseminated at ASCO 20,19[1] and published in full in January 2021 [5]. Although neither of the IDEA collaborative results met their pre-specified non-inferiority primary end-point, the difference between 3 versus 6 months of chemotherapy was small, and toxicity was significantly reduced in the shorter treatment arm. A pre-planned IDEA sub-group analysis revealed an unexpected difference in the effect of shortened treatment duration between regimens. Non-inferiority in three-year disease free survival (3y-DFS) was met in patients treated with CAPOX but not for those prescribed FOLFOX. It has been

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hypothesised that this may be due to a discrepancy in fluoropyrimidine drug intensity and mode of administration, or oxaliplatin scheduling between the two regimens, [4] or alternatively that differences in response to CAPOX versus FOLFOX may be due to a biological difference in tumour biology [6].' [7] A post-hoc analysis showed differences in outcomes for patients with stage III colon cancer depending on risk stratification. Non-inferiority in 3y-DFS was met for the 60% of patients with less locally advanced tumours and a low nodal disease burden (T1–3N1), referred to as "low-risk", but for the 40% with either T4 and/or N2 disease ("high-risk"), 6 months was superior. The Short Course Oncology Treatment (SCOT) trial, which recruited patients from six countries, was the largest contributor to IDEA stage III, one of the four trials that contributed to the stage II collaboration and the only trial that included rectal cancer patients [8].

There has been interest in if and how these clinical trial results have been interpreted by clinicians and how they have impacted on practice [9-11]. Previous published surveys of clinician opinion have been performed before the full trial results were published [26], orfocused on a small group of experts[9], one country[12] and/or on stage III colon cancer alone[13]. It is not clear if treatment preferences have changed over time since 2017, nor what influence the COVID-19 pandemic has had.

The aim of this study was to explore, at two separate time points sixteen months apart, the attitudes and self-reported clinical practice of medical professionals who prescribe adjuvant CRC chemotherapy. The objective was to understand how the IDEA collaboration and contributory trials have impacted on practice, to understand if this impact evolved over time and to assess any impact of the COVID-19 pandemic on treatment choices.

Methods

Online Surveys® was used for development, piloting ($n = 24$ pilot survey completion) and dissemination of a survey to ask clinicians about their opinions and practice. The responses from the pilot surveys were not formally evaluated and instead were used for testing validity and structure of the survey only. The final survey included four sections: i) Clinical trials and guidelines ii) Current practice iii) Attitudes towards using 3 months of adjuvant doublet chemotherapy for colorectal cancer (CRC), and iv) personal clinical practice details. All participants confirmed that they prescribed adjuvant CRC chemotherapy. Current practice at the time of survey completion was investigated using twelve hypothetical patient scenarios, six in which patients were aged under 70 years old and six in which patients were aged 70 years or older. A list of these scenarios is provided in Table S1. Scenarios relevant to stage II disease were separated by molecular disease characteristics. Specifically, scenarios describing stage II patients with tumours deficient in mismatch repair (MMR) proteins (dMMR) which are characterised by high levels of micro-satellite instability (MSI-H), were distinguished from patients with tumours proficient in MMR proteins, also known as micro-satellite stable (MSS) tumours [14]. Patients with stage II dMMR CRC tumours have better survival [15] but appear to respond less well to fluoropyrimidine chemotherapy compared to patients with pMMR tumours. MMR status does not appear to predict response to oxaliplatin-based treatment [15].

A pre-specified list of UK-based CRC oncologists was collated and used as the primary distribution list in the UK ($n = 247$). The main reason for using this list was to enable calculation of a UK response rate. It was not possible to collate a similar list for all countries external to the UK and instead dissemination to other countries relied on a generic link embedded in email correspondence which was sent to all relevant professional contacts of the study team, social media (Twitter®) and distribution lists from medical organisations (European Society for Medical Oncology GI, Clinical Oncology Society of Australia and the UK Royal College of Radiologists).

All survey respondents were asked if they would be willing to be contacted again and those who agreed were sent a follow up survey in August 2020. Any respondents to the follow up survey had therefore already answered the first survey and there were no new individuals invited to participate at the second time point. The same questions from the first survey regarding the acceptability of 3 months of doublet chemotherapy were included. The same patient scenarios were used except it was specified that patients had colon cancer rather than CRC. Also, stage II scenarios were separated into T3N0 and T4N0 (Figure S1). In the second survey, clinicians were asked to respond to patient scenarios initially disregarding the impact of COVID-19 and then asked to repeat the questions indicating changes in their practice due to the pandemic. In these answers, respondents were asked to indicate enduring changes that were likely to be maintained in their future practice, rather than temporary changes they made during the first peak of the pandemic. Responses to the second survey were linked to responses to survey one from the same participants.

The first survey was disseminated in April 2019 and kept open for 6 weeks. The follow-up survey was distributed solely by email, kept open for 6 weeks and two reminder emails were sent. Descriptive statistics and two-sided Chi[2] or Fisher's exact tests for proportions were performed using Microsoft Excel 2016 ® and STATA v14 ®. Analysis of free text answers is not included in this manuscript.

Results

In total, 265 clinicians responded to the first survey. Respondents were from UK/Europe (180/265, 68%), USA/Canada (36/265, 14%), Asia (26/265, 10%), Australia/New Zealand (20/265, 8%), South America (2/265, 1%) and Africa (1/265, 0.4%) (Figure S2). The response rate from the pre-specified list of UK oncologists was 51% (126/247). Table S3 describes the characteristics of respondents. The majority were oncologists (258/265, 97%); most had been practicing in the field of oncology for at least 10 years (196/265, 74%) and the majority treated only or predominantly patients with CRC (215/265, 81%). In total, 106/197 (54%) of clinicians who agreed to be contacted and confirmed they still treated patients with CRC in August 2020, completed the follow up survey. They were from the UK/Europe (83/106, 78%), USA/Canada (12/106, 11%), Australia (6/106, 6%), Asia (4/106, 4%) and South America (1/106, 1%).

Clinical trial findings and guidelines

In April 2019, most clinicians (252/265, 95%) reported they were aware of clinical trial findings reported in the previous two years which assessed the optimal duration of adjuvant CRC and they almost exclusively named clinical trials which contributed to the IDEA collaboration (Fig. 1a). A comparison of studies named by participants located in the UK versus countries outside the UK is shown in Figure S3 in the Supplementary material. Clinicians from the UK were most likely to name the SCOT trial, whereas those from countries outside the UK were more likely to name the IDEA collaboration and/or its contributory trials. Overall, 87% (231/265) indicated they used international/national guidelines and 72% (191/265) that they used local guidelines when deciding how to treat CRC patients in the adjuvant setting. Fig. 1b shows the national guidelines that respondents indicated they use.

Practice change in response to trial findings

The majority of respondents (243/265; 92%) reported they had changed their practice in response to the findings of the trials they had named. The mechanisms of dissemination of trial results that most influenced practice were conference presentations (61%), journal publications (54%) and discussions with colleagues (49%) (Figure S4). Clinicians who reported no practice change ($n = 19$) indicated the most common barriers were: a) the strength of evidence provided by recent clinical trials (13/19), b) no existing clinical guidelines to support a

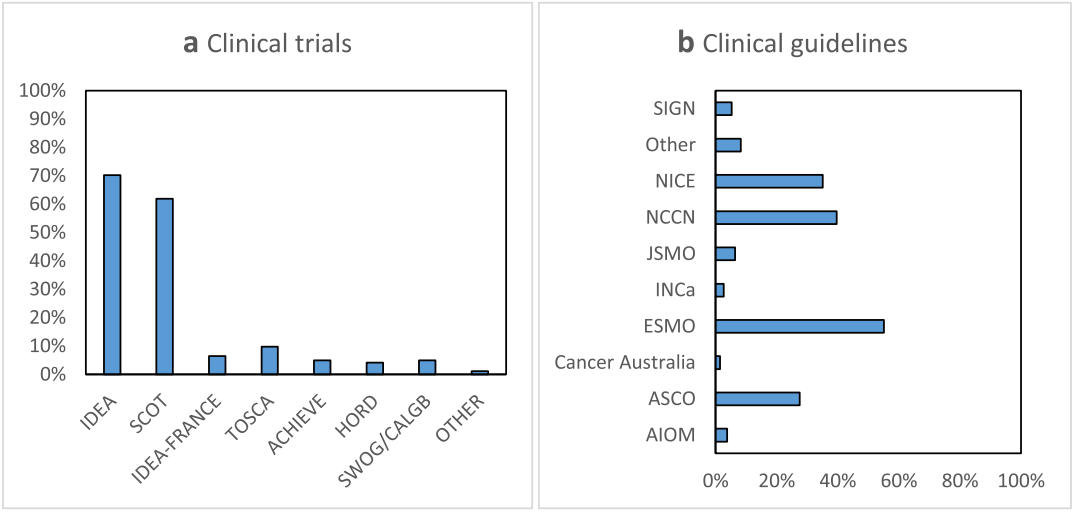

Fig. 1. Clinical trials (a) and clinical guidelines (b) named by survey respondents a) Clinicians were asked to specify which clinical trials they were aware of that had investigated the optimal duration of adjuvant chemotherapy for CRC and reported results in the previous two years, without being given a pre-specified list. Y-axis: Percentage of survey respondents. "Other" free text answers: "ACTS CC 02 trial", "SAFFA" and "Japanese trial testing 1 year of treatment but not doublet". b) Clinical guidelines names by respondents when asked which national guidelines they use to inform their practice (pre-specified list and respondents could choose more than one answer). X-axis: Percentage of survey respondents. "Other" free text answers: National Health and Medical Research Council guidelines in Australia, Danish Colorectal Cancer Group guidelines, German S3 guidelines, Greek national guidelines, Japanese Society for Cancer of the Colon and Rectum guidelines, Dutch national guidelines and guidelines from the Swedish Society of GI-Oncology. Abbreviations: SIGN, Scottish Intercollegiate Guidelines Network; NICE: The National Institute for Health and Care Excellence; NCCN, National Comprehensive Cancer Network; JSMO, Japanese Society of Medical Oncology; INCa, Institut National du Cancer; ESMO, European Society for Medical Oncology; AIOM, Associazione Italiana di Oncologia Medica .

practice change (2/19), c) their colleagues had not changed their practice (2/19) and d) they had not treated any patients yet who specifically fitted the trial criteria (1/19). The final clinician had changed their practice prior to the release of the trials' results.

In the second survey, clinicians were asked in more detail to describe if, and when, they changed their practice in response to clinical trials. Ninety-eight percent (104/106) reported practice change specifically for patients with stage III, dropping to 58% (62/106) for stage II disease. For stage III disease, the full publication of the IDEA collaboration results in March 2018 had the biggest influence on practice, whereas for stage II disease there was a more even split between the pre-specified timings provided (Figure S5).

Clinician attitudes towards using shorter treatment

In April 2019, most clinicians agreed that 3 months of CAPOX was an acceptable standard of care for patients with low-risk stage III CRC (241/265, 91%) (Fig. 2). The strongest disagreement (214/265, 81%) was with the statement that 3 months of FOLFOX was a standard of care for

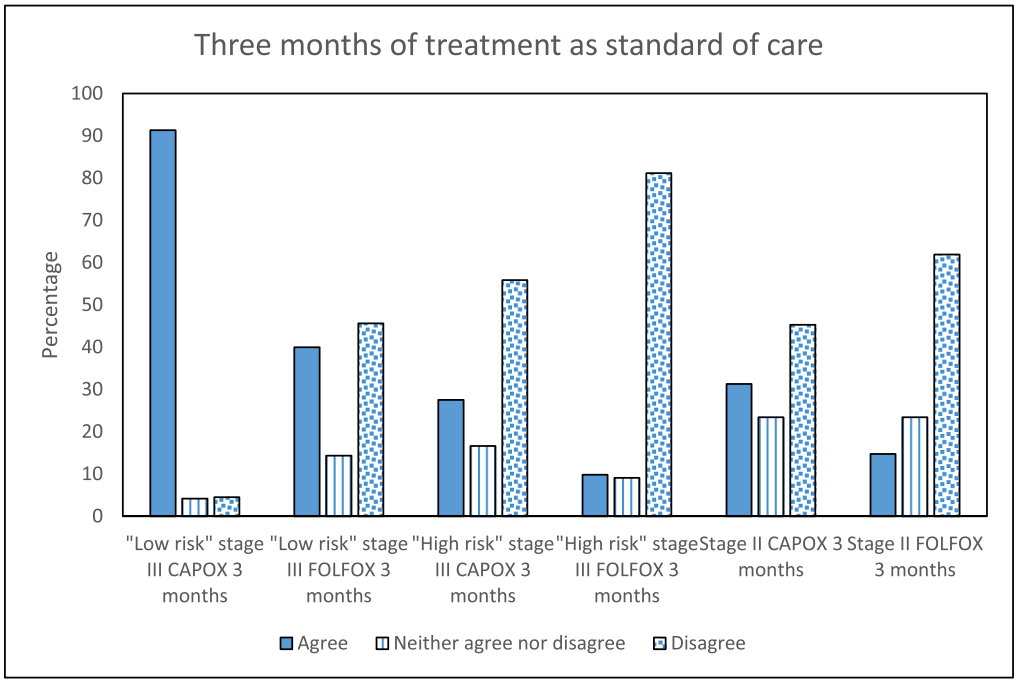

Fig. 2. Clinician agreement with statements that 3 months of doublet chemotherapy can be considered a standard of care treatment by disease stage and regimen. All patients with stage II disease assumed to have stage II disease with high-risk features if they are receiving adjuvant chemotherapy.

high-risk stage III disease. Although most clinicians disagreed with accepting 3 months of CAPOX (119/265, 45%) or FOLFOX (164/265, 62%) as a standard treatment for stage II CRC with high-risk features, approximately one quarter indicated uncertainty around these statements.

Fig. 3 demonstrates that clinician (n = 106) opinions generally remained consistent between April 2019 and August 2020. The largest changes were a shift from disagreement to agreement (13/106, 12%) that 3 months of FOLFOX could be an acceptable standard of care for patients with low-risk stage III disease, alongside an increase in agreement that 3 months of CAPOX is an acceptable standard of care for stage II disease with high-risk features. There was a corresponding rise in disagreement with 3 months of FOLFOX as a standard treatment for stage II disease.

Clinical scenarios

(i) *Patients aged under 70*

Fig. 4 shows the regimen (Fig. 4B) and duration (Fig. 4A) of treatment chosen by respondents to survey one for scenarios describing patients aged under 70. The majority indicated they used CAPOX (85%; 225/265) and 3 months (85%; 227/265) duration for patients with low-risk stage III CRC. For high-risk stage III scenarios, CAPOX was also the preferred regimen (average 67% across three scenarios) but clinicians were more likely to use 3–6 or 6 months (84%) compared to 3 months (16%). There were no significant difference in duration (^{2} p = 0.245) or regimen (^{2} p = 0.885) between the T4N1, T3N2 or T4N2 scenarios. Breaking down these results further (Supplementary Figure S6), the proportion of clinicians specifically choosing 3 months of doublet chemotherapy was 86% for the low-risk stage III scenario and on average, 16% for the three high-risk stage III scenarios.

Regarding patients with stage II MSS disease, capecitabine monotherapy was the most common regimen chosen (135/265, 51%), followed by CAPOX (72/265, 27%). Over 3 months was the preferred duration for the majority of clinicians (187/265, 71%). For the MSI-H stage II patients, active monitoring (157/265, 59%) was the preferred strategy. Focusing on potential practice change relating to the IDEA collaboration and contributory trials, in April 2019, 16% (82/529 responses) of clinicians chose 3 months of doublet chemotherapy for patients with stage II disease, 20% for MSS disease and 12% for MSI-H disease (Figure S6).

The differences in treatment choices between participants based in different locations are shown in Figure S13. Across all locations, 3 months duration was the preference for low-risk stage III disease, with over 3 months of treatment being the preferred duration for high-risk stage III disease, in particular for patients with T4N2 tumours. For stage III CRC, doublet chemotherapy was the primary regimen chosen. Clinicians from the UK, Europe and Asia preferred CAPOX for all stage III scenarios, whereas individuals from the USA and Australia preferred

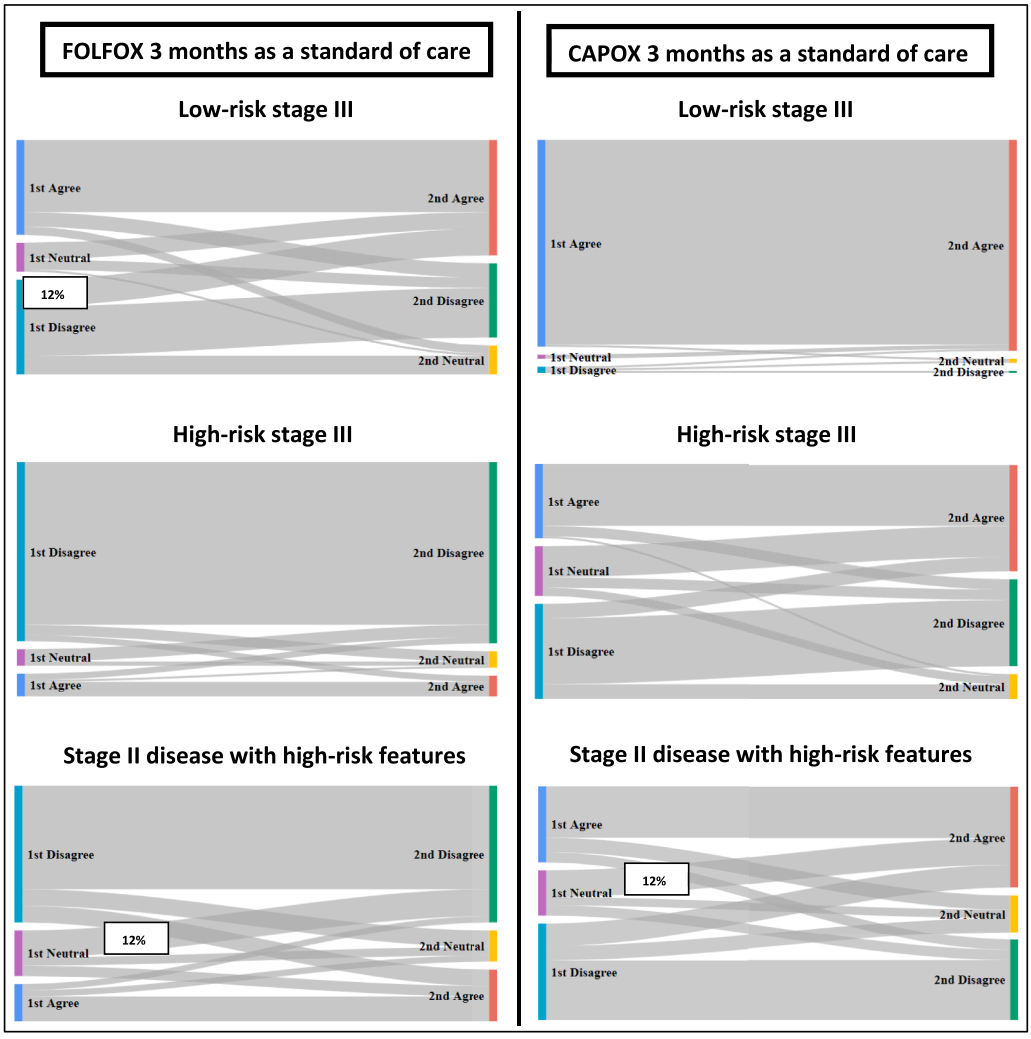

Fig. 3. Change in *individual* clinician opinions between April 2019-August 2020 for the group of clinicians who answered both surveys (n = 106). Any changes >10% are highlighted. The coloured bars within the diagrams are not significant.

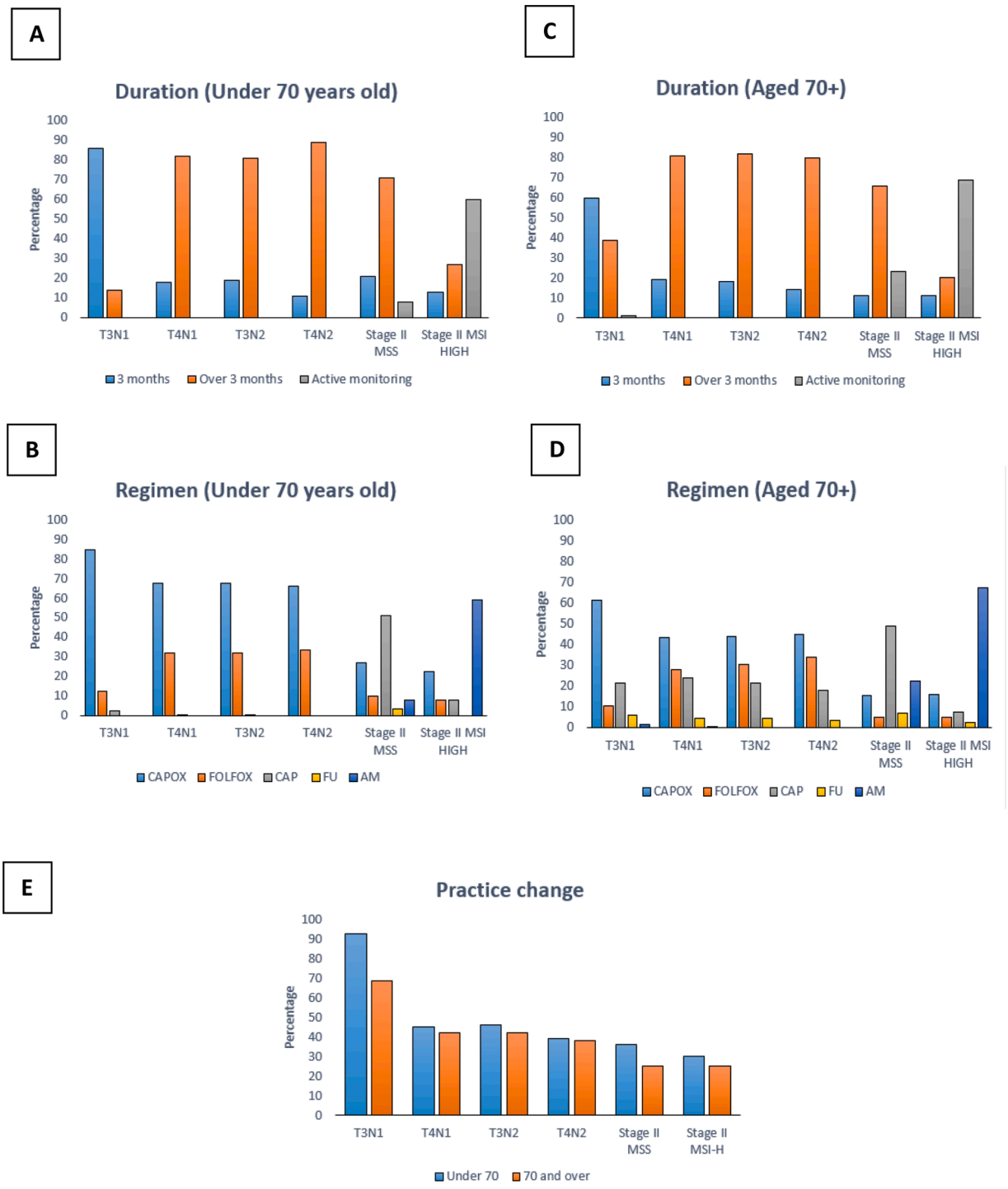

Fig. 4. Clinical scenario responses. A: Duration of treatment chosen by clinicians for six scenarios describing patients aged under 70 years. B: Regimen chosen by clinicians for six scenarios describing patients aged under 70 years. C: Duration of treatment chosen by clinicians for six scenarios describing patients aged 70 years and over. D: Regimen chosen by clinicians for six scenarios describing patients aged 70 years and over. E: Self-reported practice change in response to named clinical trials relating to the treatment choices respondents answered for the twelve patient scenarios.

CAPOX for low-risk stage III disease but FOLFOX for high-risk tumours. When treating stage II MSS, clinicians from the UK, Europe and Australia used capecitabine monotherapy most often, whereas those from the USA preferred FOLFOX and those from Asia preferred CAPOX; over 3 months of treatment was the preferred duration across locations. Stage II MSI-H patients were mainly treated with active monitoring regardless of location of the treating clinician.

(i) *Patients aged 70 and over*

The responses to the same scenarios for patients aged 70 and over (Fig. 4C/D) indicated similar overall preferences as for younger patients but more heterogeneity in the choice of regimen. Although CAPOX (163/265, 62%) and 3 months of treatment (158/265, 60%) were again the most common choices for low-risk stage III disease, fluoropyrimidine monotherapy was selected by over one quarter of respondents (71/265, 27%) versus 3% (7/265) for patients aged under 70 (Fisher's exact $p<0.001$). The same pattern was seen for the high-risk stage III scenarios, with fluoropyrimidine monotherapy chosen by 25% of clinicians

(200/795 responses over three scenarios). For stage II MSS and MSI-H disease, active monitoring was used more often than for younger patients (MSS: 22% vs 8%, ^{2} $p<0.001$; MSI-H: 68% vs 59%, ^{2} $p<0.047$). Overall, the proportion of clinicians choosing 3 months of doublet chemotherapy was 54% (143/265) for low-risk stage III disease and on average 15% (123/795 responses) for the three high-risk stage III scenarios. In total 9% of clinicians (49/530 responses) chose 3 months of doublet chemotherapy for stage II scenarios, 8% (22/265) for MSS disease and 10% (27/265) for MSI-H disease (Figure S7).

The differences in practice for respondents from distinct locations for these scenarios describing patients aged 70 and over are show in Figure S14 in the Supplementary material. As for scenarios describing younger patients, there was a strong preference for CAPOX for all stage III scenarios from clinicians in Asia and the UK, and a preference for FOLFOX rather than CAPOX for those from Australia and the USA. There was a more equal distribution of responses between CAPOX and FOLFOX for respondents from Europe compared to scenarios describing younger patients, where the preference was for CAPOX. For stage II disease, any differences in preferences between locations were similar to those described for younger patients.

(i) *Extent of practice change*

Clinicians indicated if their treatment preferences for the twelve scenarios represented a change in practice attributable to the clinical trials they had named. Fig. 4E demonstrates that the extent of change in practice aligned with the preference for 3 months of doublet treatment: highest for low-risk stage III disease, lowest for stage II disease and higher across all scenarios for younger patients. Respondents were also asked how representative their responses to the scenarios would be if the patients specifically had a diagnosis of rectal cancer. In total, 243/265 (92%) of clinicians confirmed that they treat patients with rectal cancer and 140/243 (58%) indicated they use the same management strategies for rectal cancer patients as they chose for the twelve patients' scenarios.

(i) *Change in practice over time*

When presented with the same clinical scenarios in August 2020, the biggest change in individual clinician choice ($n = 106$) compared to April 2019 was an increase (24%, 50/212) in the use of 3 months of treatment for patients with stage III disease with one high-risk feature (T4 or N2) (Fig. 5B). There was a corresponding switch by 12% (26/212 responses) from using FOLFOX to CAPOX for the same scenario. A similar but less frequent switch was seen for the T4N2 scenario with 10% of clinicians shortening duration of treatment and 9% switching from FOLFOX to CAPOX. A breakdown of responses for high-risk scenarios by location of respondents is outlined in Table S4. For patients with T4 or N2 disease, the majority (55%) of UK clinicians chose shorter treatment (3 months), whereas over 3 months of treatment was the preference for those from other locations. CAPOX was the preferred regimen for all locations except the USA. For scenarios describing patients with T4N2 disease, the preference for longer treatment was demonstrated across all locations. Regimen preferences according to location remained unchanged from scenarios with one high-risk feature. Changes in individual treatment choices were similar for scenarios describing older patients (Figure S7).

It was not possible to compare stage II responses between the time-points because of the separation of scenarios to differentiate T3 and T4 disease in the second survey. The responses from August 2020 however did highlight the influence of tumour stage in dictating treatment choices (Figure S8). For patients with T3N0 MSS disease, clinicians in 2020 were significantly more likely to use active monitoring (28% versus 4%, Fisher's $p<0.001$) and less likely to use 3 months of doublet chemotherapy (16% versus 34%, Fisher's $p = 0.004$) compared to T4N0 MSS disease. For MSI-H disease, in both April 2019 (67%) and August 2020 (90% T3 and 55% T4), active monitoring was the preferred management strategy irrespective of T stage. CAPOX for 3 months was the second most common treatment choice for MSI-H stage II disease at both time-points (10% in 2019 and 27% (T4N0)/8% (T3N0) in 2020). Similar treatment patterns were chosen for patients aged 70 and over

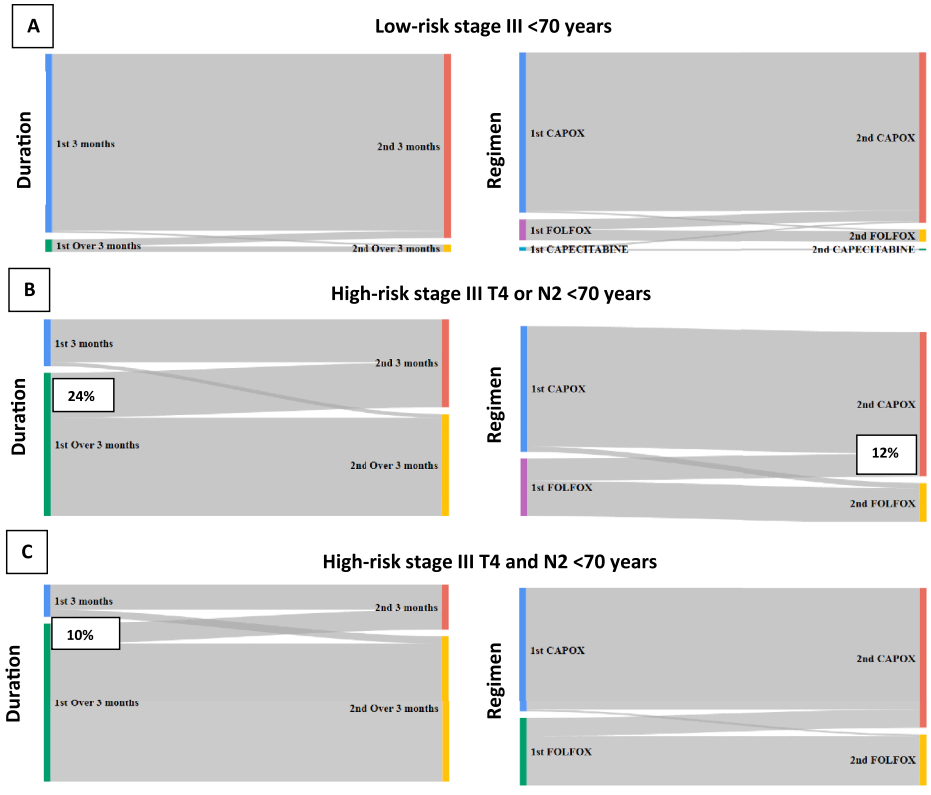

Fig. 5. Switch in individual treatment choices for scenarios describing patients with stage III disease aged under 70. The left side of each graph displays the treatment choices in April 2019. The right side of the graphs depict the treatment choices for the same group of clinicians ($n = 106$) in August 2020. If an individual has changed their choice this is shown by a diagonal, rather than straight connecting grey line. Changes relevant to 10% or more clinicians are highlighted. The coloured bars within this diagram are not significant.

(Figure S9)

The impact of the COVID-19 pandemic

The treatment choices of clinicians that answered the second survey based on clinical trial evidence alone and choices from the same clinicians accounting for changes due to the pandemic were compared. There were no significant ($p<0.05$) enduring changes in practice due to the COVID-19 pandemic for any of the patient scenarios/treatment choices.

Additional questions

In the second survey, additional questions explored clinician practice in more detail. Overall, 72% (76/106) of respondents indicated they used the post-hoc stage III risk stratification identified by the IDEA collaboration and contributory trials when making treatment choices; 34% (26/76) indicated they sub-divide this stratification further. More clinicians indicated they used doublet chemotherapy for treating stage II disease irrespective of age after the results of the IDEA collaboration were known compared to prior to the dissemination of the IDEA findings (Figure S11).

A minority of respondents indicated they never used doublet chemotherapy for patients with stage II disease (16% (17/106) for patients aged under 70, 29% (31/106) for patients aged 70+). Clinicians were asked if they ever intentionally prescribe 3 months of fluoropyrimidine monotherapy and 22% (23/106) indicated they use this treatment strategy.

Finally, the majority (92%, 98/106) of respondents reported they use biological rather than chronological age when treating patients aged 70 years and over and when asked to estimate the proportion of patients they treat that are able to continue working full time during treatment there was a large spread of answers (Figure S12).

Discussion

A critical aim of clinical cancer research is that clinical trial findings lead to real world health benefits. For this health impact to occur, clinicians must conclude that trial findings indicate or confirm a novel treatment approach compares favourably to standard care, they must change their practice in line with trial results and be free to do so within the institutional constraints in which they practice. This study has provided clear evidence that a large sample of practising clinicians are aware of the findings of the IDEA collaboration and contributory trials and have changed their practice in response to those findings. It has previously been estimated that it takes an average of eight years for cancer research findings to influence clinical guidelines [16], an impact which one might assume pre-dates practice change. This study showed that in April 2019, one year after the IDEA collaboration results were published in full, medical professionals had already changed their practice, even before many of the guidelines they use had been updated.

The change in practice was not exhaustive for all patients treated in the adjuvant setting. These trials had a bigger impact on prescribing for stage III disease, and in particular for patients with low-risk stage III disease. When deciding to investigate the change in practice at two timepoints, it was hypothesised that the acceptability of 3 months duration of treatment may increase given that maturation of results revealed little clinical difference survival outcomes between 3 versus 6 months of treatment [4]. Indeed, there was a small shift in attitudes that aligned with the new data that was published during the intervening period. For example, the increase in clinicians accepting 3 months of CAPOX for stage II and the decrease in those considering 3 months of FOLFOX as a standard of care treatment for stage II aligned with the subgroup analysis from stage II IDEA, disseminated at ASCO in June 2019 [1]. There was also a rise in clinicians agreeing that 3 months of FOLFOX was acceptable for low-risk stage III disease, in line with updated IDEA results which confirmed a minimal difference in 5 year OS between these treatment arms [3]. Despite this change, in the 2020 survey, a small minority of clinicians chose 6 months of doublet chemotherapy as their first choice for managing patients with low-risk stage III disease despite clinical[4] and health economic evidence[17] indicating minimal OS difference yet much improved toxicity and better cost-effectiveness from shorter treatment.

Clinicians indicated they were less likely to have changed practice for patients with stage II disease. The stage II IDEA findings published in abstract form aligned closely with results for the stage III population [1], therefore, the reduced uptake of study results into practice may reflect a lower use of doublet chemotherapy in this setting rather than the strength of this trial evidence. Indeed, in the August 2020 survey, some clinicians indicated they never used doublet treatment for patients with stage II disease. The avoidance of doublet chemotherapy in this context may be influenced by the results of previous trials, such as the subgroup analysis from the Multi centre International Study of Oxaliplatin/-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study which failed to confirm an overall survival advantage from adding oxaliplatin to fluorouracil specifically for stage II patients [18].' [19]

Our study has shown that patients with stage II MSI-H disease, regardless of age, are more likely to be offered doublet treatment or avoid adjuvant therapy altogether. This aligns with the results of previous clinician surveys, [20] and strengthens the case for ensuring this information is available to clinicians at the time of decision making. It also indicates that recent trials investigating shorter duration of doublet treatment are specifically more likely to influence prescribing for MSI-H rather than MSS stage II disease for which proportionally, doublet chemotherapy is used less. Overall, there was more heterogeneity in treatment approaches and more uncertainty regarding the acceptability of using 3 months of doublet chemotherapy for stage II compared to stage III CRC. This highlights an opportunity for clinicians to improve certainty in this area by increasing dialogue around the approach to treatment of this group. It also may encourage clinician trialists responsible for the stage II IDEA collaboration to focus on dissemination, and interpretation of those results in the context of previous trials assessing the merits of using doublet treatment in this patient cohort.

The extent of self-reported practice change in response to recent trials was less for older versus younger patients, concurring with results from a survey of French clinicians ($n = 213$) [12]. Reduced impact on practice for older patients is likely to again reflect the less frequent use of doublet chemotherapy for older versus younger patients generally. This may be due in part to previous individual and pooled trial subgroup analyses showing a lack of benefit from adding oxaliplatin to fluoropyrimidine for older patients, [18]' [19]' [21] although there are reports that some benefit of oxaliplatin may be maintained in older the older age group [22-24]. An age cut-off of 70 years was chosen for the practicalities of survey development, but the vast majority of clinicians indicated they use biological rather than chronological age when making treatment decisions. Therefore, it is acknowledged that clinicians are unlikely to alter their practice across such a strict age cut off in real life. This reflects the difficulty with making any treatment decisions based on age alone and explains why most national guidelines from professional bodies (NCCN, ESMO, ASCO) do not mention age. Recently updated NICE CRC guidelines do mention that age is taken into consideration but do not give direction on how this may specifically affect treatment choices [25]. In the second survey, a minority of clinicians indicated they intentionally use 3 months of adjuvant fluoropyrimidine monotherapy in some circumstances. The SAFFA trial [27] compared 3 months of protracted venous infusion 5-fluorouracil against 6 months of bolus 5-FU/leucovorin in patients with stage II/III CRC and showed there was no OS difference between the treatment arms. This strategy has not yet been tested using modern infusional regimens, such as modified deGramont, in both arms, nor with the orally administered drug capecitabine. Further investigation into clinician opinion would be helpful to understand the decision making process of those who

routinely use 3 months of monotherapy; for example are they considering and applying just the results of the SAFFA trial, are they extrapolating the results of the IDEA collaboration, or are they using the results from both trials simultaneously to inform treatment choice.

Treatment preferences differed by location and our results support those from a previous study by Iveson and colleagues[26]. Specifically, there was a preference for using CAPOX rather than FOLFOX treatment in the Europe and Asia, in particular for high-risk stage III disease, whereas the reverse was true for clinicians from Australia and the USA. As in the survey by Iveson et al.[26], there was low representation in this study from European clinicians from France and Italy. Given that clinicians demonstrated a preference for FOLFOX rather than CAPOX when recruiting to the IDEA-France and Italian TOSCA trial, higher numbers of survey respondents from these locations may have altered the European preference for CAPOX. Also aligning with the results from the previous survey[26], European, and in particular UK clinicians in our study, were more likely than those from other locations to change practice to use 3 months of treatment across the stage III scenarios.

The COVID-19 pandemic undoubtedly influenced chemotherapy prescribing during the first peak [28].' [29] Encouragingly, our study shows that, if dependant on clinician preference alone and not constrained by institutional policies, there are unlikely to be significantly enduring changes due to COVID-19 going forward that differ from practice decisions based on clinical trial evidence alone.

Finally, we asked an exploratory question to garner estimates from clinicians about the impact of adjuvant treatment on patients' ability to return to work, in the hope that this may provide insight into the potential societal impact that shortening the duration of adjuvant CRC treatment may have on productivity. This question showed a wide range of answers; either the range of patients continuing to work is truly heterogeneous across different locations or this is unknown and difficult to estimate for clinicians. A "don't know" option was not included. Prospective surveys of patients themselves could be used to explore this issue.

There are limitations to this study, some of which are inherent to survey methods. This study surveyed a sample of clinicians, so there may be response bias, where respondents may have been more engaged with research, more likely to be aware of trial findings and more motivated to change practice compared to non-responders. The study did not focus specifically on rectal cancer patients and how treatment decisions may vary compared to colon cancer; so this may warrant further investigation. There were four separate patient scenarios for each patient age group with stage III disease used in these surveys, however there are 16 possible combinations of stage III disease dependant on T and N stages, with differences in survival between each combination [30]. In a real world setting treatment choices may be diluted based on patient, disease and other external variables. For this reason, an analysis of actual prescribing records could be a stronger indicator of current overall practice, although this would not give insights into clinicians' decision-making processes. Lastly, larger and more even numbers of respondents from different locations would have made any between country comparisons more reliable.

In conclusion, the IDEA collaboration and contributory trials have impacted on clinician attitudes and changed self-reported practice. Across several countries, CRC patients are now being offered shorter durations of adjuvant treatment, leading to the health benefits of less toxicity whilst maintaining survival gains. Trial sub-group analyses, as well as pre-existing attitudes towards using doublet chemotherapy in certain disease/patient scenarios (stage II/aged 70+) have influenced the proportion of patients who will be affected by the IDEA collaboration and contributory trial findings. It is likely that chemotherapy prescribing will have been significantly affected during the first peak of the COVID-19 pandemic, but based on our survey, we found that the pandemic is unlikely to have a significant enduring impact on practices relevant to this patient cohort. The results of this study will show clinicians how their colleagues in different countries are interpreting and applying trial results and will add to the dialogue regarding adjuvant treatments delivered in real world settings and the approaches that should be used as the control arm for clinical trials for patients with CRC going forward.

Ethics approval and consent to participate

University of Glasgow Medical and Veterinary and Life Sciences Ethics Committee (Ref: 200,180,056)

Respondents indicated their consent to proceed in the initial part of the survey.

Consent for publication

Respondents were made aware of the plans to publish results when they consented to participate.

Availability of data and materials

NA

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2021.100445.

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