Highlights

- The differences in DFS between left and right colorectal tumours were investigated in patients recruited to the SCOT study
- Right sided colorectal tumours have a worse DFS compared to left sided tumours
- Tumour sidedness did not impact upon outcomes for 3 months vs. 6 months adjuvant oxaliplatin based chemotherapy

Original Study

SCOT: tumour sidedness and the influence of adjuvant chemotherapy duration on disease free survival (DFS)

Authors:

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ABSTRACT

Aim: Patients with loco-regional right-sided colorectal tumours have a worse overall survival (OS). Here we investigate the difference in DFS between colorectal patients with right and left sided tumours in the SCOT study.

Methods: The SCOT study showed 3-months of oxaliplatin-containing adjuvant chemotherapy (OxFp) is non-inferior to 6-months for patients with stage III and high-risk stage II colorectal cancer. We divided the cohort into patients with left and right sided tumours, and evaluated the effect on DFS and the principle 3 vs 6-months analysis.

Results: 6088 patients with Stage III/high risk Stage II colorectal cancers were randomised between 27th March 2008 and 29th November 2013 from 244 centres internationally. In February 2017 (3-years FU) information on sidedness was available for 3309 patients (1238 R-sided, 2071 L-sided). Patients with right-sided tumours had a significantly worse DFS (3-year DFS right: 73.3% (se = 1.3%), left: 80.2% (se = 0.9%) HR 1.423 (95% CI 1.237-1.637; p < 0.0001). Adjusting for T and N-stage reduced the HR to 1.230 (95% CI 1.066 – 1.420, p = 0.005). The data did not suggest that sidedness affected the impact of chemotherapy duration on 3-year DFS (R: HR 1.024 (0.831 -1.261), L: HR 0.944 (0.783-1.139)). Test for heterogeneity, p = 0.571. Further sub-set analysis was limited due to cohort size.

Conclusions: This is the first study to show that unselected patients with right-sided tumours had a worse DFS compared to left-sided tumours. Tumour sidedness did not impact upon the 3-months v 6-months comparison in SCOT.

MICROABSTRACT

3-years FU information from the SCOT study showed that unselected patients with right-sided tumours had a worse DFS compared to left-sided tumours. (3-year DFS right: 73.3% (se = 1.3%), left: 80.2% (se = 0.9%) HR 1.423 (95% CI 1.237-1.637; p < 0.0001). Tumour

sidedness also did not impact upon the 3-months v 6-months comparison in SCOT (R: HR 1.024 (0.831 -1.261), L: HR 0.944 (0.783-1.139)).

Keywords: SCOT, adjuvant chemotherapy, sidedness

INTRODUCTION

The SCOT study is an international, randomised, phase 3 trial that showed non-inferiority for 3 months of oxaliplatin-containing chemotherapy compared to 6 months for Stage III and high-risk Stage II colorectal cancer[1]. This is a cost-effective approach that also reduces patient toxicity [2]. The SCOT trial yields a substantial, unique data-set representative of adjuvant treatment in colorectal disease. The International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration pooled the results of this study with 5 randomised, phase III trials to establish 3 months adjuvant CAPOX as a new standard for most patients [3]. The IDEA collaboration did not show statistically significant non-inferiority, however the absolute difference in 5 year overall survival was 0.4% and therefore 3 months adjuvant treatment is now recognised as a treatment option in clinical practice [4].

Colorectal cancer is the fourth most common cancer internationally. Historically, colon and rectal cancers are considered distinct disease groups. However, as our knowledge continues to evolve in the era of personalised targeted medicine there is a greater need to accurately classify and group malignancies. This is of particular importance in the trial setting as we define the stage for future advances. The left side of the colon may be considered to extend from the splenic flexure to the rectum. This is derived from the hindgut embryologically and receives blood from the inferior mesenteric artery. The right side of the colon is formed from the embryological midgut and supplied by the superior mesenteric artery. Previous attempts to define ‘tumour sidedness’ vary in the literature, and some ambiguity relates to the transverse colon [5]. Right sided tumour location is well established as both a negative

predictive and prognostic predictor in the metastatic setting with distinct genetic and phenotypic traits. Right sided cancers typically present in older females at a more advanced stage. They are known to have a distinctive appearance endoscopically compared with left sided cancers. The microbiome is recognised as increasingly central in the aetiology and treatment of colorectal disease and varies significantly among right and left sided malignancies. Right sided tumours characteristically demonstrate greater BRAF mutations and microsatellite instability while left sided tumours express greater chromosomal instability [5].

Right sided tumours consistently demonstrate poorer prognosis in the metastatic setting with statistically significant differences in PFS and OS [5]. KRAS WT tumours right sided tumours are predicted to respond poorly to EGFR targeted therapy, independent of known prognostic features associated with right sided tumours (i.e. stage), while bevacizumab demonstrates greater efficacy among patients with right sided tumours [6]. In the adjuvant setting, randomised clinical trial data and meta-analyses have demonstrated statistically worse OS, particularly among Stage III patients with right sided tumours [7]. However, to our knowledge, no data has demonstrated a statistically significant difference in DFS in a randomised controlled trial. Here we use the data generated as part of the SCOT trial to evaluate the differences in right and left sided tumours in terms of their DFS with 3 or 6 months of adjuvant oxaliplatin-based chemotherapy.

METHODS

The methods used to conduct the SCOT trial have previously been described [1]. To summarise, SCOT is an international multi-centre non-inferiority trial comparing 3 months and 6 months of adjuvant chemotherapy in high risk Stage II and Stage III colorectal cancer

patients. Patients were allowed either FOLFOX or CAPOX based on physician discretion and patient choice. The primary outcome was disease free survival over 3 years.

Patients required a clear staging CT thorax, abdomen and pelvis scan and a CEA level below 1.2 times the upper limit of normal prior to commencing treatment. Treatment began within 2 weeks of enrolment and patients were recruited within 11 weeks of surgery. Patients were also required to have a World Health Organisation Performance status of 0 or 1 with adequate end organ function and life expectancy greater than 5 years from non-colorectal cancer related co-morbidities.

Data on tumour sidedness was not recorded at randomisation but was subsequently collated from pathology reports. Right sided tumours were defined as those arising the caecum, ascending and transverse colon. Left sided tumours included all cancers distal to and including the splenic flexure.

Statistical Analysis

SCOT was designed as a non-inferiority trial aimed at excluding a maximum 2·5% reduction in three year DFS for patients on the three month treatment arm (from 78% on six month arm; this corresponds to a hazard ratio(HR) of 1·13) with 90% power at the 2·5% 1-sided level of statistical significance and recruited 6088 patients. This subset analysis includes the 3309 patients with data on tumour sidedness.

The comparison of disease-free survival between the tumour sidedness groups was based on unadjusted and adjusted Cox regression models. The HRs associated with the tumour sidedness groups were derived from these models along with the associated 95% CIs and p-values. Kaplan-Meier techniques were used to plot disease-free survival. The p value for heterogeneity was derived from a comparison of the log-likelihoods of a model with separate terms for the effect of duration within each tumour sidedness category with the

model with a single overall term. The aim of this analysis was to establish whether the impact of treatment duration varied across these patient subgroups.

Chi-square tests of association and for trend, and the Mann-Whitney U test were used for the comparison of categorical variables.

To adjust for multiple testing, the false discover rate (FDR) was calculated using the p.adjust function in R (http://www.r-project.org) [8] The p value threshold for statistical significance was 5% after adjustment.

RESULTS

6088 patients were recruited and randomised to the SCOT trial between March 27th 2008 and November 29th 2013. Pathology reports to determine tumour location were available on 3,309 patients as of January 2020. 2,419 patients (73.1%) were under the age of 70 and 890 (26.9%) were 70 years or over. In total there were 2,071 patients with left sided tumours (62.6%) and 1,238 patients with right sided tumours (37.4%). The median age of patients with right and left sided tumours were both 66 and 64 years respectively. A larger proportion of patients with left sided tumours were under the age of 70 (75.7%) compared with right sided tumours (68.6%) ($p<0.01$). A greater proportion of males were diagnosed with left sided tumours 65.4% ($p<0.01$) compared with females 55.6% ($p<0.01$). This data is summarised in table 1.

There were significant differences observed in the tumour size and differentiation between left and right sided tumours (Table 2). The median size for right sided tumours was 4.5cm compared to 3.5cm for left sided tumours ($p<0.001$). A larger portion of right sided tumours were T4 (41 vs. 24%, $p<0.001$). 20.2% of right sided tumours were poorly differentiated compared with 8.8% of left sided tumours of the 3,236 tumours evaluated ($p<0.001$) (See Table 2).

Extramural vascular invasion (EMVI) status is available for 3,186 patients. It was positive in 1,475 specimens (46.3%). The proportion of left sided and right sided tumours exhibiting EMVI was equivalent (left (46.8%) and right (45.5%) p=0.466). 488 tumours demonstrated perineural infiltration (PNI). Of these, 155 were right sided and 333 left sided with no statistically significant difference seen between both groups (p=0.353).

The number of involved nodes ranged from 0-27 among left sided and 0-42 with right sided tumours. There was no difference in the number of involved nodes between right and left sided tumours (p=0.948). Nodal involvement was similarly well-balanced among left and right sided tumours staged as Dukes C2.

Analysis reveals there is no statistical benefit for extended treatment among patients with six or more (p=0.310) or eight or more (p=0.412) nodes involved. There was also no statistically significant advantage of 6 months of treatment for patients with Dukes C2 tumours compared to C1 tumours (p=0.496). Patients with EMVI did not statistically benefit from 6 months of chemotherapy (p=0.681). However, there was a trend for patients with T4 / N2 disease and also EMVI to benefit from a longer course of chemotherapy, but again this was not statistically significant (p=0.069). Patients with larger tumours did not statistically benefit from 6 months of chemotherapy (p=0.739).

There were no statistically significant differences in toxicity outcomes between left and right sided tumours (Table 3). Sensory neuropathy was the only toxicity that approached statistical significance (p=0.058) (Table 4). This is prior to adjustments for the effect of carrying out multiple statistical tests and remains non-significant (p=0.746). 694 patients reported sensory neuropathy and of these 412 patients had left sided tumours (59.4%). However only 27 patients (6.6%) had G3 or greater toxicity among patients with left sided tumours compared with 16 with right sided tumours (5.67%) [Table 2].

Patients with R-sided tumours had a significantly worse DFS (3-year DFS right: 73.3% (se = 1.3%), left: 80.2% (se = 0.9%) HR 1.423 (95% CI 1.237-1.637; p < 0.0001). Adjusting for T and N-stage reduced the HR to 1.230 (95% CI 1.066 – 1.420, p = 0.005). The data did not suggest that sidedness affected the impact of chemotherapy duration on 3-year DFS (Figure 1)(R: HR 1.024 (0.831 -1.261), L: HR 0.944 (0.783-1.139)). Test for heterogeneity, p = 0.571.

DISCUSSION

Our results demonstrate patients with Stage II and Stage III right sided colorectal tumours have a poor prognosis with a statistically significant worse 3-year DFS. There is a significant body of work that demonstrates primary tumour location is a prognostic biomarker in colon cancer. Metastatic colorectal cancer originating in the right colon consistently demonstrate worse prognosis and OS [9]. Although right sided colorectal tumours are associated with known poor prognostic factors such as age, sex, stage and differentiation etc. primary tumour location is still a proven independent prognostic factor [7][10].

Left sided malignancies by contrast demonstrate better prognosis. Boeckx and colleagues carried out a retrospective analysis of two panitumumab trials (PRIME and PEAK) in metastatic colorectal cancer. They report a worse prognosis among right sided tumours regardless of the first-line treatment received and left sided RAS WT tumours derived the greatest benefit from panitumumab-containing treatment [11]. A further pooled retrospective analysis of patients with RAS WT metastatic colorectal cancer in six randomised trials reported by D Arnold et al. demonstrates a better prognosis among patients with left sided tumours. Left sided tumours also demonstrate a greater benefit from the addition of EGFR antibody therapy [7].

Chemotherapy still forms the backbone of colorectal cancer adjuvant and palliative treatment. There are several heterogenous phenotypical and mutational characteristics

among this cohort of patients that have long held the potential to influence future management.

The right side of the gut is embryologically distinct from the left side. The gut microbiota and associated immunogenicity; a balance of the immune system and commensal flora, reflects this. We understand there are three main oncogenic pathways generating colon cancers; chromosomal instability, microsatellite instability and CPG island methylator phenotype. These distinct processes also vary between right and left sided tumours and is likely a reflection of these phenotypic differences [5][12].

Right sided tumours are associated with a high-grade histology, CpG island methylation, BRAF mutations and increasingly significant deficient DNA mis-match repair (MMR) and the expression of this; Micro-satellite instability (MSI). Left sided tumours more commonly feature p53 and APC mutations coupled with overexpression of EGFR and VEGF-1 [5].

In locoregional colorectal cancer, right sided tumours are also associated with a poorer prognosis. The GISCAD group produced the largest pooled analysis of primary tumour location as a prognostic biomarker in the adjuvant treatment of colon cancer. The multivariate analysis did not demonstrate a statistically significant difference in disease free survival between left and right sided colorectal tumours. However, there was a significant association with overall survival with a HR:1.37 (95% CI=1.14-1.62, $p<0.001$). Subgroup analysis only revealed a demonstrable difference in overall survival among Stage III malignancies [13]. Several studies have demonstrated an increased mortality rate among Stage III right sided colon tumours although there is a diminished effect among stage II tumours, suggestive even of a worse mortality among left sided tumours [14][15].

Weiss et al. analysed the outcomes of patients registered on the SEER database with stages I to III primary adenocarcinoma of the colon who underwent surgery and demonstrated no

statistical difference in 5-year mortality. However, they did note right sided malignancies carry a higher mortality among Stage III patients, but a lower mortality among Stage II patients [15]. A similar analysis performed by Brungs et al. using the New South Wales Clinical Cancer registry demonstrates right sided colon cancer is associated with a higher all-cause mortality in Stage III disease only [16].

The SCOT trial is the first study to our knowledge to demonstrate patients with right sided colorectal tumours have a worse 3-year DFS compared to left sided tumours in an unselected adjuvant cohort. Thus, worse overall survival among patients with right sided tumours may be due to earlier recurrence as well poor survival after relapse. The left and right sided tumour cohorts were well balanced for nodal involvement, EMVI and PNI, although as is consistent with other studies – right sided tumours were larger and more poorly differentiated. The primary tumour location did not predict treatment toxicity as was expected. The original SCOT data demonstrated equivalent 3-year DFS of 3 months of oxaliplatin-based chemotherapy compared to 6 months in patients with high-risk Stage II and stage III disease. The findings from this paper and IDEA collaboration suggested a trend for patients with T4 and N2 disease to benefit from 6 months of treatment. However, even though we have shown that right-sided tumours have a statistically worse 3-year DFS, there was no benefit of an extended course of chemotherapy. The conclusion of the SCOT trial was that 3 months of oxaliplatin-containing adjuvant chemotherapy was non-inferior to 6 months of the same therapy for patients with high-risk stage II and stage III colorectal cancer and was associated with reduced toxicity and improved quality of life. Sidedness does not change this recommendation and we should continue to recommend 3 months of oxaliplatin-based chemotherapy for the majority of patients, whether their tumour originates from the left or right sided of the colon.

Table 1 – Patient demographics

		Left Sided Tumours (n=2071)	Right Sided Tumours (n=1238)
		n (%)	n (%)
Gender (p<0.001)	Female	717 (55.6%)	572 (44.4%)
	Male	1354 (67.0%)	666 (33.0%)
Age (p<0.001)	<70	1567 (64.8%)	852 (35.2%)
	≥70	504 (56.6%)	386 (43.4%)
		Median (IQR*)	Median (IQR*)
		64 (58 – 69)	66 (60 – 71)
Stage II		359	267
Stage III		1712	971
3 months arm		1042	629
6 months arm		1029	609

* Interquartile range

Table 2 – Tumour characteristics

	Left Sided Tumour Cohort	Right Sided Tumour Cohort	p-value
Number of nodes ([Median (range)]	17 (1-86)	19 (1-69)	p<0.001
Number of Involved nodes	2 (0-27)	2 (0-42)	p=0.948
Size (median)	3.5cm	4.5cm	P<0.001
T Stage			P<0.001
T1	87 (4.2%)	13 (1.1%)	
T2	238 (11.5%)	60 (4.8%)	
T3	1250 (60.4%)	661 (53.4%)	
T4	496 (23.9%)	504 (40.7%)	
Differentiation	(n=2022)	(n=1214)	P<0.001
Poor	178 (8.8%)	245 (20.2%)	
Well/ moderate	1884 (91.2%)	969 (79.8%)	
EMVI	(n=1983)	(n=1203)	P=0.466
Yes	928 (46.8%)	547 (45.5%)	
No	1055 (53.2%)	656 (54.5%)	
PNI (488 PNI +)	333 (68.2%)	155 (31.8%)	P=0.353

Table 3 - Toxicity Outcomes: Adverse events affecting 5% or more of patients at Grade 2 or above

Toxicity	Left Sided Tumour Cohort (n=412)	Right Sided Tumour Cohort (n=282)	p-value	p-value (adjusted)
	n (%)	n (%)		
Anaemia Missing: n = 3 (2 Left, 1 Right)	23 (5.6%)	17 (6.0%)	0.286	0.746
Anorexia Missing: n = 9 (5 Left, 4 Right)	28 (6.9%)	24 (8.6%)	0.750	0.898
Diarrhoea	124 (30.1%)	80 (28.4%)	0.434	0.898
Fatigue	149 (36.2%)	107 (37.9%)	0.749	0.898
Hand-Foot Syndrome	37 (9.0%)	19 (6.7%)	0.744	0.898
Mucositis	26 (6.3%)	15 (5.3%)	0.922	0.959
Nausea	72 (17.5%)	45 (16.0%)	0.760	0.898
Neuropathy	128 (31.1%)	76 (27.0%)	0.058	0.746
Neutropenia	57 (13.8%)	35 (12.4%)	0.959	0.959
Taste Alteration Missing: n = 10 (6 Left, 4 Right)	25 (6.2%)	27 (9.7%)	0.157	0.746
Thrombocytopenia Missing: n = 4 (3 Left, 1 Right)	17 (4.2%)	10 (3.6%)	0.259	0.746
Vomiting	38 (9.3%)	23 (8.2%)	0.514	0.898

Missing: n = 4 (3 Left, 1 Right)				
Pain	**20 (4.9%)**	**8 (2.8%)**	**0.287**	**0.746**

Table 4 – Toxicity outcomes: Sensory neuropathy breakdown

Neuropathy Grade	Left Sided Tumour Cohort (n=412)	Right Sided Tumour Cohort (n=282)
G0	**55 (13.3%)**	**55 (19.5%)**
G1-2	**330 (80.0%)**	**211 (74.8%)**
G3-4	**27 (6.6%)**	**16 (5.7%)**

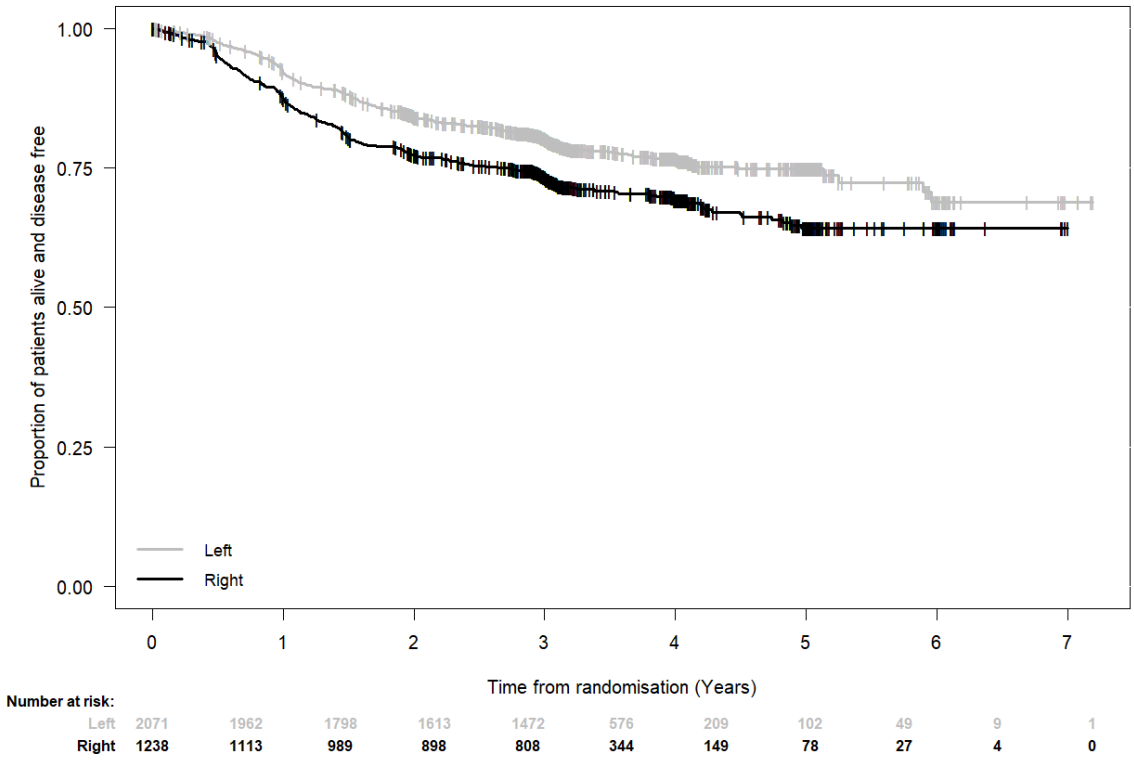

Figure 1 – Kaplan-Meier plot of disease-free survival DFS by sidedeness

Disclaimers

Nil

Ethical approval

This study was approved by the West Glasgow Research Ethics Committee (version 1.1 of the protocol) on 21st January 2008 and all subsequent amendments approved by the Committee (where required). REC reference number: 07/S0703/136.

Author Contribution Statement

Mark P. Saunders: Conceptualization, methodology, investigation, resources, writing – original draft, visualization, supervision.
Rohan Iype: Methodology, investigation, writing – original draft, visualisation.
Caroline Kelly: Conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing – review and editing, visualisation.
Jana Crosby: Investigation, resources, data curation, writing – review and editing.
Rachel Kerr: Conceptualization, methodology, investigation, resources, writing – review and editing.
Andrea Harkin: Software, data curation, writing – review and editing, project administration, funding application.
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Timothy Iveson: Conceptualization, methodology, investigation, resources, writing – review and editing.
Noori Maka: Investigation, resources, data curation, writing – review and editing

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.

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

Mark P. Saunders has received fees for meetings, travel and lectures from Servier, Amgen and Merck in the last 5 years.

Richard Ellis has received fees for meeting support from Ipsen, and honoraria from Servier and Amgen.
Anne L. Thomas provides consultancy and paid expert testimony for Bristol Myers Squibb.
Timothy Iveson has received fees for meetings, travel and lectures from Servier, Amgen, Bristol Myers Squibb, Pierre Fabre and MSD Oncology in the last 5 years.

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