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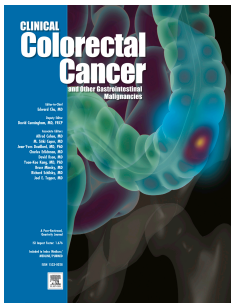

Efficacy And Cardiotoxic Safety Profile Of Raltitrexed In Fluorouracil Pre-Treated Or High-Risk Cardiac Patients With Gi Malignancies- A Large Single-Centre Experience

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EFFICACY AND CARDIOTOXIC SAFETY PROFILE OF RALTITREXED IN FLUOROURACIL PRE-TREATED OR HIGH-RISK CARDIAC PATIENTS WITH GI MALIGNANCIES- A LARGE SINGLE-CENTRE EXPERIENCE

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RUNNING TITLE: EFFICACY AND CARDIOTOXICITY SAFETY PROFILE OF RALTITREXED TREATED PATIENTS

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MICROABSTRACT:

In this large cohort of gastro-intestinal cancer patients with high cardiac risk factors or those with previous fluorouracil based cardiac toxicities, we demonstrate the safety and efficacy of raltitrexed-based chemotherapy in patients. This study will offer reassurance to physicians, who may encounter a clinically challenging situation.

ABSTRACT:

Background:

Gastro-intestinal (GI) cancers patients may not be for considered for fluoropyrimidines (FPs) due to previous cardio-vascular (CV) toxicity or pre-existing risk factors; such patients may benefit from raltitrexed-based therapy.

Patients and Methods:

Patient, tumour and treatment characteristics, and clinical outcomes of all consecutively treated patients with raltitrexed at the Royal Marsden (RM) Hospital between October 1998 and July 2011 were examined. GI cancer patients who developed CV toxicity secondary to FUs and those with significant CV risk factors receiving raltitrexed were included in this analysis.

Results:

A total of 247 patients (155 and 92 with CV FPs-related CV toxicities and significant CV risk factors respectively), treated by raltitrexed alone or in combination were examined in this analysis after a median follow up of 47.1months. CV toxicity profile of patients receiving capecitabine (n=110) and 5-FU (n=45) were largely similar. Of raltitrexed-treated patients, 13 (5%) experienced CV toxicities and 1 (<0.1%) died due to myocardial infarction. The median progression free survival (PFS) and overall survival (OS) was 36.0 months (95% CI: 26.5 to 48.6) and 44.3 months (95% CI: 33.1 to 56.8) respectively. The 5-year survival for early stage GI malignancies (n=140) was 62.0% (95% CI: 50.1 to 71.9). Median PFS and OS was not reached in this group (IQR; 38.4 months-NR); median PFS and OS for advanced GI

malignancies (n=107) was 18.8 (95% CI: 11.9 to 25.7) and 23.7 months (95% CI: 17.0 to 26.9) respectively.

Conclusion:

Raltitrexed-based regimen is well-tolerated therapy with comparable efficacy to FPs in patients with GI malignancies with significant CV toxicities or risk factors.

KEYWORDS:

Raltitrexed, gastro-intestinal cancers, 5-fluorouracil, capecitabine, cardiotioxicity, colorectal cancer, gastro-oesophageal cancer

INTRODUCTION:

Fluoropyrimidines (FPs) including, 5-Fluorouracil (5-FU) and Capecitabine are the backbone of chemotherapy regimens for many cancers including gastrointestinal (GI), breast and head and neck malignancies[1]. FPs principally act by inhibiting thymidylate synthase (TS) enzyme causing depletion of thymidine, which is necessary for DNA synthesis[2]. These agents are the mainstay of cytotoxic chemotherapy either alone or in combination both in early stage and metastatic GI cancers[3-6].

The common toxicities associated with FPs such as oral mucositis, diarrhoea and hand-foot syndrome are reasonably well managed in majority of the patients, however up to 1.6-12.5% of patients may experience overt cardiac toxicity [7]. More recently, a study measured a marker of left ventricular ejection fraction - N-terminal probrain natriuretic peptide (NT-pro BNP) in patients treated with 5-FU, demonstrating elevated BNP levels in 29% of the patients [8] suggesting sub-clinical cardiac toxicity of FPs with indeed unknown late consequences. The likely mechanism for the cardiotoxicity are the dose and schedule dependent coronary vasospasm and damage at the cellular level in red blood cells (RBCs), myocardial and endothelial cells mainly driven by reactive oxygen species[9-11]. Coronary artery spasm causing angina-like symptoms is the most widely reported symptomatic cardiac toxicity of FPs[12, 13]. More serious cardiac toxicities such as myocardial infarction (MI), major arrhythmias, heart failure and pericarditis have also been reported[12, 13].

Pre-existing heart and renal disease are established factors for developing cardiac toxicity on FP treatment [7]. Managing the side effects by discontinuing the treatment is possible, but pre-mature chemotherapy discontinuation may compromise the desired oncological outcomes. Re-challenging with the same therapy is not always possible as cardiac toxicity may recur in 20-

100% of cases [14], with fatal outcome in as many as 13% of the patients [13]. Therefore, patients suffering from cardiac toxicity on FP based regime have limited treatment options.

Substitution of FPs with raltitrexed, a folate analogue with inhibitory TS enzyme activity is an alternative treatment strategy for patients who experienced FPs related cardiac side effects. Raltitrexed demonstrated equal efficacy when compared to 5-FU in studies involving patients with metastatic colorectal cancer (mCRC)[15-17]; however, the use of this drug in the clinic is often limited due to increased mortality reported in a large clinical trial[18]. It is however noteworthy that frequent protocol violations were reported in this trial due to lack of appropriate dose adjustments on drop in creatinine clearance, which may have resulted in high mortality[18].

As patients with known cardiovascular disease are more likely to be prone to FPs-related cardiac side effects [7]; we hypothesised that patients with a significant cardiac history might be spared from cardiac symptoms and potentially severe complications by up-front treatment with single agent raltitrexed or other appropriate combinations. At the Royal Marsden (RM) Hospital, patients with significant cardiovascular disorders and those who experienced 5-FU or capecitabine induced cardiac side effects receive a raltitrexed containing chemotherapy regimen instead of re-challenging with FPs. The data on safety and efficacy of such a substitution strategy are sparse and apart from some recent[12, 19] retrospective studies with limited patient numbers, the available clinical information is largely based on anecdotal experiences of the physicians. The current study examines the presentation of 5-FU/capecitabine induced cardiac side effects and the safety and efficacy of raltitrexed substitution strategy in patients who develop symptoms on FPs and in those with significant underlying cardiovascular conditions who receive upfront raltitrexed containing regimens.

PATIENTS AND METHODS:

Study design

This retrospective study included all patients consecutively treated with raltitrexed at the RM, from October 1998 to July 2011. Only patients who had confirmed histological diagnosis of any GI malignancies and those who were treated with raltitrexed as single agent or in combination due to high cardiac risks or because of cardiovascular complications from FPs were included. Patients were divided into two groups: those who were switched to raltitrexed due to cardiac toxicity from FPs and those who received raltitrexed upfront due to previous cardiovascular risk factors. Electronic patient records (EPR) were reviewed and the following clinico-pathologic parameters prospectively collected for this study included: age, gender, site of origin of the primary tumour, histological subtype, details of chemotherapy regimens, therapeutic responses, reasons for raltitrexed use, cardiac toxicity during and 4 weeks after treatment, and timings of toxicities associated with raltitrexed were recorded. The study was approved by the Institute's Research Ethics Committee.

Patient follow-up and response evaluation

Surveillance strategy for CRC patients with no metastatic disease at our institute included 3 monthly follow up in year 1, 6 monthly follow up in years 2 and 3 and annual follow up for years 4 and 5 with CEA test performed on each visits; annual CT scans were performed for the first three years and routine colonoscopies were performed every 2-3 years. PET scan was not routinely performed in these patients. For patients who underwent localised therapeutic options with curative intent after being diagnosed with oligo-metastatic disease, surveillance strategy included 3 monthly follow up with CEA during year 1, 6 monthly follow up during years 2-5 and annual follow up during years 6 and 7, with CEA performed on each attendance. CT scans were performed every 6 month for years 1 and 2, followed by annual CT scans during years 3-5. Colonoscopies were performed as per the routine follow up scheme described above.

Patients with other GI tumours were monitored 3 monthly in year 1, 6 monthly in years 2 and 3 and annually in years 4 and 5; CEA and CA19-9 were checked on each visit but CT scan was only performed when clinically indicated.

Baseline tumour measurements in advanced metastatic disease patients were performed within four weeks prior to Cycle 1 Day 1. Tumour measurements were repeated every 12 weeks while on treatment using Response Evaluation Criteria In Solid Tumours (RECIST) version 1.0. Tumour responses were confirmed prospectively by a radiologist. Toxicity data were collected as originally recorded in the electronic medical records. In all patients included in the present analysis, toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 or 3.0. Survival data were obtained from the hospital electronic medical record, and when necessary, by contacting the general practitioner or referring institution.

Statistical methods

OS was defined as the interval between diagnosis date and either the date of death or censored at the date of last follow-up (if death was not observed during the follow-up period). For evaluable patients, progression-free survival (PFS) was defined by the time elapsed between diagnosis date until radiological progression or disease-related death (which ever occurred first); if no evidence of progression was documented at the last follow-up, PFS was censored at the date of last follow up.

Categorisation of numeric variables was undertaken based on considerations of the standard reference values (normal range versus low/elevated) or according to the median values. Estimates of median PFS and OS (and 95% confidence interval [CI]) were determined using

the Kaplan-Meier method, and Cox regression was used to compare the survival rates and to produce hazard ratios (HR) along with 95% CIs.

RESULTS:

Patient characteristics:

Two hundred and forty seven patients [72.5% females; mean age 65.5 years (range 31-88)] were treated with raltitrexed during the study time period at the GI Unit in the RM Hospital. Colon (46.1%), rectum (21%), adenocarcinoma oesophagus (14.6%), squamous cell carcinoma oesophagus (8%) and gastric cancers (7.7%) were the commonest cancers in the examined group **(Table 1 and Supplementary table 1)**. Of the 247 patients who fulfilled inclusion criteria of the study, 155 had developed cardiac toxicities on 5-FU or capecitabine and 92 patients had a high cardiac risk based on physicians discretion and thus were treated with a raltitrexed containing regimen to avoid 5-FU/capecitabine associated cardiac toxicity (**Supplementary table 2**).

Presentation of cardiac toxicity while receiving 5-FU- or capecitabine-containing chemotherapy

155 patients received raltitrexed after they had developed cardiac 5-FU or capecitabine induced cardiac side effects. Cardiac complications started during the first treatment cycle in 70% of these patients (**Table 2**). The medium time from starting 5-FU or capecitabine to cardiac symptom onset was 6 days with the range of 1-63 days (**Figure 1**). The commonest side effect was angina (86% of patients). Seven patients suffered from myocardial infarction. There was no difference in the type or timing between side effects that occurred on 5-FU and on capecitabine. Nine patients underwent coronary angiography and 1 patient had a thallium scan shortly after they experienced angina episodes. One patient was found to have a tight left anterior descending (LAD) artery and a critically tight circumflex artery on angiography, which required stenting. The remaining 8 patients showed no detectable coronary abnormalities.

These results are consistent with previous reports that cardiac toxicities with TS inhibitors frequently occur despite normal coronary blood vessels [7].

Raltitrexed treatment dosage

The standard raltitrexed dose of 3mg/m^2 was administered as a 15-minute infusion in 80 (32%) patients. 55 (22%) patients received reduced dose (range: 1.3-2.8 mg/m^2) due to one of the following reasons: thrombocytopenia (n=2) renal impairment (n=13), pyrexia (n=1), neutropenic sepsis (n=2), diarrhoea (n=2), tiredness (n=1), and reason not specified (n=34). The remaining patients (n=108, 44%) received higher doses within the range of 3.10-6.60 mg/m^2. The records of 4 patients did not specify dose.

Safety of substituting 5-FU or capecitabine with Raltitrexed in patients with cardiac toxicities

Of the 247 patients, 31% and 68% received single agent raltitrexed and raltitrexed combination chemotherapy respectively (data not available for 2 patients). The 155 patients who were switched to raltitrexed because of cardiac toxicities on 5-FU/capecitabine subsequently received a median number of 5 cycles of raltitrexed treatment (range=1-8). The remaining 92 patients with pre-existing cardiovascular conditions received a median of 6 cycles (range= 1-11). 80.5% and 73% patients of the patients with FPs-related cardiotoxicities and pre-existing cardiovascular conditions respectively received at least one standard dose of raltitrexed (3 mg/m^2) while the remaining patients were started on lower raltitrexed doses because of renal impairment, general frailty or based on physician discretion.

A total of 13 (5%) patients developed cardiac toxicities while receiving raltitrexed-based chemotherapy (**Table 3**); of those 4 received single agent treatment and 9 received

combination chemotherapy. Three patients suffered with arrhythmias and palpitations and one patient had angina like symptoms. All of these toxicities were graded as mild to moderate and these patients continued chemotherapy without delay or dose reduction. Two patients in the high-risk cardiovascular risk group developed a myocardial infarction, one of which was fatal. The total cardiovascular mortality was 0.004% (1/247) in the whole group. This patient was a 59-year old male with the background of ischaemic heart disease and heart failure who suffered myocardial infarction after 2 cycles of raltitrexed (2.6 mg/m^2) and carboplatin combination.

Efficacy of substituting 5-FU/capecitabine with Raltitrexed

The median PFS and OS of all patients in the study was 36.0 (95% CI: 26.5 to 48.6) and 44.3 months (95% CI: 33.1 to 56.8) respectively. The 5-year survival for early stage GI malignancies (n=140) was 62% (95% CI: 50.1 to 71.9). As expected 5-year survivals were 73.5% (95% CI: 58.8 to 83.7) and 17.6% (95% CI: 3.6 to 40.4), when divided into lower and upper GI malignancies respectively. Median PFS and OS was not reached in the early stage group (IQR; 38.4 months-NR).

The median PFS and OS for all the advanced stage GI cancers was 18.8 months (95% CI: 11.9 to 25.7) and 23.7 months (95% CI: 17.0 to 26.9) respectively. 5-year survival was 16.3% (CI: 9.5 to 24.7) for advanced stage GI cancers. Significant differences were noted in the median PFS [HR 3.7 (CI 2.6 to 5.3); p<0.001] and OS [HR 4.1 (2.8 to 6.0); p<0.001] of early and advanced stage GI (**Figure 2**). Interestingly, significant PFS [HR 1.9 (1.1 to 3.2); p=0.02] and OS [HR 4.0 (2.4 to 6.6); p<0.001] rate differences were also noted depending on site (upper vs. lower) of the evaluated cancer. Upper GI cancers had significantly worse outcomes compared to lower GI cancers (**Figure 3**). Efficacy details for all examined subgroups are provided in **Table 4**.

There was one death attributed to myocardial infarction after treatment with raltitrexed. Patients were followed up for a median period of 47.1 months (IQR 32.4m - 65.7m).

DISCUSSION:

This retrospective study represents the largest examination of GI cancer patients with pre-existing cardiac risk factors or cardiovascular toxicities due to FPs treated with raltitrexed based therapy. Consistent with previously published literature, these data demonstrate the safety of this approach. The unique and novel aspect of this study is that we present efficacy data of raltitrexed-based therapy in this high-risk patient population encompassing early and advanced upper and lower GI malignancies.

It is well documented that raltitrexed treatment and its dosing schedule is convenient to patients[20]. We found that raltitrexed was well tolerated by the majority of patients. Only 5% of the treated patients developed cardiac toxicity and more than half of these patients were able to have continuation of treatment without further cardiac complications. Our data suggest that the standard dose of 3 mg/m^2 is safe in this high-risk population and that the cardiac side effects of raltitrexed were not found to be dose dependent. We have shown that appropriate dose adjustments based on renal function may be necessary for a better safety profile; however, precautionary dose reduction in view of previous cardiac AEs or high risk factors is not required.

Raltitrexed related deaths[15, 18, 21], have raised concerns about the safety of this treatment, although other studies did not demonstrate similar treatment related deaths rates [22-26]. One of the large phase III study found that reported 26 (3.8%) deaths causally related to raltitrexed[18], when examined in details showed that 17/26 deaths were associated with major protocol variation when raltitrexed dose was not adjusted according to renal function [18, 19]. As the kidney accounts for 40–50% of the drug's clearance[20], special care should be exercised in

patients with creatinine clearance rate is < 65mL/min [7]. In our high-risk cohort, only one treatment related was noted.

Given that our study revealed large differences in the incidence of CV AEs between patients who received FPs and those who received raltitrexed, it is likely that there are mechanistic differences underlying the development of cardotoxicity between the two types of drug. Raltitrexed induced CV AEs were generally observed in patients who had already received a few cycles of treatment. Intriguingly, relatively more patients presented with palpitations contrary to 5-FU and capecitabine induced chest pain suggesting coronary artery vasospasm [24, 25] as the main mechanims behind FP-related CV toxicity. Consistent with this observation, when coronary angiography was performed, it was found to be unremarkable in most of the patients on the current study. It is thus possible that cardiac side effects seen in patients who received raltitrexed are the manifestation of indirect effects secondary to hyperdynamic states secondary to chemotherapy or renal impairment etc. rather than direct cardio-toxicity. Randomised controlled trials assessing raltitrexed indeed did not provide any evidence for direct cardio-toxicity of raltitrexed[19].

The efficacy of raltitrexed containing regimes in our cohort can be compared favourably with contemporaneous treatment options in lower GI malignancies[27, 28, 29]. It is interesting to note that all the previous studies comparing raltitrexed with 5-FU have also shown similar efficacy of in lower GI malignancies[15-18, 30]. However none of these studies focused on a high-risk patient population as reported in the current study. On contrary, the efficacy outcomes for early upper GI malignancies in our cohort were somewhat variable. Whilst, peri-operative chemotherapy with surgery achieved 5-year survival of 36% (95 % CI, 29.5 to 43.0) in MAGIC trial[31], 5-year survival was found to be 17.6% (95% CI: 3.6 to 40.4) in our cohort. In advanced upper GI

malignancies, the results with raltitrexed were however comparable with other existing treatment options[32]. These data overall provide a strong rationale for use of raltitrexed based therapy in patients with CV risk/toxicities in all lower GI and advanced upper GI malignancies; however, raltitrexed-based treatment in early upper GI malignancies should be considered with caution, specially within the context of new available peri-operative chemotherapy options[33].

While our study provides valuable information on the relative cardiac safety of raltitrexed versus 5-FU/capecitabine, we recognise that the analysis has some limitations. The main limitation of this study is its retrospective nature and associated biases. However, given the stark differences in the incidence of cardiac AEs in patients receiving raltitrexed versus those receiving FPs, a prospective trial in high-risk CV patients would be ethically questionable. The lack of treatment options for such patients would also mean that prospective trials would be difficult to design and recruit. Our analysis may have also underestimated the incidence of cardiac side effects that would occur if all patients without a clear indication for raltitrexed dose reduction (e.g. those with renal failure) had been offered the full dose. However, in all likelihood patients with renal impairment would have received appropriate dose reduction with other chemotherapies as well, thus making our results applicable to such patients.

CONCLUSION:

This study demonstrates the safety and efficacy of raltitrexed in upper and lower GI cancer patients who either experienced mild to moderate cardiac toxicity after FPs or those who had significant cardiac risk factors. Allowing extrapolation of data and comparison with available contemporaneous regimens, we recommend use of raltitrexed-based therapy in high risk cardiovascular patients with all lower and advanced upper GI malignancies. In patients with early stage GI malignancies and curative treatment options, the use of raltitrexed based therapy should be restricted to patients, where no alternative therapeutic options are available.

CLIINICAL PRACTICE POINTS:

- This study represents the largest examination of raltitrexed-treated GI cancer patients with CV toxicities following FPs or CV risk factors precluding them from receiving or continuing with FPs- based therapy.
- Consistent with previously published literature, we demonstrate the safety of this approach with less than 5% cardiac toxicity and low fatality (<0.1%).
- The novel aspect of this study is that efficacy data with long median follow up in a patient population with significant cardiac toxicities or risk factors were found to be comparable to contemporaneous standard of care, 5-FU/capecitabine based regimes.
- Despite retrospective nature of the study, these findings support use of raltitrexed-based regimens in a patient population with limited systemic therapy options.

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TABLES:

FIFURES

Table 1: Baseline patient characteristics

Participant numbers	
All (%)	247 (100)
5FU (%)	45 (18.2)
Capecitabine (%)	110 (44.5)
CV risk factors (%)	92 (37.3)
Age at study entry, years	
Median - All (range)	67 (31-88)
Gender	
Female	179 (72.5%)
Male	68 (27.5%)
Tumor types	
Upper GI	75 (30.4%)
Gastric	19 (7.7%)
Gastro-oesophagial	4 (1.6%)
Oesophageal	52 (21.1%)
Lower GI	162 (65.6%)
Anal	3 (1.2%)
Colorectal	159 (64.4%)
Miscellaneous	10 (4.0%)
Caecal	7 (2.8%)
Cholangiocarcinoma	1 (<0.1%)
Neuroendocrine	1 (<0.1%)
Unknown origin	1 (<0.1%)
Intent of chemotherapy	
Neoadjuvant	22 (8.9%)
Neoadjuvant + Radiochemotherapy	29 (11.7%)
Radiochemotherapy	5 (2%)
Adjuvant	84 (34%)
Palliative chemotherapy	107 (43.3%)
Staging	
All early stage, N (%)	140 (56.7%)
Upper GI	37 (15.0%)
Lower GI	101 (40.9%)
Miscellaneous	2 (0.8%)
All advanced metastatic, N (%)	107 (43.3%)
Upper GI	38 (15.4%)
Lower GI	61 (24.7%)
Miscellaneous	8 (3.2%)

Table 2: Presentation and timing of cardiac toxicity associated with 5-FU and Capecitabine treatment

	Total (N=155)	**5-FU (N=45)**	**Capecitabine (N=110)**
Cardiac Toxicity:			
Angina, N (%)	133 (85.8%)	37 (82.2%)	96 (87.3%)
Angina + Palpitations, N (%)	3 (1.9%)	0	3 (2.7%)
Angina + Arrhythmia, N (%)	1 (<0.1%)	0	1 (<0.1%)
Left ventricular hypertrophy, N (%)	1 (<0.1%)	0	1 (<0.1%)
Palpitations, N (%)	3 (1.9%)	1 (2.2%)	2 (1.8%)
Arrhythmia, N (%)	3 (1.9%)	1 (2.2%)	2 (1.8%)
Atrial Flutter, N (%)	2 (1.3%)	2 (4.4%)	0
Myocardial infarction, N (%)	7 (4.5%)	4 (8.9%)	3 (2.7%)
Ventricular flutter, N (%)	2 (1.3%)	0	2 (1.8%)
Treatment cycle:			
After 1st cycle, N (%)	93 (60.0%)	18 (40.0%)	75 (68.2%)
After 2nd cycle, N (%)	32 (20.6%)	15 (33.3%)	17 (15.4%)
After 3rd and subsequent cycles/other, N (%)	30 (19.4%)	12 (26.7%)	18 (16.4%)
Days after starting drug administration			
Median days (range)	6 (1-63)	5 (1-60)	6 (1-63)
Number of patients with missing data, N (%)	49 (31.6%)	15 (33.3%)	34 (30.9%)

Table 3: Cardiac toxicity associated with raltitrexed treatment

	All (N=247)	**5-FU/Capecitabine (N=155)**	**CV risk factors (N=92)**
Total number of patients with cardiac side effects	13 (5.3%)	8 (5.2%)	5 (5.4%)
Angina	5	3	2
Arrhythmia	3	3	0
Palpitations	2	1	1
Myocardial infarction	2	1	1
Myocardial infarction and death	1	0	1

Table 4: Efficacy of raltitrexed based therapy in all study participants

Cancer type	**5-year PFS (CI)**	**5-year OS (CI)**
All cancers	36.9% (29.1 to 44.7)	38.7% (30.9 to 46.4)
Early stage upper GI cancers	24.7% (8.2 to 45.9)	17.6% (3.6 to 40.4)
Advanced stage upper GI cancers	0.0%	0.0%
Early stage lower GI cancers	71.1% (58.7 to 80.4)	73.5% (58.8 to 83.7)
Advanced stage lower GI	12.6 (5.3 to 23.3)%	24.1% (13.4 to 36.5)
Advanced Miscellaneous	12.5% (0.7 to 42.3)	25% (3.7 to 55.8)
All early stage cancers	60.7% (49.9 to 69.8)	62% (50.1 to 71.9)
All advanced stage cancers	10.9% (5 to 19.2)	16.3% (9.5 to 24.7)

Figure 1: Cardiac side effects after starting 5-FU or capecitabine

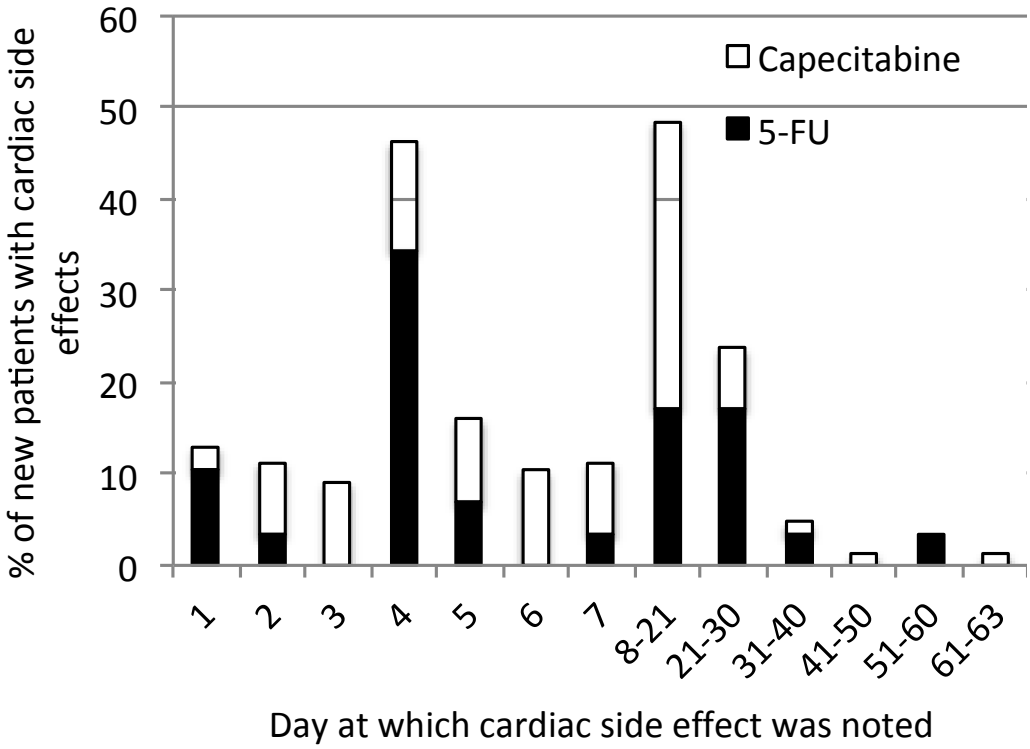


Figure 2: Kaplan–Meier estimates of progression-free survival (Panel A) and overall survival (Panel B) for early stage and advanced stage GI malignancies

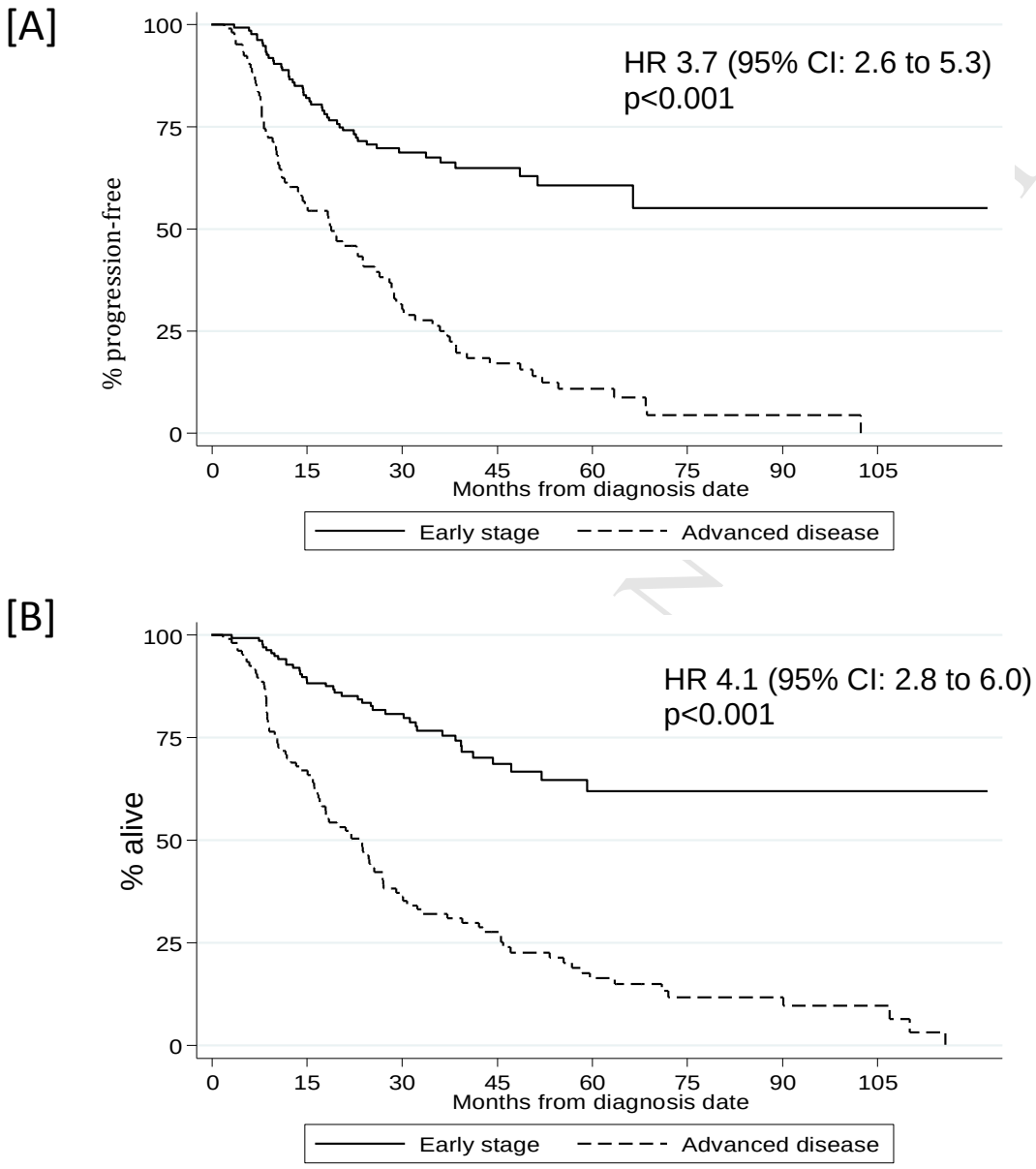
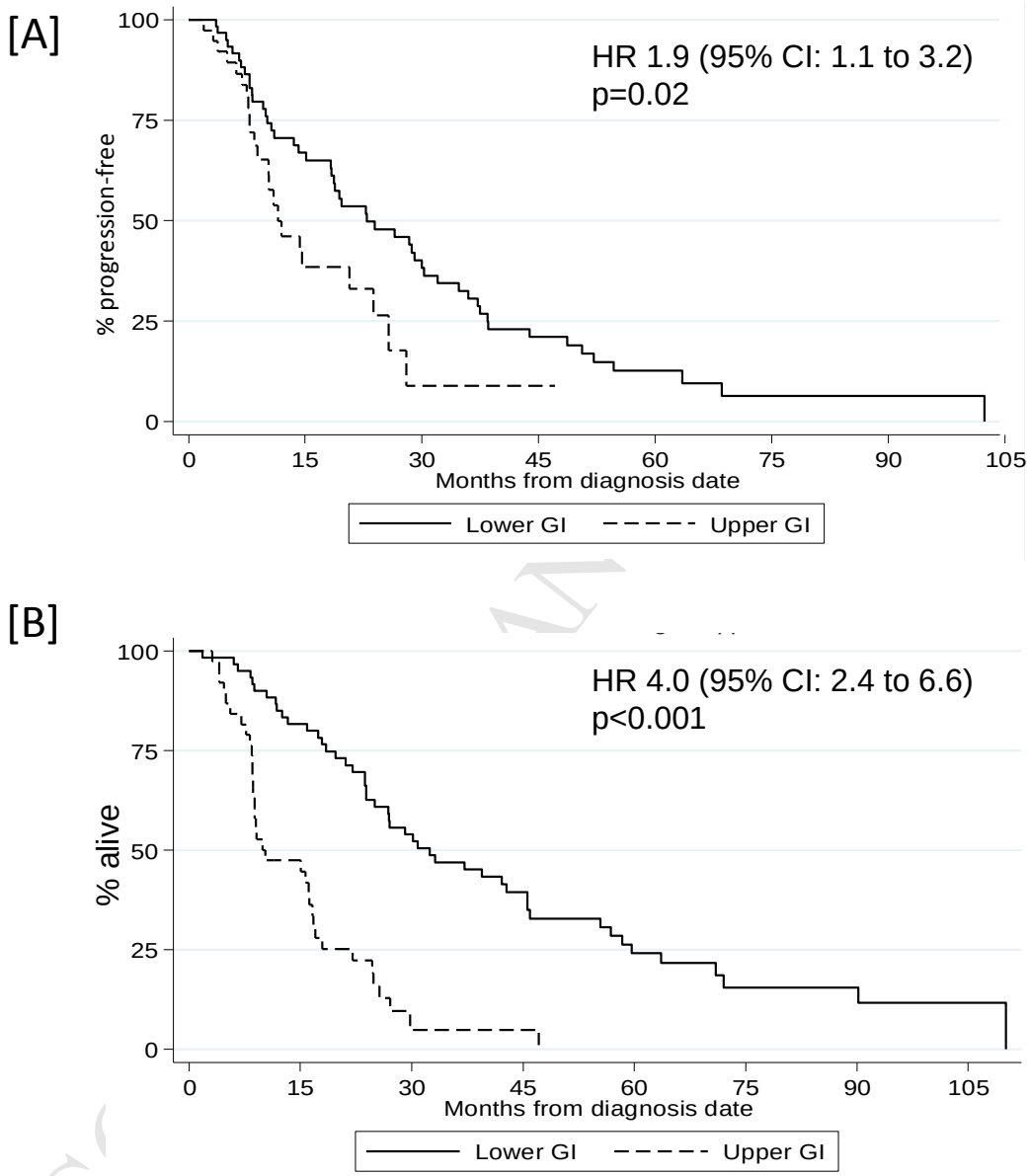


Figure 3: Kaplan–Meier estimates of progression-free survival (Panel A) and overall survival (Panel B) for upper and lower GI malignancies



Supplementary files

Supplementary table 1: Intent of chemotherapy in different groups. 5FU-patient who had 5FU pre-treatment, Cap-patient who had capecitabine pre-treatment

	5FU	**Cap**	**CV-risk factors**	**Total**
Neoadjuvant	1	8	13	22
Neoadjuvant + Radiochemotherapy	2	13	14	29
Radiochemotherapy	0	2	3	5
Adjuvant	23	35	26	84
Palliative chemotherapy	19	52	36	107

Supplementary table 2: Cardiac background for patients considered having high cardio-vascular risk factors

Condition	**Frequency**
Angina	9
Heart Failure	1
Cardiomegaly + Arrhythmia	1
Ischaemic heart disease + heart failure	3
Ischaemic heart disease + Atrial fibrillation	7
Cardiomyopathy	3
Heart block	1
Angina +Atrial fibrillation	1
Palpitations	1
Arrhythmia	4
Atrial fibrillation	6
Paroxysmal atrial fibrillation	6
Myocardial infarction	23
Ischaemic heart disease	22
Arrhythmia + Ischaemia heart disease/Myocardial infarction	3
Pacemaker	1
Total	92