1. INTRODUCTION

1.1 Colorectal cancer

Colorectal cancer develops in the colon or the rectum. The colon and rectum are parts of the digestive system, also called the gastrointestinal or GI system.

The colon has 4 sections (Figure 1):

- The first section is called the ascending colon. It begins where the small intestine attaches to the colon and extends upward on the right side of a person’s abdomen.
- The second section is called the transverse colon because it crosses the body from the right to the left side.
- The third section, the descending colon, continues downward on the left side.
- The fourth section is known as the sigmoid colon because of its “S” shape. The sigmoid colon joins the rectum, which in turn joins the anus.

Fig 1: Segments of colon (Anatomy)
Colorectal cancer usually develops slowly over a period of 10 to 15 years[1]. The tumour typically begins as a noncancerous polyp. A polyp is a growth of tissue that develops on the lining of the colon or rectum that can become cancerous. Certain kinds of polyps, called adenomatous polyps or adenomas, are the most likely to become cancers, though fewer than 10% of adenomas progress to cancer[2]. Adenomas are common; an estimated one-third to one-half of all individuals will eventually develop one or more adenomas[3-4].

1.1.1 Epidemiology: current status and future challenges

1.1.1.1 World wide

Colorectal cancer is a major cause of cancer related morbidity and mortality throughout the world [5]. It is the third most common cancer worldwide for both sexes together and the fourth most common cause of death [6]. Colorectal cancer (CRC) is the 3rd most common cancer in men (746,000 cases, 10.0% of the total cancers) and the 2nd in women (614,000 cases, 9.4% of the total cases) [7]. There is a large geographic difference in the global distribution of colorectal cancer. Colorectal cancer is mainly a disease of developed countries with a Western culture [8] and the developed world accounts for over 63% of all cases [9]. The incidence rate varies up to 10-fold between countries with the highest rates than those with the lowest rates [5,10]. It ranges from more than 40 per 100,000 people in the United States, Australia, New Zealand, and Western Europe to less than 5 per 100,000 in Africa and some parts of Asia [6]. However, these incidence rates may be susceptible to bias; with a high degree of underreporting in developing countries.
1.1.1.2 Prevalence in India

The age adjusted incidence rates of CRC in all the Indian cancer registries are very close to the lowest rates in the world [11]. Hospital based and population based data also show that the incidence rates for rectal cancer is higher than colon cancer in all parts of India [11, 12]. Limited data from the rural population based registries indicate that the incidence rates of colon cancer are very low in the rural settings. However the incidence rates of rectal cancer is disproportionately higher in rural India [11–13]. Population based time trend studies show a rising trend in the incidence of CRC in India [14]. Incidence rates of colorectal cancer in India is 4.3 among Male and 3.4 among female per 100,000 (a Age adjusted rates for world standard population) and the projected number of cases by 2021 is represented in table 1.1[15-16]. In Chennai, 2003-2013 data indicate the Age Adjusted Rates (AARs) was 7.73 for colon cancer and 2.57 for rectum [12].

Table 1.1 Projected Number of Annual New Cancer Cases in India During Quinquennial Years by Site in Males and Female, 2011-2026

Male

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>2011</th>
<th>2016</th>
<th>2021</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>16085</td>
<td>18733</td>
<td>21974</td>
<td>25794</td>
</tr>
<tr>
<td>Rectum, Anus</td>
<td>20181</td>
<td>23520</td>
<td>27593</td>
<td>32398</td>
</tr>
</tbody>
</table>

Female

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>2011</th>
<th>2016</th>
<th>2021</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>12754</td>
<td>15012</td>
<td>17528</td>
<td>20449</td>
</tr>
<tr>
<td>Rectum, Anus</td>
<td>13294</td>
<td>15556</td>
<td>18112</td>
<td>21053</td>
</tr>
</tbody>
</table>
The trend in the incidence of colon and rectum has been shown increasing in all the registries. Statistical significant increase was noticed in Chennai, Bangalore and Delhi registries for cancer of colon. For rectum, there has been increase in the incidence for Chennai and Bangalore registries [14]. The observed and estimated (based on model fitting) age adjusted incidence rates for each site for all registries is shown in Table 1.2.

**Table 1.2. Average Age-Adjusted Incidence Rates per 100,000 Populations for colon and Rectum Cancers**

<table>
<thead>
<tr>
<th>Registry</th>
<th>Colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumbai</td>
<td>3.06</td>
<td>2.65</td>
</tr>
<tr>
<td>Chennai</td>
<td>1.70</td>
<td>2.66</td>
</tr>
<tr>
<td>Bangalore</td>
<td>2.43</td>
<td>2.67</td>
</tr>
<tr>
<td>Delhi</td>
<td>2.39</td>
<td>2.00</td>
</tr>
<tr>
<td>Bhopal</td>
<td>2.14</td>
<td>1.94</td>
</tr>
</tbody>
</table>

1.1.2 Symptoms of colorectal cancer

- Bleeding from the rectum
- Blood in the stool or in the toilet after having a bowel movement
- Prolonged altered bowel habits (alternating diarrhoea with constipation)
- Cramping pain in the lower stomach
- A feeling of discomfort or an urge to have a bowel movement when there is no need to have one
- New onset of constipation or diarrhoea that lasts for more than a few days
- Unintentional weight loss
1.1.3 Staging of CRC

The extent to which a colorectal cancer has spread is described as its stage. Staging is essential in determining the choice of treatment and in assessing prognosis. More than one system is used for the staging of cancer. The two most common staging systems are the TNM system, typically used in clinical settings, and the Surveillance, Epidemiology, and End Results (SEER) summary staging system, used for descriptive and statistical analysis of tumor registry data. The colorectal cancer stages using the SEER summary staging system:

- **In situ**: Cancers that have not yet begun to invade the wall of the colon or rectum; these preinvasive lesions are not counted in cancer statistics.

- **Local**: Cancers that have grown into the wall of the colon and rectum, but have not invaded nearby tissues

- **Regional**: Cancers that have spread through the wall of the colon or rectum and have invaded nearby tissue, or with or without regional involvement.

- **Distant**: Cancers that have spread to other vicera such as lungs, liver, bone

Once cancer forms in the large intestine, it can grow through the lining and into the wall of the colon or rectum (Figure 2). Cancers that have invaded the wall can also penetrate blood or lymph vessels. Carcinomas typically spread first into nearby lymph nodes. And later spread through blood vessels to the liver or lungs. They can also spread to the abdominal cavity to other areas, such as the ovary. The process through which cancer cells travel to distant parts of the body through blood or lymphatic vessels is called metastasis.
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A Pharmacokinetic And Pharmacogenetic Study of Capecitabine in Colorectal Cancer Patients Among South Indian Population

Figure 2: Stages in Colon Cancer

TNM Staging for colorectal cancer, 7th edition

**Primary tumor (T)**

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria*
- **T1** Tumor invades submucosa
- **T2** Tumor invades muscularis propria
- **T3** Tumor invades through the muscularis propria into pericolorectal tissues
- **T4a** Tumor penetrates to the surface of the visceral peritoneum
- **T4b** Tumor directly invades or is adherent to other organs or structures

**Regional lymph node (N)**

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
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N1 Metastasis in 1-3 regional lymph nodes
N1a Metastasis in one regional lymph node
N1b Metastasis in 2-3 regional lymph nodes
N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2 Metastasis in four or more regional lymph nodes
N2a Metastasis in 4-6 regional lymph nodes
N2b Metastasis in seven or more regional lymph nodes

Distant metastasis (M)

M0 No distant metastasis
M1 Distant metastasis
M1a Metastasis confined to one organ or site
   (eg, liver, lung, ovary, nonregional node)
M1b Metastases in more than one organ/site or the peritoneum

1.1.4 Colorectal Cancer Treatment

Treatment decisions are made by the physicians after considering the best options available for the stage and location of the cancer, as well as the risks and benefits associated with each.

Most people with colon cancer, particularly in earlier stages, will undergo surgery to remove the tumor. Adjuvant therapy (additional treatments after surgery) such as chemotherapy /radiation therapy may also be used depending on the histopathology report. Adjuvant chemotherapy (anticancer drugs) or radiation
for colon cancer is as effective in Post operative elderly patients otherwise healthy as in younger patients. Toxicity in older patients can be limited by avoiding IV drugs and by appropriate dose reduction.

1.1.4.1 Carcinoma in situ

Surgery to remove the growth of abnormal cells may be accomplished by polypectomy or local excision through the colonoscope. Resection of a segment of the colon may be necessary if the tumor is too big to be removed by local excision.

1.1.4.2 Localized stage

Surgical resection to remove the cancer, together with a length of colon on either side of the tumor and nearby lymph nodes, is the standard treatment. Here depending on the location of the tumor a hemicolecction/anterior resection is done. Based on the post operative specimen pathological report if the doctor thinks the cancer is likely to come back (recur) because of its appearance under the microscope adjuvant radiation therapy and/or chemotherapy may be recommended as well. If the regional disease cancer has spread to nearby lymph nodes, in colonic malignancy surgical resection of the segment of colon containing the tumor is the first treatment, usually followed by chemotherapy. In the rectal lesion with nodal spread the patient undergoes preoperative radiation therapy and chemotherapy followed by surgery. 5-fluorouracil (5-FU) based chemotherapy shown to improve survival in patients with stage II or stage III disease, primarily by reducing disease recurrence [17].
1.1.4.3 Distant stage

At this stage, the cancer has spread to distant organs and tissues, such as the liver, lungs, peritoneum (lining of the abdomen), or ovaries. The goal of surgery (segmental resection or diverting colostomy) in this stage is usually to palliate symptoms only such as relieve or prevent blockage of the colon and to prevent other local complications. Curative surgery is not recommended for all patients. If there are only a few metastases to the liver or lungs, surgery to remove these, as well as the colon tumor, may be an option.

Chemotherapy, radiation, and biologically targeted therapies may be given alone or in combination to relieve symptoms and prolong survival. Three targeted monoclonal antibody therapies have been approved by the US Food and Drug Administration (FDA) to treat metastatic colorectal cancer. Bevacizumab blocks the growth of blood vessels to the tumor and both cetuximab (Erbitux) and panitumumab block the effects of hormone-like factors that promote cancer cell growth; however, tumors with certain genetic mutations do not benefit from treatment with cetuximab or panitumumab[18].

1.1.5 PROGNOSIS

Despite the enormous number of correlative studies exploring the prognostic significance of various histologic, molecular, and clinical features, the pathologic stage at diagnosis remains the best indicator of long-term prognosis for both colon and rectal cancer.
A Pharmacokinetic And Pharmacogenetic Study of Capecitabine in Colorectal Cancer Patients Among South Indian Population

**Introduction**

Colon cancer

Five-year survival rates for all stages of colon and rectal cancer are 65 percent [19]. Disease stage is the most important prognostic factor. As an example, five-year survival rates for colon cancer, stratified by stage, in data collected from the SEER database between 1998 and 2013 were as follows [20]

**Table 1.3 (a): Five-year survival stratified by tumour stage**

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>All Races</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both Sexes (%)</td>
</tr>
<tr>
<td>All Stages</td>
<td>64.1</td>
</tr>
<tr>
<td>Localized</td>
<td>90.7</td>
</tr>
<tr>
<td>Regional</td>
<td>71.7</td>
</tr>
<tr>
<td>Distant</td>
<td>13.6</td>
</tr>
<tr>
<td>Inadequately staged</td>
<td>27.0</td>
</tr>
</tbody>
</table>

Rectal cancer

As with colon cancer, the survival of patients with stage III disease is variable and depends both upon the T stage and the extent of nodal disease. Five-year survival stratified by tumor stage at diagnosis for rectal cancer, derived from the SEER database and stratified according to staging criteria, is illustrated in the following table 1.3(b) [21].
Table 1.3(b): Five-year survival stratified by tumour stage

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>All Races</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both Sexes (%)</td>
<td>Males (%)</td>
<td>Females (%)</td>
</tr>
<tr>
<td>All Stages</td>
<td>66.7</td>
<td>65.5</td>
<td>68.2</td>
</tr>
<tr>
<td>Localized</td>
<td>88.2</td>
<td>87.5</td>
<td>89.0</td>
</tr>
<tr>
<td>Regional</td>
<td>70.3</td>
<td>70.0</td>
<td>70.6</td>
</tr>
<tr>
<td>Distant</td>
<td>14.6</td>
<td>13.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Inadequately staged</td>
<td>49.5</td>
<td>48.7</td>
<td>50.4</td>
</tr>
</tbody>
</table>

These outcome estimates were derived from studies in which surgical resection was not preceded by neoadjuvant therapy. Outcomes may differ in patients who undergo pathologic staging after preoperative treatment.

1.2. Capecitabine

Capecitabine an oral prodrug of 5FU is currently approved for four indications: (a) monotherapy in the first line of treatment of advanced colorectal cancer, (b) adjuvant treatment of patients with stage III (Duke’s stage C) colon cancer, (c) in combination with docetaxel in the treatment of locally advanced or metastatic breast cancer, and (d) as monotherapy in advanced breast cancer after failure of a taxane- and anthracycline-containing chemotherapy or for patients for whom an anthracycline is contraindicated [21]. Capecitabine is becoming increasingly popular and has largely replaced 5-fluorouracil (5-FU) in several indications, including gastric cancer. Clinical activity of a 14-day schedule of capecitabine given every 21 days is therapeutically equivalent to bolus 5-FU with low-dose leucovorin given every 4 weeks in colorectal cancer [22].
1.2.1 Mechanism of action

Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the $G_1$ and $S$ phases of the cell cycle.

1.2.2 PHARMACOKINETICS

1.2.2.1 Absorption

After oral administration, capecitabine is rapidly taken up from the gut and converted into its main metabolites $5'$-deoxy-5'-fluorocytidine ($5'$-DFCR) and $5'$-deoxy-5'-fluoro-uridine ($5'$-DFUR). Systemic levels of 5-FU are low. Concomitant food intake significantly reduces the systemic exposure to capecitabine. It is recommended to take the drug after a meal because this has also been done in the clinical trials. The time to reach the maximal plasma concentration after food ingestion is around 2 hours. Oral pharmacokinetics are linear. The absolute bioavailability is estimated to be 40%–45% [23].

1.2.2.2 Protein Binding

Binding is mainly to albumin and is 54% for capecitabine and 10%, 62%, and 10% for its metabolites $5'$-DFCR, $5'$-DFUR, and 5-FU, respectively [24]. No relevant interactions at this level are to be expected.
1.2.2.3 Metabolism

After oral uptake, capecitabine is first metabolized to 5′-DFCR, which takes place mainly in the liver by carboxyl-esterase. The metabolite is converted to 5′-DFUR by cytidine deaminase in liver and tumor tissue and converted to 5-FU intracellularly by thymidine phosphorylase, an enzyme that is often expressed in tumor tissue. Catalytic inactivation of 5-FU proceeds by dihydropyrimidine dehydrogenase (DPD), which is polymorphically expressed. The metabolic pathway is represented in figure 4.

**Fig 3: Metabolic pathway of capecitabine**

5-10 CH=FH4, 5-10 methenyltetrahydrofolate; 5-10 CH2FH4, 5-10 methylene-tetrahydrofolate; 5-CH3FH4, 5-methyltetrahydrofolate; 5-CHOFH4 (FA), 5-formyltetrahydrofolate; DHFR, dihydrofolate reductase; FdUMP, 5-fluorodeoxyuridine 5′-monophosphate; FdUrd, 5-fluorodeoxyuridine; FH2, dihydrofolate; FH4, tetrahydrofolate; MS, methionine synthase; TK, thymidine kinase; TP, thymidine phosphorylase.
1.2.2.4 Elimination

Capecitabine is largely eliminated as metabolites (> 95% of the dose). The terminal half-life of the parent drug and its metabolites is short (< 1 hour). Excretion proceeds via the urine. No clinically relevant demographic factors or ethnic differences affecting the pharmacokinetics have been found to date.

1.2.3 DOSING:

1.2.3.1 ADULT

Colorectal cancer, metastatic: Oral: 1250 mg/m\(^2\) twice daily for 2 weeks, every 21 days till disease progression or cessation due to drug toxicity.

Dukes’ C colorectal cancer, adjuvant therapy: Oral: 1250 mg/m\(^2\) twice daily for 2 weeks, every 21 days each cycle consists of 2 weeks of drug administration and 1 week rest period, for a recommended total duration of 8 cycles. In this protocol oxaliplatin is administered as infusion on D1.

Colorectal cancer (unlabeled dosing): Oral: 1000 mg/m\(^2\) twice daily (in combination with oxaliplatin) on days 1-14 of a 3-week cycle for 8 or 16 cycles [25-27].

1.2.3.2 Dosing: Renal Impairment

Renal impairment at treatment initiation:

\(\text{Cl}_{\text{cr}} \geq 51 \text{ mL/minute}: \) Initial: No dosage adjustment necessary.

\(\text{Cl}_{\text{cr}} 30-50 \text{ mL/minute}: \) Initial: Administer 75% of usual dose. [28]

\(\text{Cl}_{\text{cr}} < 30 \text{ mL/minute}: \) Use is contraindicated.

Renal toxicity during treatment: dosage adjustments made based on the toxicity.
1.2.3.3 Dosing: Hepatic Impairment

- Hepatic impairment at treatment initiation:
- Mild-to-moderate impairment: No starting dose adjustment is necessary [28-29]; however, carefully monitoring of the patients is essential.
- Severe hepatic impairment: No dosage adjustment provided in manufacturer’s labeling (has not been studied).
- Hepatotoxicity during treatment: Hyperbilirubinemia, grade 3 or 4: Interrupt treatment until bilirubin ≤3 times ULN.

1.2.3.4 Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient’s actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved [30].
### 1.2.3.5 Dosing: Adjustment for Toxicity

**Table 1.4: Recommended Dose Modifications**

<table>
<thead>
<tr>
<th>Toxicity NCI Grades</th>
<th>During a Course of Therapy (Monotherapy)</th>
<th>Dose Adjustment for Next Cycle (% of starting dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>2nd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>3rd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>4th appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>2nd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>3rd appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st appearance</td>
<td>Discontinue permanently or</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1</td>
<td></td>
</tr>
</tbody>
</table>
1.3 Population Pharmacokinetics

Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest [31]. Certain patient demographical, pathophysiological, and therapeutical features, such as body weight, excretory and metabolic functions, and the presence of other therapies, can regularly alter dose-concentration relationships. For example, steady-state concentrations of drugs eliminated mostly by the kidney are usually greater in patients suffering from renal failure than they are in patients with normal renal function who receive the same drug dosage. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified.

Pharmacokinetic variability is due to several factors like

1. Demographic factors mainly include gender, body weight or surface area, age, and race [32, 33].
2. Environmental factors mainly being smoking, diet, and exposure to pollutants.
3. Genetic phenotype can also affect clearance (eg, CYP2D6, 2C19, 2C9, 2A6).
4. Drug-drug interactions also come into play.
5. Physiologic conditions like pregnancy and
6. Additional factors like circadian rhythm, also
### Table 1.5 Comparison of Traditional versus Population PK Approaches

<table>
<thead>
<tr>
<th></th>
<th>Traditional</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Healthy volunteers</td>
<td>Target patient population (pediatric, elderly, AIDS)</td>
</tr>
<tr>
<td></td>
<td>Highly selected Patients</td>
<td></td>
</tr>
<tr>
<td><strong>Study Size</strong></td>
<td>Small</td>
<td>Large or integrated(observational, experimental)</td>
</tr>
<tr>
<td><strong>Sampling Data</strong></td>
<td>Dense (typically 1 to 6 time points) following drug administration.</td>
<td>Sparse, few samples for many patients</td>
</tr>
<tr>
<td><strong>Inter-individual Variability</strong></td>
<td>Minimized through restrictive criteria</td>
<td>Demographics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pathophysiological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concomitant medications</td>
</tr>
</tbody>
</table>

1.3.1 Basic pharmacokinetic parameters

1.3.1.1 Clearance (CL)

CL is a measure of removal of drug from the body. It is the most important pharmacokinetic parameter when designing a rational regimen for long-term drug administration. Moreover, CL can also determines the maintenance dose that is required to obtain a given steady-state serum concentration. For most drugs, clearance is constant over the concentration range encountered in clinical settings, thus the rate of drug elimination is directly proportional to the drug concentration. This is usually referred to as first-order elimination.
1.3.1.2. Volume of distribution (V_d)

V_d relates the amount of drug in the body to the measured concentration of
drug in the blood or plasma. A large volume of distribution usually indicates the
drug distribute into body tissues and fluids. V_d is also an important
pharmacokinetic parameter because it determines the loading dose required to
achieve a particular steady state drug concentration immediately after the dose is
administered.

1.3.1.3. Half-life (t_{1/2})

t_{1/2} is the time required to change the amount of drug in the body by one-half during elimination.

1.3.1.4. Creatinine Clearance (CLCr)

CLCr is important in accurate estimation of renal function as many drugs
are partially or totally eliminated by the kidney. CLCR may be estimated using
serum creatinine value from the laboratory test. Increase in serum creatinine
concentrations are proportion to the decline in glomerular filtration rate (GFR),
which is a key parameter in determining kidney function.

1.3.2 Importance of Population PK Analysis

- Assess effects of covariates (age, weight, lab values, concomitant
  medications, other diseases, etc.) on PK and/or PK/PD
- To define optimal dosing regimen that will maximize efficacy and/or
  safety, guidance for choosing dosing regimens for pivotal studies and
  labeling and for future studies (Hepatic status, drug-drug interaction).
Introduction

- To estimate the parameters listed above with either dense and/or sparse data
- To estimate the magnitude of inter-patient variability
- To estimate the random residual variability (including intra-patient measurement error)
- To assist in developing a preclinical, clinical pharmacokinetic program for an NDA submission
- To provide Bayesian priors for forecasting in Randomized Concentration Controlled Trials and in the refinement of patient dosing regimens
- To help explain failed or less than successful trial based on PK and/or PK/PD relationships

1.3.3 Types of Population PK Analysis

1. Naïve Pooled Data

Combines all the data as if they came from a single reference individual and fit into a model using classical fitting procedures. It is simple, but cannot investigate fixed effect sources of variability, distinguish between variability within and between individuals.

2. Two-Stage Approach

It first estimates the individual subjects PK and/or pharmacodynamic (PD) parameters from dense data using classical fitting procedures (e.g. WLS), then estimate the population parameters across subjects (mean, variance, covariance). The standard error of the estimates for the coefficients can be calculated. However, it is only suitable for dense data. The variance-covariance across subjects (inter-
individual, intra-individual variability) may be biased. Since the imbalance is ignored, the estimates of interindividual errors are upwardly biased as residual error increases. Mixed-effects modeling results in less biased estimates when residual error is present.

3. Bayesian Estimation

The prior distribution of the parameters across a population of subjects and the actual data from an individual are used when estimating the parameters for an individual. The estimation of parameters in the individual uses the posterior probability of the parameters. The prior distribution determines individual parameters. It needs the estimates of the priors for the parameters (mean, covariance). The fit may be dependent on priors (and uncertainty in the priors).

4. Nonlinear Mixed Effects Modelling

Population PK utilises nonlinear mixed effects models, where the term ‘mixed’ denotes the combination of fixed and random effects. The population PK model can be viewed as comprising three sub-models: structural, statistical and covariate. The structural (PK-PD) sub-model describes the overall trend in the data (e.g. one-compartment model, or Emax-model), using fixed effects parameters (e.g. clearance (CL), or Emax). The statistical sub-model accounts for variability by using two levels of random effects, interindividual variability (IIV) and residual variability. The covariate sub-model expresses relationships between covariates and model parameters, using fixed effects parameters.
The individual parameter (e.g. CLi) can be described by:

$$CL_i = \theta_{CL} + \eta_i \quad (1.1)$$

The subscript i denotes individual, the fixed effects parameter $\theta_{CL}$ represents the mean (typical) value of CL in the population, and $\eta_i$ is a random effect accounting for the individual difference from the typical value (IIV). The $\eta_i$ values are assumed to be normally distributed in the population, with a mean of zero, and an estimated variance of $\omega^2$. The variance-covariance matrix of the $\eta_s$ ($\Omega$) is estimated. If CL is dependent on renal function, $CL_i$ can be described as a function of a covariate reflecting renal function, e.g. creatinine clearance (CLCR):

$$CL_i = \theta_{CL} + \theta_{CLCR} \times CLCR + \eta_i \quad (1.2)$$

$\theta_{CLCR}$ is a fixed effects parameter describing the linear dependence of CL on the fixed effect CLCR. Even if the mean parameters for an individual were known, and these were used to predict the drug concentration in that individual at a certain point in time, j, the measured (or observed) concentration ($C_{obs,ij}$) would differ from the predicted ($C_{pred,ij}$). This discrepancy, $\epsilon_{ij}$, is referred to as residual error; it may be the result of assay error, errors in dose or sampling time, and model misspecification.

$$C_{obs,ij} = C_{pred,ij} + \epsilon_{ij}(1.3)$$

The $\epsilon_{ij}$ values are assumed to be normally distributed with a mean of zero, and an estimated variance of $\sigma^2$.

In equations 1.1 and 1.3, the models for the residual error and the IIV are additive, i.e. a constant (homoscedastic) error is assumed, although different
models may be used. The error may be proportional to the predicted concentration (or the parameter), Cobs,ij= Cpred,ij(1+εij), and the distribution may be assumed to be lognormal (rather than normal), e.g. CLi=θCL×expηi. In these cases, the error increases proportionally with increases in the concentration/parameter (with a constant coefficient of variation), and thus is heteroscedastic. The additive and proportional residual error models can also be combined, and in some situations more elaborate models are required, e.g. using log-transformation, including auto-correlation [34] or varying residual error magnitude between subjects [35].

If parameters show random variation within individuals between study occasions, known as inter-occasion variability (IOV), this variability can also be quantified in the population PK model [36]. Equation 1.4 shows the model for IOV, where the CL of drug in individual i at occasion k (CLik) differs from the mean CLi by an additional (zero mean, variance π2) random effect, κik, which accounts for the intraindividual, between-occasion variability.

\[ \text{CL}_{ik} = \theta_{CL} + \eta_i + \kappa_{ik} \quad (1.4) \]

The three sub-models are interrelated, and the choice of structural (and statistical) model may affect the choice of covariate model and vice versa [37]. The process of finding a model that adequately describes the data is thus an elaborate task, where model refinement/checking must be performed in several steps. In a general approach to build the population PK model, after identifying an acceptable structural model, including adequate random effects, the influences of covariates are explored, and finally the model components are re-tested for relevance.
1.3.4 Identification of Patient Subgroups for Dose Individualization

Covariate-based dosing

Population pharmacokinetics and pharmacodynamics have been extensively used for the identification of patients or subgroups at risk for toxicity and/or under treatment. Including patient characteristics (also called covariates) in PK-PD modelling can quantify the effect of covariates on PK-PD parameters [38]. Variability between patients in drug exposure and/or pharmacodynamic effects may be partly explained by a covariate effect. Subsequently, covariates may be used to guide adjustment of a chemotherapeutic regimen for individual patients. This may contribute to the optimization of safe and effective dosing regimens for anticancer drugs.

Dose adjustments based on patient-related factors are often performed routinely. The dosage of multiple anticancer drugs is conventionally scaled to the body surface area (BSA) of a patient. However, the rationale behind BSA based dosing is up for debate [39]. For several anticancer drugs that are dosed based on BSA, no relevant relationship between the pharmacokinetics and BSA could be demonstrated [40,41]. However, for other drugs, relevant relationships have been identified [42, 43].

Besides measures of body size (BSA, weight), multiple other patient-related factors that might be considered for dose-individualization, such as age, gender, race, renal function, liver function, plasma protein levels, genotype and co-medication. For 5-FU, the mean clearance was estimated at 65 L for women and
125 L for men [44]. This suggests that therapy with 5-FU might be optimized when women would be treated with a lower dose than men.

In order develop rational dosing regimens; the selection of statistically significant and clinically relevant covariate relationships is required. Multiple techniques have been described to select significant and relevant covariate relationships [38]. Importantly, covariate-based dosing is only warranted if the magnitude of the inter individual variability explained by the covariate relationship is large. Characterization of the magnitude of variability within a patient population can aid the interpretation of the clinical impact of covariate relationships. For example, body weight and BSA were both statistically significant covariates in a pharmacokinetic model of pertuzumab. However, these demographic variables only explained a small percentage of the variability of pertuzumab pharmacokinetics between patients. The variability of trough levels at steady state was not relevantly reduced in a BSA- or weight-based dosing regimen. This analysis demonstrated the feasibility of fixed dosing of pertuzumab, which was subsequently used in the further development of the compound [45]. Covariate-based dosing regimens are eventually aimed to improve drug safety and/or efficacy. The clinical benefit of a dosing regimen is preferably evaluated in a clinical study. This was proposed for docetaxel. High alfa1-acid glycoprotein levels were related to less toxicity, efficacy and survival in patients with non-small cell lung cancer. This effect was believed to have a pharmacokinetic and a pharmacodynamic component. A phase III study of docetaxel was proposed to evaluate the benefit of a higher dose for patients with high alfa1-acid glycoprotein
levels. The clinical trial was never performed, because a simulation study had demonstrated low power to detect a difference in survival due to dose intensification [46].

In clinical practice, the physiological rationale for a covariate relationship should always be considered to judge if a covariate-based dose adjustment is indicated. This is exemplified by a case study of an obese patient, who had received a carboplatin dose that was based on the Cockcroft-Gault equation[47]. This equation is in fact not reliable for obese patients, but was nevertheless applied in routine clinical practice. The high body weight and low serum creatinine level resulted in a high individual dose for this patient. Exposure to carboplatin was 71% above the target exposure [47].

**Pharmacogenetics**

Population pharmacogenetic studies can be performed to identify relationships between genetic polymorphisms and pharmacokinetic or pharmacodynamic parameters. The field of pharmacogenetics is rapidly expanding. Population pharmacogenetic analyses have mainly been used to identify and quantify the effect of genetic polymorphisms of drug transporters and metabolizing enzymes on pharmacokinetic parameters. A gene mutation can be considered as any other potential covariate, as described above. However, some special considerations should be taken into account. In Pharmacogenetic studies, patients are commonly screened for multiple polymorphisms of multiple genes. In a subsequent population Pharmacogenetic analysis, the relationship between each polymorphism and one or more pharmacokinetic parameters of interest can be
investigated. The strategy of this analysis should be carefully designed, because the Pharmacogenetic effects of various polymorphisms may be correlated. It is therefore important to perform a multivariate analysis in pharmacogenetic studies. Furthermore, pharmacogenetic effects may be over predicted if all possible relationships are evaluated in a multivariate analysis. This may be partly precluded by constraining the analysis to an evaluation of physiologically plausible pharmacogenetic relationships. Significant pharmacogenetic effects have been identified for various anticancer drugs, but additional studies were warranted to evaluate the potential benefit of pharmacogenetically-guided dose individualization [48-52]. Simulation studies can also be conducted to verify the clinical implications of significant pharmacogenetic effects. For instance, elimination of the investigational anticancer agent indisulam was shown to be impaired by CYP2C9*3,CYP2C19*2 and CYP2C19*3 mutations. A simulation study was performed to evaluate the resultant relative risk of dose limiting neutropenia and a pharmacogenetically-guided dosing strategy was proposed [52].

1.3.5 When to Use the Population PK Approach

In drug development, use of the population PK approach can help increase understanding of the quantitative relationships among drug input patterns, patient characteristics, and drug disposition [30]. This approach is helpful when wishing to identify factors that affect drug behavior, or explain variability in a target population. The nonlinear mixed-effects modeling approach is especially helpful in certain adaptive study designs, such as dose-ranging studies (e.g., so called titration, or effect controlled designs). Population modeling is most likely to add
value when a reasonable a priori expectation exists that intersubject kinetic variation may warrant altered dosing for some subgroups in the target population. Likely circumstances would include (1) when the population for which the drug is intended is quite heterogeneous and (2) when the target concentration window is believed to be relatively narrow. The population PK approach can be used to estimate population parameters of a response surface model in phase 1 and late phase 2b of clinical drug development, where information is gathered on how the drug will be used in subsequent stages of drug development [53]. The population PK approach can increase the efficiency and specificity of drug development by suggesting more informative designs and analyses of experiments. In phase 1 and, perhaps, much of phase 2b, where patients are sampled extensively, complex methods of data analysis may not be needed. Two-stage methods can be used to analyze the data, and standard regression methods can be used to model dependence of parameters on covariates. Alternatively, data from individual studies in phases 1 and 2b can also be pooled and analyzed using the nonlinear mixed-effects modeling approach.

The population PK approach can also be used in early phase 2a and phase 3 of drug development to gain information on drug safety (efficacy) and to gather additional information on drug pharmacokinetics in special populations, such as the elderly [54-56]. This approach can also be useful in post marketing surveillance (phase 4) studies. Studies performed during phases 3 and 4 of clinical drug development lend themselves to the use of a full population pharmacokinetic
sampling study design. This sampling design can provide important information during new drug evaluation, regulatory decision making, and drug labelling.

1.4 Rationale for the Study

Most studies incorporate participants from broad range of ethnic and racial groups. No studies to date have examined the influence of genetic and non genetic factor that attribute to response/ toxicity with capecitabine therapy in colorectal cancer among south Indian population. This study aims at analysing pharmacogenetic profile of south Indian colorectal cancer patients who have been prescribed oral Capecitabine as per Internationally Recommended standards and their genetic factors which might interfere with tolerance of the same.