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Colorectal cancer in a Sri Lankan teaching hospital

- A descriptive and comparative study

Degree Project in Medicine

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Abstract

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Background: The economy in Sri Lanka has improved the last decades. Along with the prosperity of the country comes an increase in non-communicable diseases, such as colorectal cancer. Previous studies in South Asia suggests that the colorectal cancer differs in character from in the West regarding tumour location, age, tumour stage and survival.

Aim: To compare patterns and long term outcome of colorectal cancer in a Sri Lankan hospital and two Swedish National Colorectal cancer Registers.

Method: A retrospective medical record study including 185 patients diagnosed with colorectal cancer at Colombo South Teaching Hospital, Sri Lanka. Data was collected from the 5th of February to the 16th of Mars 2020. Swedish data was obtained from two National Colorectal Cancer Registers.

Results: 18% of the patients were younger than 50 years old, a more than three times higher proportion than in Sweden (5%). The mean age differed with almost 10 years, 62 in Sri Lanka and 71 in Sweden. Tumour location was also different. 60% rectal and 40% colon tumours in Sri Lanka versus 29% rectal and 71% colon tumours in Sweden. 9 of the 68 patients that were followed for 5 years died and 13 encountered recurrence. The absolute 5-year survival was 88% and the risk for recurrence within 5 years was 24%. Corresponding Swedish numbers for absolute 5-year survival was 82%, which resulted in no significant difference between the two countries.

Conclusion: Differences could be detected between Sri Lanka and Sweden regarding age and tumour location, since Sri Lanka has a younger group of CRC patients with primarily rectal

tumours. No statistically significant difference in absolute 5-year survival was found between the studied groups.

Key words: Colorectal cancer, Sri Lanka, Sweden, disease pattern, long term outcome

Introduction

About Sri Lanka

The Democratic Socialistic Republic of Sri Lanka is an island nation in South Asia and has a total population of 21.2 million people [1]. In spite of being hit by the tsunami in 2004 and suffering from a three-decade-long destructive civil war, which ended first in 2009, the country has been on steady road towards development. For the last decades the economy has improved. Gross National income (GNI) per capita (2011 PPP $) has increased more than eightfold from 1990 to 2018 [2]. Also, many health parameters have encountered substantial improvement. Life expectancy at birth has reached 75.5 years [1]. The under-five mortality rate per 1000 live births has reduced from 22 (1990) to 7.5 (2018) [3]. The maternal mortality ratio (MMR) per 100 000 live births has gone from 92 (1990) to 33.7 (2015) [4]. In contrast to India with MMR 145, Pakistan 140 and South Asia in total 163 it becomes clear how far Sri Lanka has reached when it comes to development [5].

Another indication of the progress in the country is the Human Development Index, HDI. HDI is an index made by the UN Development Programme. It summarizes the key aspects of the human development in each country: life expectancy at birth, access to knowledge and standard of living. A new index is set every year, making it possible to follow trends [6]. HDI in Sri Lanka was 0.770 in the year of 2018, compared to 0.625 in 1990. That places the country above the average level, rank 76 [1]. Corresponding figure for Sweden in 2018 was 0.937 [7].

The robust health care system in the country is partly liable for the good results in health

indicators. Free health care for all citizens is provided by the government [8]. Hospitals and other kinds of health service facilities are located in the whole country, though more peripheral areas still remain without physical availability. Public health care provides 95% of inpatient and 45% of outpatient care. The remaining part is taken care of by the private sector [4]. Private care started in the 1980's and though the engagement now is limited, it has a gap to fill and opportunities to grow. The long waiting time for specialist care indicates that the capacity of the public sector is insufficient [9].

The epidemiological transition and NCD's

As previously mentioned, Sri Lanka has an increasing prosperity making up the foundation for the epidemiological transition, shifting from infectious disorders to non-communicable diseases, NCD's. The NCD's are generally divided into four groups: cardiovascular diseases, chronic respiratory diseases, diabetes and cancer [10]. There are also other groups included, such as mental disorders. Risk factors are related to Western lifestyle and the consequences of it. Some examples are hypertension, obesity, use of alcohol, use of tobacco, dyslipidemia and physical inactivity. According to WHO these factors are expected to increase in Sri Lanka [8]. NCD's are the leading cause of death in the world (63%) and the majority of these deaths are in low-middle income countries [10]. Also, in Sri Lanka, NCD's are the leading cause of death, responsible for 75% of the total deaths each year. The part attributable to cancer has gone from fourth to second biggest group the past ten years [4]. The burden will continuously grow due to the ageing population [4] and the higher prevalence of risk factors. To manage the increasing demand of medical care, 900 healthy lifestyle centers, HLC's, were introduced

all over the country in the year of 2011. The function of these centers are to screen for these diseases and spread information to the population about risk factors [11].

The cancer transition

A component of the epidemiological transition is the increasing incidence of malignancies. In a study published in Lancet Oncology 2012 it was predicted that the incidence of all cancers globally will increase from 12.7 in 2008 to 22.2 million by 2030. The same study declares the geographical differences between cancer types. Cancer of the colorectum, female breast, lung, and prostate stands for more than half of the total cancer burden in countries with very high and high HDI. Compared to those regions, the countries with medium HDI had a higher incidence of malignancies of the oesophagus, stomach and liver. The most frequent cancer types in countries with low HDI was cervix, female breast, Kaposi's sarcoma and non-Hodgkin lymphoma. The conclusion was that socioeconomic progress leads to reduction in cancers that are related to infections and an increase in cancers related to the Western lifestyle, the so called cancer transition [12].

Colorectal cancer is globally the third biggest group of cancers and is the fourth most common reason for cancer-related death. The differences in incidence can be up to tenfold between different countries [13]. According to *Arnold M. et al (2017*) the increase of CRC will run up to more than 2.2 million new cases by 2030, a 60% increase. Similar to the study in Lancet Oncology 2012, they report a clear difference regarding geographical incidence depending on the level of Human Development Index [14]. Since Sri Lanka places above the average HDI, the country is more frequently exposed to cancer types associated with a higher

HDI than before, such as CRC.

According to WHO GLOBOCAN in 2018, CRC represents 6.1% of the total number of new cancer cases in Sri Lanka and is the fourth most frequent cancer (excluding non-melanoma skin cancer) in the country [15]. The National Cancer Control Programme (NCCP) in Sri Lanka presented in 2014 that CRC had an age-standardized rate of 6.9 per 100,000 world population [16]. This is an upward trend. WHO estimated the crude rate in the year of 2000 to be 3.2 per 100,000 women and 4.9 per 100,000 men [17]. Other countries in South Asia, such as China, Japan and South Korea, also reported a higher incidence during the past few decade [18]. Sweden is no exception from this trend. Beside an ageing population, this can be addressed to a real increase which in Sweden mainly consists of colon cancer. CRC is the third most common cancer type in Sweden and 6500 people were diagnosed in the year of 2017. The age standardized incidence of colon cancer per 100,000 population in 2017 was approximately 38 for women and 46 for men. The corresponding numbers for rectal cancer were 14 for women and 25 for men [19, 20], which is in line with the European average.

Development and clinic of CRC

Thus far, this report presents that an increasing HDI induces the epidemiological transition, which includes the cancer transition and a higher incidence of CRC. The etiology of CRC is multifactorial and not fully defined. It can be caused either by spontaneous or hereditary mutations. Spontaneous mutations stand for the greater part. Established risk factors are ageing, inflammatory bowel diseases, radiation towards the pelvic area and factors related to lifestyle. Red meat, physical inactivity, obesity, diabetes and use of alcohol and tobacco are some of them - the same as for all NCD’s. Hereditary forms stand for approximately 10-15%

[21], were familiar adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer syndrome (HNPCC) are the most well-known [22].

The predominate model to explain the development of most of the CRC, is malignant transformation of adenomas into adenocarcinomas. This is via multiple steps involving series of genetic alterations and mutations. The process can take 5-10 years [22]. The problem with CRC, as with many other cancers, is that symptoms often come in a late phase. In addition to that, symptoms often are ambiguous. Fecal blood, anemia and change in bowel habits are some examples [13]. An acute debut is less common. It occurs in 25% of the colon cancers and is considered rare for the rectal cancers. The initial diagnostic work up is by taking a history, digital rectal palpation, rigid sigmoidoscopy and laboratory tests for detection of anemia, as well as fecal occult blood. If suspicion of CRC, further investigation with colonoscopy and radiology is required [22].

Classification and treatment

Prognosis and composition of the treatment are dependent on the stage of the cancer and the general health of the patient, which can be defined by ASA classification and eventual comorbidities. In order to stage colon cancer, CE CT (contrast enhanced computer tomography) scan of the thorax, abdomen and pelvis is done. For rectal cancer, MRI of the pelvis replaces the CE CT pelvis as the most accurate method. At CSTH, CT chest and MRI pelvis are not considered mandatory [23].

Based on the imaging reports, the tumour is classified according to the UICC (International

Union Against Cancer) TNM classification. T describes how deep the tumour penetrates locally in the bowel wall, while N covers metastasis to regional lymph nodes. M indicates whether distant metastasis have been found or not [13]. The primary treatment is surgery. Both laparoscopic and open techniques can be used. In Sweden the majority is laparoscopic, while standard in Sri Lanka still is open. After surgery, a temporary or permanent ostomy often is needed. Different types of surgical procedures are made depending on the localization of the tumour [23]. In addition to surgery, oncologic treatment can be used in selected cases. The oncologic treatment can be neoadjuvant or adjuvant, e.g. preoperative or postoperative, and consist of radiotherapy, chemotherapy or the combination, chemoradiotherapy. Radiotherapy is given to rectal cancers that are locally advanced according to MRI pelvis and have high risk factors for recurrence. It has proven to decrease the risk of local recurrence and has the best effect given prior to surgery. Neoadjuvant chemoradiotherapy is given to more advanced rectal tumours. Adjuvant chemotherapy is preferably given to colon cancer with spread to regional lymph nodes being a high risk factor for recurrence. The purpose of adjuvant chemotherapy is to eradicate micro metastasis and has greater evidence for colon than rectal cancer. Colon cancer is not treated with radiotherapy [13].

Follow up and screening

There is weak evidence for the benefit of follow up programs. Therefor the composition and value of it is controversial and each country has their own national guidelines. The purpose of the follow up is to detect recurrence in time to be able to treat with curative intension. Recurrences are of different types: local, regional and distant. Local recurrence means at the site of the index cancer (including nearby tissue and lymph nodes), regional means close to

the primary site and distant considers spread to other organs (the same as distant metastasis or metastasis). The majority of the recurrences occur within 2-3 years after surgery and appear to be primarily located outside the lumen of the bowel. Liver is the most common location of distant metastasis, followed by lung and para aortic lymph nodes. Therefor follow up investigation should concentrate upon these areas [13, 22]. The tumour marker carcinoembryonic antigen (CEA) is one way of follow up. An increase in the serum level of CEA after treatment can be a sign of recurrence of the tumour. Though, recurrence can go without higher levels of CEA [22].

At CSTH the opinion is that comprehensive follow up is needed. All patients go through the same routine postoperatively, regardless of staging. This includes serum CEA 3 monthly and CE CT abdomen or pelvis 6 monthly during the first 2 years after surgery. The period 2 to 5 years after the surgery CEA is done 6 monthly and CE CT yearly. Colonoscopy is done annually. The intention is to follow the patients for at least 5 years [*B. Gamage, 2020-02-06*]. In Sweden, the composition of the follow up is decided by an algorithm, depending on the stage of the cancer and the health condition of the patient. The question "would the patient benefit from early detection?" is central. For instance, CRC stage I that has been through radical surgery gets no follow up since the risk for recurrence is so low. Patients with more advanced tumours are selected for a systematic follow up program which has similar constitution to the one at CSTH (colonoscopy, CEA, CE CT liver and thorax and MR pelvis) [13].

Both Sweden and Sri Lanka still remain without national screening programs, in spite of the

fact that WHO has qualified CRC for screening. Trials are pending in Sweden. None of the methods fecal occult blood test (FOBT) or endoscopic examinations (rigid or flexible sigmoidoscopy, colonoscopy) has yet shown to be both safe, easy and have a specificity and a sensitivity high enough [13]. Though, the incidence of CRC in Sri Lanka is still too low to benefit from screening.

Survival measurements

Estimation of survival can be done with different measures that are more or less relevant when it comes to cancer survival. Absolute survival (also called overall survival or just survival) is the percentage of patients alive after diagnosis or start of treatment [24]. Relative survival means the probability to survive in the absence of other causes of death besides cancer. It is defined as the ratio between observed survival and expected survival. This is done using population data based on gender, age and time period [25]. Another way of measuring survival rate is by looking at cause-specific survival. Cancer-specific survival excludes patients who died from other diseases than cancer. It is considered a more accurate estimation than overall survival. Overall survival risks presenting a lower survival than what is actually true for the specific cancer type [24].

The Sri Lankan CRC compared to the Swedish CRC

Despite the fact that the Asian countries follow the path of the countries with higher Human Development Index (HDI) regarding increased incidence of CRC, several studies have suggested a difference in the Asian pattern of this malignancy compared to the Western pattern. The distinctions regard tumour location, age at diagnosis, tumour stage and survival.

Both the National Sri Lankan registers [26] and studies that have been conducted in Colombo, Sri Lanka [17, 18], presents rectum as the major tumour location. On the contrary to Swedish registers, reporting a preponderance of colon tumours [19, 20]. The studies have shown that Sri Lankan patients with CRC are of younger age [17, 18] in comparison to Swedish CRC patients [13]. Also, a poorer absolute 5-year survival in Sri Lanka than in Swedish reports could be seen [17, 19, 20].

The Sri Lankan Cancer Registry (SLCR) has been maintained by the National Cancer Control Program (NCCP) since 1985. There is no legal liability for the hospital or pathology laboratories to report data to it. Still, in 2014 the registry was said to cover more than 80% of the total number of cancers in the country. Though the data in SLCR does not include mortality. The current mortality rates are numbers that are collected in the district of Colombo [27]. Even though improvements have been made regarding data collection and reporting, this register is still incomplete, and data are of insufficient quality. Altogether, there is a clear research gap since the pattern and long term outcome of the Sri Lankan CRC have not been fully surveyed.

The hypothesis of this study was that because of the considerably higher incidence of CRC in Sweden compared to Sri Lanka and the general diversities of the countries, there may be differences in long term outcomes and pattern of the disease.

Aim

The main aim of this thesis was to compare the long term outcomes after Colorectal cancer surgery at Colombo South Teaching Hospital in Sri Lanka, with corresponding Swedish data. The secondary aim was to determine the patterns of the Sri Lankan colorectal cancer and to outline potential differences from the Swedish version of the disease.

Specific research questions

What are the long term outcomes 5 years after Colorectal cancer surgery regarding absolute survival and recurrence rate?

What are the patterns of the Sri Lankan Colorectal cancer regarding TNM classification, tumour location, ASA class, gender and age?

Is there any association between 5-year absolute survival and TNM classification, ASA class, tumour location, gender and age?

Can differences between the Swedish and the Sri Lankan Colorectal cancer be detected?

Material and Methods

Study design

The thesis was a descriptive and retrospective medical record study. It took place between the 5th of February until the 16th of Mars 2020 at the Professorial Surgical Unit at Colombo South Teaching Hospital (CSTH), Sri Lanka.

Data collection

Information was collected from three different sources. The data register was the main source. It covered patients that had been diagnosed with Colorectal cancer (CRC) by Doctor Bawantha Gamage. Access to this was granted by him. The register was not complete. To enlarge the sample size and complement data, the medical records were used. These were compiled in cooperation with Stina Lindholm. The Sri Lankan patients do not have identification numbers. After discharge from a hospital stay, the medical record of the patient was filed under a temporary BHT, bed head ticket number. One person can therefore have many BHT's, making it hard to keep track of the medical history. In the operation theater at the hospital, a book of all the BHT's of patients that had undergone surgery at CSTH were stored. A list of the BHT's of the CRC cases was made. This contained the BHT of the patient, the name of the patient, type of surgery and date of surgery. With help from the staff at the medical record department, the correct medical record for those specific surgeries was obtained; all in paper form. Also, MDT sheets in paper form were added continuously from the recent clinic meetings during the time of the study. Those were patients either newly diagnosed with CRC or with recurrence of CRC. The variables were collected according to

the Data Collection Form (see Appendix A). All patients did not have contact information. The ones that had available telephone numbers were contacted to obtain more information regarding the long term outcome. To conduct the telephone calls, a list of questions was made (see Appendix B). The calls were carried out by medical students or practicing doctors at CSTH between the 17th of February to the 12th of Mars

Study population

All patients with the diagnosis of CRC were eligible for inclusion. Cases with missing information about one variable were excluded from that specific analyze. The study group for the long term outcome analysis was limited to the patients that had undergone surgery of the colon or the rectum, regardless of the type of procedure. Both acute and elective operations were included, as well as laparoscopic and open methods. The 104 patients that had available telephone numbers were called. 26 did not answer and 1 patient did not want to participate. 77 were reached, resulting in the answering frequency 74%. Out of these, 7 patients had not had any surgery yet and 3 had died before surgery was done. These 10 were excluded from the follow up. A total of 185 patients were included in the study, all diagnosed with CRC. 180 were taken from the register and the medical records while 5 were taken from the MDT sheets of the recent clinic meetings. 37 patients from the register were excluded from the beginning due to missing diagnosis or other diagnosis than CRC. When adding the data from the telephone follow up, in total 77 patients had data of long term outcome, whereof 68 had 5-year follow up. The surgery dates stretched from February 2010 to January 2020. A flow chart of the data collection is presented in Figure 1.

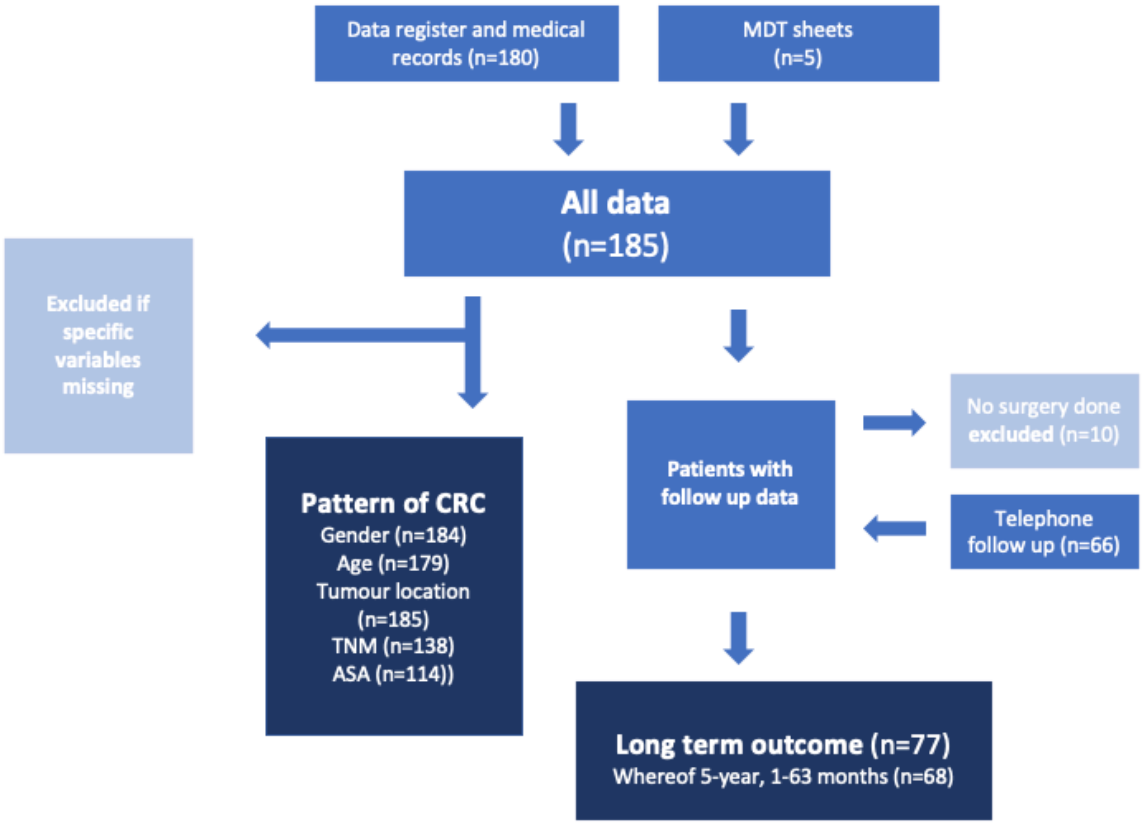

Figure 1. Flow chart of data collection. n= number of patients.

Age, gender and ASA class

179 patients had data about age and 184 about gender. The age of the Sri Lankan patients was defined as age at surgery in whole years. For cases when there was no information about date of surgery, the age was set as age at diagnosis. This was based on the assumption that the age of the patient was reported the year when it was put in the register. Data about ASA class, the American Society of Anesthesiologists physical status classification, was obtained for 114 patients.

Tumour location

185 patients had reported data about tumour location. When dividing into colon and rectal tumours, lesions located aborally to the level 15 cm from the anal verge were set at rectal and the rest as colon. The ones in the rectosigmoid junction, RSJ, were classified as rectal if a rectal surgery (anterior resection, abdominoperineal resection) was done and as colon if a colon surgery (sigmoid colectomy) was done. RSJ tumours were classified as a colon cancer in cases when no surgery had been done or information about it was missing.

TNM staging

The TNM stage was specified from histopathological reports (n=32), radiological reports (CE CT abdomen thorax and MRI pelvis, n= 40) or combinations of them (n=22). Subclassifications were not included. Histopathological reports were considered to be most accurate regarding the T- and N-stage, wherefor it was the primary source. The second most accurate was considered to be MRI. If the report had a description of the tumour but no TNM classification, then the TNM staging could be estimated for some cases (n=32) based on the radiological and/or histological report. 12 patients were lacking TNM staging. All together 138 patients were staged according to the TNM classification.

Long term outcome

Follow up time was calculated in months from the date of surgery until either the date of the latest investigation, the date of the telephone call or the date of death. If the patient underwent an investigation (radiological, endoscopic, blood sample) he or she was assumed to be alive at that date. Time until recurrence was calculated from the date of the surgery until the date of

the earliest imaging or endoscopic examination that discovered the recurrence or the date of the first treatment of the recurrence. If no information about recurrence was found in the report from the investigation, it was registered as no recurrence. The dates were specified in years and months. 5-year follow up included patients that were followed from between 1 to 63 months.

Swedish data collection and study population

Swedish data of all the CRC cases about age groups, gender and tumour location was collected from registers of the Health and Human Services Department of all new cases in 2018, in total 6809 patients. Age was specified as age at diagnosis. Raw data from the Colorectal Cancer Register, Regional Cancer Centre North, was applied for and used to estimate absolute survival and mean age at diagnosis. It contained all the 23,772 patients that had gone through resections in Sweden from 2015 to 2019 and included data about gender, age at diagnosis, colon or rectal cancer, date of resection, date of death or date of censorship. The resections included were AR (anterior resection), Hartmann's procedure, right sided hemicolectomy, ileoceacal resection, colectomy, sigmoid resection, transverse colon resection, left sided hemicolectomy and APR (abdominal perineal resection).

Statistical methods

Data was collected and stored in an excel file. The statistical analyzes were done with IBM SPSS statistics version 26. Frequencies and cross tables were used for the descriptive statistics. The Kaplan-Meier method was used to calculate survival rates and binomial distribution to calculate risk for death and recurrence. Univariate survival analyses for death

were performed using the logistic regression. P-value <0.05 was considered significant. Age was analyzed both as a continuous variable and by age-groups in the descriptive statistics, and as a continuous variable for the logistic regression.

Ethical considerations

Ethical clearance was received from Colombo South Teaching Hospital (see Appendix C) and from the Ethical Review Committee at CSTH, University of Sri Jayewardenepura (see Appendix D). The study aligns to the principles of the WMA Helsinki declaration for medical research and obeys the human rights. Data was treated anonymously using given ID numbers instead of names and coding key in a separate document.

Results

Gender, age and ASA class

The mean age of the Sri Lankans was 62 years with a range from 15 to 89. In the Swedish context mean age was 71.2 years. The age group with most patients in Sri Lanka were 60-69 years (34%) and 50-59 years (20%). Swedish patients were older, with the biggest age groups 70-79 years (38%) and 80 years and above (27%). The age groups are presented in Figure 2. There were 105 (57%) men and 79 (43%) women in the study group. Similar distribution of gender was seen in the Swedish patients (52.5% versus 47.5%). 68 Sri Lankan patients were ASA class 1, 43 class 2 and 3 class 3.

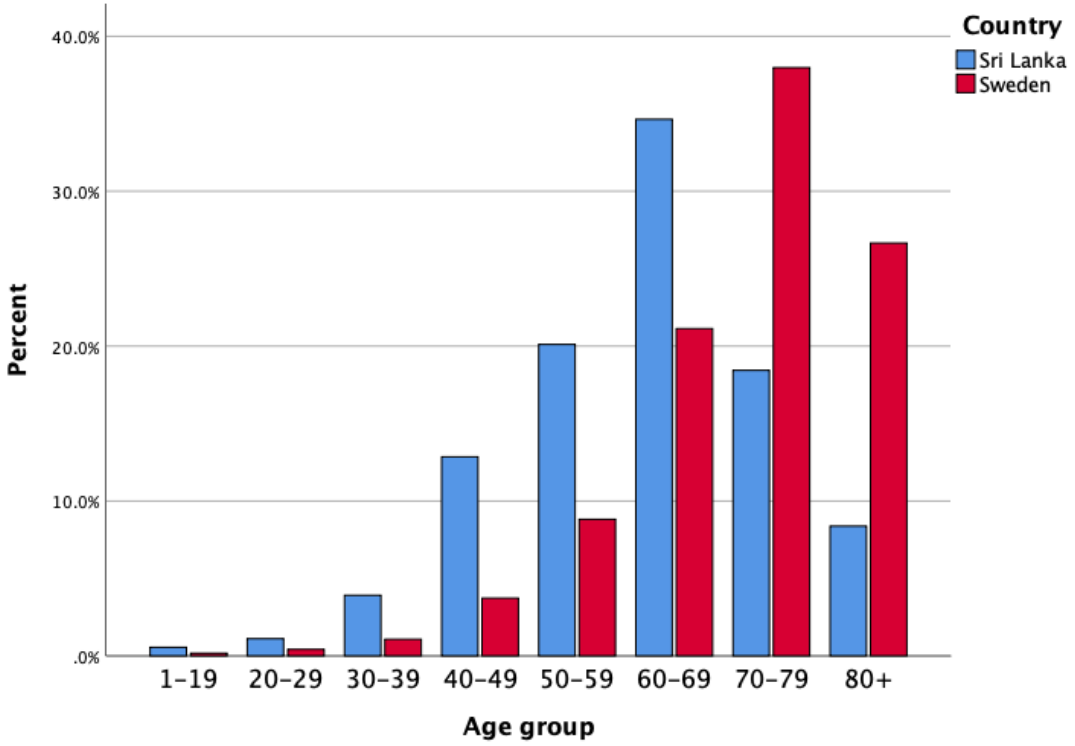

Figure 2. Comparison of age groups between Sri Lanka and Sweden. X-axis presents age groups in years and y-axis presents percentage of patients in each country.

Tumour location

In Sri Lankan patients rectum was the most common site with 60% (111) compared to colon 40% (74). 3 of the patients with rectal cancer had involvement of the anal canal. In the Swedish population colon represented 70.7% (4,815) and rectum 29.3% (1,994). See Figure 3.

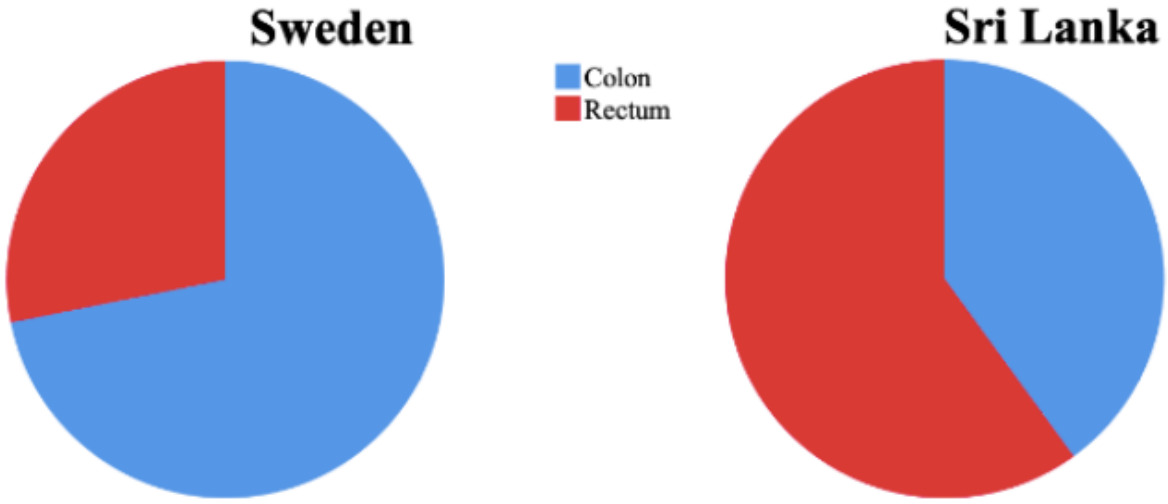

Figure 3. Tumour location in Sri Lanka compared to Sweden. Rectal tumours are 60% of the Sri Lankan and 29.3% of the Swedish patients, while corresponding numbers for colon tumours are 40% and 70.7%.

TNM staging

12% of the patients had distant metastasis, M1, when discovered and the majority of the tumours had grown through muscularis propria (T3) or had trans serosal spread (T4), 32% and 30%, respectively. See Figure 4.

		Count	Column N %
T-classification	1	3	2%
	2	32	23%
	3	44	32%
	4	41	30%
	X	18	13%
N-classification	0	45	33%
	1	50	36%
	2	20	14%
	3	1	1%
	X	22	16%
M-classification	0	61	44%
	1	16	12%
	X	61	44%

Table 4. Frequencies and percentages of stages in the TNM classification of the Sri Lankan patients with data about TNM staging. X means unclassified. Count = number of patients. Column N % = percentages of patients.

Overall survival

9 of the 68 patients that were followed for 5 years (1 to 63 months) died. After 5 years (69 to 120 months) there were 9 patients followed up, all alive. The mean follow up time was 27 months (range 1 to 120 months). Out of the 8 deaths, 2 were cancer related, 4 were due to other cause and 2 with unknown cause. The risk for death was estimated with binomial distribution. 0-5 years after resection the risk in Sri Lanka was 13.2% [95% CI 5.8-21.9] compared to 18.4% [95% CI 18 to 19] in Sweden. The difference in proportion of deaths was not significant, 6.6% [95% CI -4 to 13]. Absolute 5-year survival was 86.8% in Sri Lanka and 81.6% in Sweden.

Kaplan-Meier survival analysis failed to show significant differences in survival 0-5 years after surgery between the Sri Lankan and the Swedish study groups (see Figure 5). The

difference was estimated to 15 days with overlapping confidence intervals. The mean survival time for Sri Lanka was 52.5 months [95% CI 45.6-59.5] and for Sweden 52.0 [95% CI 51.8-52.3]. Neither with overall comparisons with Log Rank, Breslow nor with Tarone-Ware any significant difference could be found.

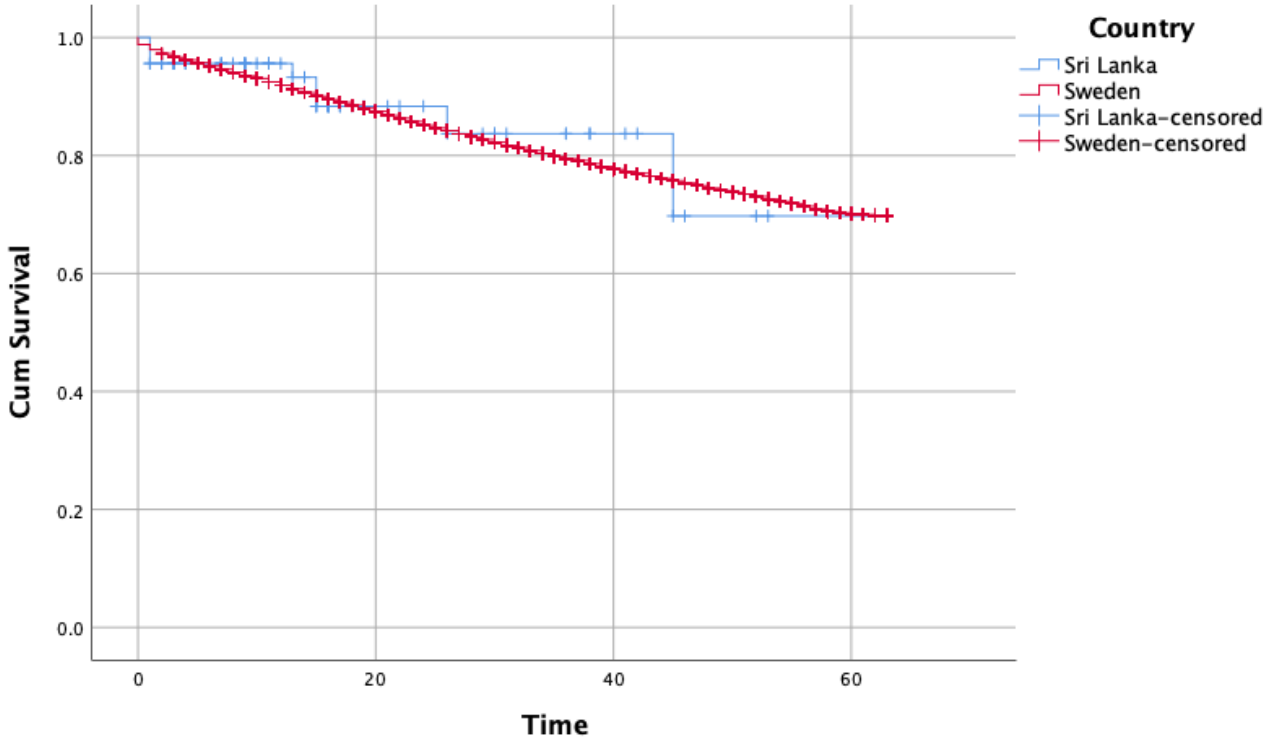

Figure 5. Kaplan-Meier plot for 5-year overall survival among Colorectal cancer patients in Sri Lanka versus Sweden. Time is reported as time after surgery, specified in months (1 to 63 months). Cum survival = cumulative survival.

In attempt to estimate correlation between death and time until death and the variables, logistic regression was used, analyzing each variable individually. The results are shown in Table 1. Age, solemnly, had significant correlation with death. No correlation with gender,

ASA class, TNM classification (T and M-classification) or tumour location was seen.

Variables		n (%)	Death		Odds ratio		
			No (%)	Yes (%)	OR	CI (95%)	p-value
Age		77 (100)	69 (90)	8 (10)	1.086	1.008-1.170	0.031
Gender							
	Male	47 (61)	42 (89)	5 (10.1)	Reference		
	Female	30 (39)	27 (90)	3 (10)	0.933	0.206-4.228	0.929
Tumour location							
	Colon	27 (35)	24 (89)	3 (11)	1.125	0.247-5.116	0.879
	Rectum	50 (65)	45 (90)	5 (10)	Reference		
ASA class							
	ASA 1	37 (59)	33 (89)	4 (11)	Reference		
	ASA 2+3	26 (41)	22 (85)	4 (15)	1.500	0.339-6.637	0.593
T-staging							
	T1	3 (5.0)	2 (67)	1 (33)	Reference		
	T2	19 (31.6)	18 (95)	1 (5)	0.111	0.005-2.550	0.169
	T3	25 (41.6)	25 (100)	0 (0)	0.000	0.0-0.0	0.998
	T4	13 (21.6)	12 (92)	1 (8)	0.167	0.007-3.890	0.265
M-staging							
	M0	18 (69)	16 (89)	2 (11)	Reference		
	M1	8 (31)	7 (87.5)	1 (12.5)	1.143	0.088-14.776	0.919

Table 1. Variables of Colorectal cancer patients potentially affecting risk for death within 5 years after surgery. Logistic regression was used for analysing odds ratio for each variable individually. OR = odds ratio. CI = confidence interval. n = number of patients.

Out of the 68 patients that were followed for 5 years (1 to 63 months), 13 encountered a recurrence. No recurrences happened after 5 years (69 to 120 months). The recurrences were allocated to liver metastasis (5 patients), liver and lung metastasis (3 patients), local recurrence (1 patient) and unknown type of recurrence (4 patients). 0-5 years after surgery the risk for recurrence was 24% [95% CI 14-35], estimated with binomial distribution. 2 deaths were due to distant metastasis and therefor included in the group of recurrences. Remaining deaths were excluded from the calculation. The mean time until recurrence was 91 months

[95% CI 76-105].

Comparisons of patients below and above 50 years

33 of the total 179 Sri Lankan patients, 18.4%, were younger than 50 years old. That is more than a 3 times higher proportion than in Sweden (5.4%). See Figure 6.

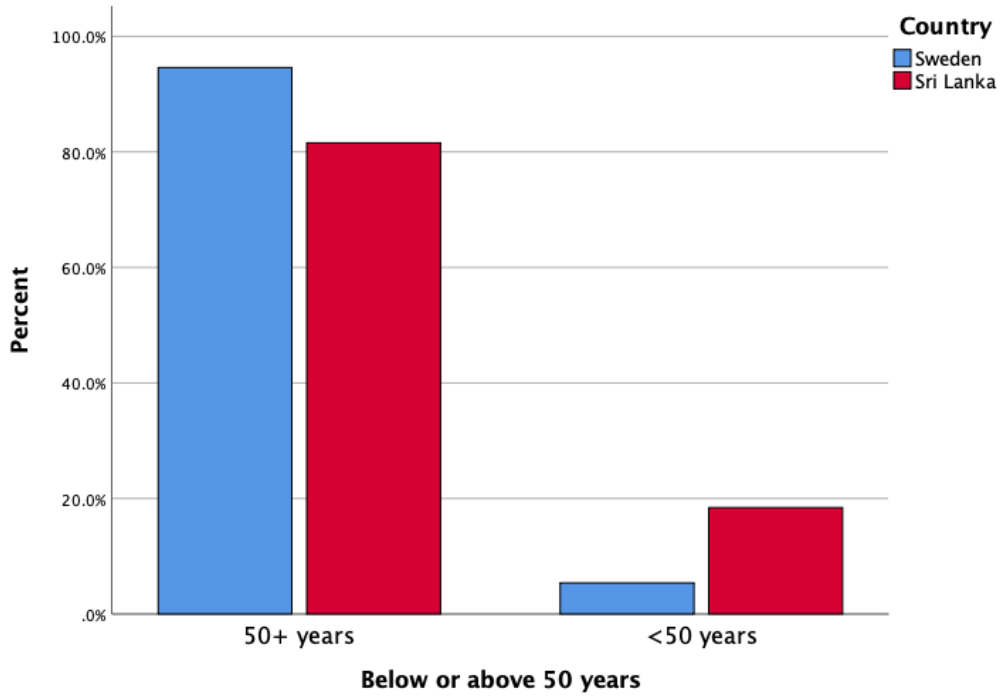

Figure 6. Percentage of patients below and above 50 years in Sweden compared to Sri Lanka.

The two age groups had comparable distributions of gender. The younger group had a higher proportion of rectal tumours (66.7%) and lower proportion of colon tumours (33.3%), compared to the older group (59.6% and 40.4%). The difference in tumour location between the age groups did not occur in the Swedish population. Rectal tumours stood for 29.2% (1,882) in the older group and 30.4% (112) in the younger group. Corresponding numbers for colon tumours were 70.8% (4,559) and 69.6% (256).

112 of the older and 24 of the younger patients had data about TNM classifications, see Figure 7. More than half of the young patients had tumour staged T4 (54%) compared to hardly one fourth of the older (24%). Regarding distant metastasis the two age groups had a hardly noticeable differences (older 12% versus younger 13%). The frequency of deaths within 5 years after surgery was 0% in the younger groups and 6.2% (9 of 146) in the older group. Recurrence had the same pattern, 0% among the patients below 50 years and 8.9% (13 of 146) among the patients above 50 years old.

		Below or above 50 years	
		50+ years Count	<50 years Count
T-classification	1	1	2
	2	31	1
	3	37	7
	4	27	13
	X	16	1
N-classification	0	37	7
	1	41	9
	2	13	7
	3	1	0
	X	20	1
M-classification	0	49	10
	1	13	3
	X	50	11

Figure 7. TNM classification for patients below and above 50 years old. X means unclassified.

Discussion

Key findings

This thesis set out with the aim to investigate patterns and long term outcomes of the Sri Lankan Colorectal cancer (CRC) and determine whether differences from the Swedish CRC could be detected. It was found that the CRC population in Sri Lanka was younger than in Sweden. Mean age differed with almost 10 years (62 versus 71) and the percentage of patients younger than 50 years old was more than 3 times higher (18.4% versus 5.4%). The majority of the patients were 60-69 (34%) and 50-59 (20%) years old, a substantial difference from Sweden where 70-79 (38%) and 80+ years (27%) were the biggest age groups. These findings are in line with results from other theses. Two studies in Colombo showed that almost one third of the patients were younger than 50 years old (26-28%) when diagnosed [17, 18]. The median age at presentation was 60 (range 9 to 88) [17] and the highest proportion was in the age between 50 and 80 [18]. The Ceylon Medical Journal presented in the year of 2000 that 19.7% of the Sri Lankan patients with CRC were 40 years or less [28]. In Sweden the percentage of colon and rectal cancer patients below 50 years old stand for 4% respectively 5% of the total amount of CRC patients [13]. The median age at diagnosis was 74 years [22]. A possible explanation to the considerably big group of young patients in the Sri Lankan CRC patients can be a generally younger population. The socioeconomic improvement in Sri Lanka brought an increase in the life expectancy which is closing in to the level of Sweden, 75.5 (2018) [1] compared to 82.2 years (2016) [29]. Still, the proportion of the population in each age group differs between the two countries. The population pyramid in Sweden shows greater number of people in the older ages compared to in Sri Lanka. Only 5.1% of the Sri Lankan population is 70-79 years old, while the corresponding Swedish number is 9.6% [30,

31]. This is likely to have an influence in the age comparison of the CRC patients between the two countries.

Furthermore, another key finding was the tumour location. The distribution of CRC's in Sri Lanka was almost opposite to that in Sweden; 60% rectal and 40% colon tumours in Sri Lanka, versus 29% rectal and 71% colon tumours in Sweden. The preponderance of rectal or left sided tumours in Asia compared to the West is in line with previous studies. Both *Zhang S. et al (2009)* and *Fang YJ. et al (2013*) present rectum as the major tumour site in China [32, 33]. Higher rates of rectal cancer was also found in China, including Shanghai and Hong Kong, when comparing with the US [34]. According to Sri Lanka's Cancer incidence data in the year of 2011 rectum is the most common site for CRC, followed by sigmoid colon [26]. A study in the Colombo region in Sri Lanka by *Chandrasinghe et al. (2017)* found left sided CRC in 82% and rectosigmoid in 77% of the cases [18]. These results were supported by another study of CRC patients in the same region [17]. This in contrast to what Swedish CRC registers formerly reported. Swedish patients show preponderance of right sided colon and with a proportion colon versus rectal cancer in approximately 70% and 30%, respectively [19, 20]. These numbers are in line with the other Western countries.

Arnold M. et al (2016) suggest that CRC in Asian countries have poorer survival than the Western countries [14]. Medium HDI (Human Development Index) countries, such as the Philippines, show increase in both incidence and mortality of CRC. Western countries, that generally have high HDI's, present declining incidence, as well as mortality of CRC. The correlation between tumour staging and survival is well established. A possible explanation

for poorer survival could be later discovery of the disease, thus a more advanced stage of the tumour. Reasons for later diagnosis might be the constellation of the health care system and the shortage of knowledge in the population. In this thesis survival after surgery was investigated. The absolute 5-year survival in the Sri Lankan group was higher than in the Swedish one, 88% versus 82%. Mean 5-year survival differed with 15 days. The difference was not statistically significant. *Perera et al (2008)* presented an absolute 5-year survival in Sri Lanka of 52% [17]. Corresponding numbers for Sweden, estimated by the Regional Cancer Centre North, were 57-60% [19, 20]. The survival rate of the Sri Lankan patients in this thesis is considerably higher. If these numbers are true, one explanation might be that the health care has improved the standard and that information spread about NCD's has succeeded. An important factor for discovering CRC is that the doctor is aware about the disease. Along with the rise in incidence that awareness might have been strengthened. Another explanation could be sampling bias. Only the patients that were healthy enough to undergo surgery were included in the long term outcome analysis. It creates a study group with risk of having survival rates that does not reflect the whole group of CRC patients. In addition, there is a risk that deceased patients become drop-outs, increasing the survival rates even more. Furthermore, important factors affecting the survival rates are the high expertise of the surgeons at the teaching hospital in combination with young patients operated.
The small sample size and the substantial amount of missing data have an impact as well. It is probable that Sri Lanka would have a lower survival due to the constitution of the health care system and more delays in the discovery of the disease than in Sweden. Taking these factors in consideration, a poorer survival in the Sri Lankan patients cannot be rejected. As mentioned in the previous section, the structure of the population pyramids in the two

countries differs [30, 31], which is also probable to affect the comparison of the survival. Age is not only a risk factor for CRC, but also for death. The effect on the survival rates could be, at least partly, evaded by performing age stratification on the data. Besides failing to show difference in survival, this study also failed to present more advanced M-stage in the Sri Lankan patients, of which only 12% of the patients had distant metastasis. A lesser part set against the Swedish numbers of 20-25% [22].

Risk for recurrence 5 years after surgery was estimated to 24% (range 14-35) for CRC. The numbers for recurrence presented in the Swedish registers are in the range 5-13% [19-21]. Swedish registers reported separately depending on staging, time after surgery, type of recurrence and tumour location which makes comparison hard to interpret. It is therefore of limited value. Since there were only 13 recurrences in the Sri Lankan group, type of recurrence was not analyzed. Due to the small sample size of the Sri Lankan group the risk might have been overestimated. Also, the Swedish data behind these numbers is known to be subject for under-reporting. Thus, the low frequency of recurrence in Sweden and the high frequency in Sri Lanka might not be representable. Another indication of the small sample size is the non-significant results in the correlation tests. The only true correlation found to increase risk for death was age. No correlation was found for neither ASA class or TNM stage, variables that otherwise are mostly probable to affect the risk for death. Once again, this puts light on the substantial shortage of data in Sri Lanka and the need for further research in this area.

The patients younger than 50 years had more locally advanced tumours, stage T4, than the older ones (54% versus 24 %). No difference in frequency of distant metastasis at diagnosis was found. As previously discussed, the staging is a high predictor of the prognosis. Implicating that the advanced stage in younger patients would provide poorer prognosis. Thus, this does not reflects in the long term outcome analysis. Nothing in the results speaks for a higher risk for death or recurrence for patients younger than 50 years old. None of the young patients had any recurrence or died. Though, it is impossible to say whether the lack of difference is due to small sample size or if it actually reflects the reality.

So far, results from this and several other studies suggest that different patterns of the CRC exist and many possible explanations are discussed. Besides age, environmental factors and lifestyle are known to affect the risk for sporadic forms of CRC. *Deen et al. (2016)* declared that countries with high incidence of young CRC cases are not the ones with high red meat consumption [35], opening up for other theories. Diverse ethnicities not only come with their specific lifestyles, but also with genetical variations which some studies point out to play a role in the diverse character of the malignant disease [34, 36]. Migrated South Asians in Great Britain had more rectal cancers, were of younger age and had more advanced stage at presentation compared to the Caucasians [36]. Japanese patients both in Japan and those migrated to the US had higher rates of rectal cancer than other ethnic groups in the US [34]. These circumstances are all suggestions of the importance of the genetics in the presentation of CRC in different ethnicities. Though, since ethnicity is a combination of lifestyle and genetical compositions it becomes hard to define what would play the key role in this context.

Study Limitations

The biggest limitation of the study is the low number of patients and lack of data. The way of reporting data, conducting registers and follow ups is not well established in Sri Lanka. One reason to this is the setup of the medical records in paper form and the usage of BHT's instead of identification numbers. Also, that contact information is missing in many cases or that patients do not own telephones makes long term outcome hard to survey.

While the Sri Lankan material had lot of shortages, the Swedish study group was of good size and had good coverage, resulting in precise estimations. This cannot be rejected to affect the estimation of the differences between the two countries. The age of the Swedish CRC patients was taken from the data of new cases in 2018. In contrary to the Sri Lankan patients that are collected from different years. Though, the distribution of ages most likely do not differ between years so it would not affect the results. The Swedish data about age was specified as age at diagnosis. Data about age in Sri Lankan differed in report occasion. It could be either at surgery or at diagnosis. However, reporting date is not the only parameter affecting. It is probable that there is less delay in diagnosing in Sweden than in Sri Lanka. When interpreting the age comparisons these factors need to be kept in mind.

The age groups and the distribution of gender were consistent with data from the National Cancer Control Program (NCCP) in Sri Lanka, making it credible that the study group is representable for the Sri Lankan population. Though this deviates regarding the tumour location. NCCP presents a close to even distribution between colon and rectum [16]. It brings up the question about how well the NCCP have surveyed the CRC patients in Sri Lanka and

also how well the majority of rectal cancers in this thesis reflects the actual truth.

Another limitation is that the absolute survival has been calculated, not the relative. Relative survival estimations require life tables and sufficient amount of data for accuracy. In addition, the calculations are advanced. Therefor it could not be carried out. Neither could cancer-specific survival calculations be done. This was due to inadequate quantity of deaths and information about cause of death. Absolute survival or overall survival is less representative for the survival of CRC alone. It is also harder to interpret and compare with other countries since relative survival is the measure predominantly used. The same goes for recurrence. Type of recurrences could not be analyzed due to the small study group. Tumour stage was not compared since there were no available data in the public Swedish registers about TNM class and due to shortage of time.

The retrospective study design provided more patients than a prospective would have. Though there is a risk of missing out on people who have died. A prospective design would not have been possible to conduct under these circumstances, because of the short observation time and the aim to follow up for 5 years. Due to the system of the medical records and bed head tickets (BHT's), the only way of follow up patients is by contacting them. One option would be to meet the patient at the clinic. Though that would be too time-consuming. Telephone follow up was the remaining workable alternative. The credibility of telephone follow ups in low-income countries can be discussed. Reporting of recurrence, age and dates might be doubtable. Patients are often uninformed and have shortage of knowledge. The fact that no other alternatives were available for follow up and the answering frequency of 74%, makes it

acceptable. Furthermore, only the patients that answered the telephone calls and had available telephone numbers were reached. Patients with lower standard of living who cannot afford a telephone are not represented in the results. Also, deceased and patients sick due to recurrence might be undiscovered. The survival results in this thesis therefor risk being higher than the actual number.

Future studies with similar settings should have longer observational time and a bigger study group, especially for the long term follow up. More patients would make it possible to study different types of recurrences and different causes of deaths. Divisions into subgroups should be done. For instance, analyzing rectal and colon cancer separately. Estimation of the relative survival and for shorter time periods, both 0-3 years and 3-5 years after surgery, would be interesting to do. It would also be desirable to have equivalent data about all variables when comparing the two countries.

Conclusion and Implications

This study provides support for the theory of a diversity in the pattern of the disease comparing Sri Lanka and Sweden, though only regarding tumour location and age. The conclusions that can be made are that the Sri Lankan patients are younger and have preponderance of rectal tumours. Though, these findings are limited by a small study group, data from only one hospital and highly competent surgeons performing the surgeries studied. The results are not fully conclusive when it comes to the complete character of the disease, especially for survival and tumour stage. This implies the need for more studies. If true diversities in the pattern of the disease can be detected, it may be favourable with different constitution of national guidelines regarding information programs, investigation, treatment and follow up. One suggestion is to increase the awareness of Colorectal cancer (CRC) in the general population Also, to make sure that doctors are aware of that CRC is not uncommon among young patients. Left sided and distal tumours (in rectum, rectosigmoid junction and sigmoid colon) are more easily detected than the right sided, opening up for usage of flexible sigmoidoscopy as investigation or screening method. From the results of this study, it would be probable that at least 60% of the tumours would be found with this technique. Earlier detection leads to less advanced stage and hopefully better prognosis.

The differences in the character, above all the incidence of CRC, age of the patients and tumour location between Asian and Western countries of the CRC awaken new questions. Further research should be carried out to investigate the cause of the differences in the patterns and the incidence of the disease. Is it due to biological diversities of different ethnicities or varying environmental factors, such as red meat consumption or obesity?

Populärvetenskaplig sammanfattning

Kolorektalcancer på ett Lankesiskt universitetssjukhus

- En beskrivande och jämförande studie

Tjock- och ändtarmscancer är den tredje vanligaste cancertypen i världen. Graden av insjuknande fortsätter att öka. Livsstilsrelaterade faktorer som rött kött, fysisk inaktivitet, övervikt, diabetes samt användning av tobak och alkohol är väl belagda riskfaktorer. Det har tidigare varit en sjukdom som företrädelsevis drabbar de västerländska länderna. Ekonomisk utveckling och höjd levnadsstandarden i låg- och medelinkomstländer medför ett västerländskt levnadssätt, som ökat förekomsten av de ovan nämnda riskfaktorerna. Sri Lanka har genomgått en betydande samhällsutveckling de senaste decennierna, vilket åtföljts av en ökad förekomst av tjock- och ändtarmscancer.

Tidigare studier på tjock- och ändtarmscancer i Sydasien, däribland specifikt i Sri Lanka, har visat tecken på att den sydasiatiska tjock- och ändtarmscancern skiljer sig från den västerländska i sitt sjukdomsmönster. Det rör sig om en större andel yngre patienter, mer avancerade stadie på tumören, sämre överlevnad och majoritet av tumörer lokaliserade i ändtarmen istället för tjocktarmen, vilket är det som dominerar i väst. Ännu har register, data och studier varit otillräckliga för att till fullo fastställa detta. Kartläggning av sjukdomens karaktär skulle kunna få betydelse för utformning av informationsprogram, utredning, behandling och uppföljning, som förhoppningsvis resulterar in en förbättrad överlevnad.

Syftet med denna studie var att undersöka 5-årsresultat och sjukdomsmönstret av den lankesiska tjock- och ändtarmscancern samt att fastställa om det fanns skillnader gentemot

den svenska tjock- och ändtarmscancern. Data samlades in under knappt två månader på ett universitetssjukhus i södra Colombo. Journaler, register och telefonuppföljning resulterade i ett studiematerial omfattande 185 patienter, varav 68 hade uppgifter om 5-årsutfall. Svenska data erhölls från Nationella cancerregister för tjock- och ändtarmscancer.

Det man fann var att 18% av patienterna i Colombo var yngre än 50 år, mer än 3 gånger så stor andel som i Sverige. Medelåldern i de olika länderna skiljde sig med nästan 10 år, 62 år i Sri Lanka jämfört med 71 år i Sverige. Majoriteten av de lankesiska patienterna var mellan 59-69 år, medan merparten av de svenska var över 70 år gamla. 60% av de lankesiska tumörerna fanns i ändtarmen och 40% i tjocktarmen. Ett nära motsatsförhållande till Sverige, där fördelningen är 29% ändtarm och 71% tjocktarm. Av de 68 lankesiska patienter som följdes i 5 år skedde 8 dödsfall. 13 fick återfall av sjukdomen. Den absoluta 5-årsöverlevnaden var 88% och medelöverlevnaden 52,5 månader. Någon signifikant skillnad i 5-årsöverlevnad jämfört med den svenska gruppen kunde inte påvisas. Risken för återfall inom 5 år var 24% hos de lankesiska patienterna. Resultaten stödjer de teorier om att cancersjukdomens karaktär skiljer sig mellan de två länderna med avseende på ålder och tumörlokalisation. Studien kunde inte påvisa skillnader gällande överlevnad. Det är troligt att detta har sin grund i det knappa antalet patienter i studiegruppen samt att mycket data saknades i de register som fanns tillgängliga för denna studie, men kanske framförallt att studien var förlagd till ett universitetssjukhus med hög kompetens hos de verksamma kirurgerna.

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Appendices

Appendix A: Data collection form

Date is reported in year and month.

Name
Telephone number
Age or date of birth
Gender
ASA classification
Anatomical distribution of the tumour
TNM stage
Histopathological and/or radiological report
Date of surgery
Type of surgery
Follow up after surgery - Date and result of examinations (endoscopic examinations, imaging, blood samples) - Date and type of recurrence - Date and cause of death (cancer related or other cause)

Appendix B: Telephone follow up

Hello, I am XX from Colombo South Teaching Hospital.

Please can I confirm, is this ……..?

Questions:

1. Date of birth (year and month)?

2. Date of surgery (year and month)?

3. Alive or not alive?

3a. If alive:

Recurrence or no recurrence of cancer?

Date (year and month) and type of recurrence?

3b. If not alive:

Date of death?

Cause of death?

Thankyou very much for your time!

Appendix C: Ethical approval from CSTH

தொலைபேசி Telephones 011-2763261-62 011-2736363-64 011-2763069-70

பணிப்பாளர் Director 011-2764160

தொலைநகல் Fax 011-2765505

மின்னஞ்சல் E-mail lsmpcolowila@sltnet.lk

எனது நிலை My Ref MO/PLEC/2020

உமது நிலை Your Ref

திகதி Date 2020.01.13

දකුණු කොළඹ ශික්ෂණ රෝහල, කළුබෝවිල, දෙහිවල, ශ්‍රී ලංකාව
கொழும்பு தெற்கு போதனா மருத்துவசாலை, களுபோவில, தெஹிவளை, இலங்கை
COLOMBO SOUTH TEACHING HOSPITAL, KALUBOWILA, DEHIWALA, SRI LANKA

Sofia Lindskogen,

Medical student,

Sahlgrenska Academy,

University of Gothenburg, Sweden.

Dear Ms. Lindskogen ,

Request for Ethical Clearance - Application No.821

Title: Long term outcomes 3 and 5 years after colorectal cancer surgery -A descriptive and comparative register study at CSTH

I am pleased to inform you that the Ethical Review Committee Meeting held on 2020.01.13 at Colombo South Teaching Hospital has granted ethical approval for your proposal.

The ethical approval for your project is effective from the above mentioned IERC meeting date which is valid until one year from the date of sanction. You may make written request for renewal / extension of the validity, along with the submission of annual status report.

As the principal Investigator you are expected to ensure that procedures performed under the project will be conducted in accordance with all relevant national and international policies and regulations that govern research involving human participants.

The approval letter is attached herewith for your reference.

Dr. ASELA GUNAWARDENA
Director
Colombo South Teaching Hospital
Kalubowila.
Dehiwala

Director

කැපවීමෙන් රැකවරණයට சேவை மனப்பாங்குடனான பராமரிப்பு DEDICATION TO CARE

Appendix D: Ethical approval from University of Sri Jayewardenepura

Ethics Review Committee

A SIDCER (Strategic Initiative for Developing Capacity in Ethical Review) recognized ERC

Faculty of Medical Sciences, University of Sri Jayewardenepura
Gangodawila, Nugegoda, Sri Lanka

Date: 27.01.2020 Our ref: 69/19

ERC meeting date: 23rd January 2020

Ms. Sofia Lindskogn
Lilatorpsgatan, 2a lgh 1201
416 55, Gothenburg , Sweden

Dear Ms. Lindskogn

Application Number: 69/19

Title: Long term outcomes 3 and 5 years after colorectal cancer surgery – A descriptive and comparative register study at CSTH in Colombo, Sri Lanka

Principal Investigator: Ms. Sofia Lindskogn
Co-investigators/ Supervisors: Prof. Bawantha Gamage, Prof. Goran Kurlberg

I am pleased to inform you that the FMS/USJP ERC at its meeting held on the above mentioned date has reviewed your application and considered it exempt from review for the following reasons.

The study is an audit and it has no direct patient involvement.
The following documents have been reviewed by the committee

Document	Version No

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