

Survival Analysis Of 335 Patients With Colorectal Cancer Undergoing Combined Treatment

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Abstract

Purpose: If colorectal cancer (CRC) is diagnosed in the early stages, the patients will have higher survival rates. Although there might be some other factors which affect the survival rate, the kind of treatment available based on existing health and therapeutic facilities, is very important as well. The aim of this study was to explore the best type of treatment in colorectal cancer patients.

Methods: The data of 335 patients with CRC in Kurdistan province were collected using population-based cancer registration system from first of March 2009 to 2014. Demographic and clinical- pathologic data of the patients were gathered through their medical and pathology records and going to the door of their houses. The cancer-specific survival rate were calculated using Kaplan-Meier survival curve, log-rank test, univariate and multivariate Cox regression. The data was analyzed using Stata 12 software.

Results: One-year, three-year and five-year survival rates were %87, %57 and %33 respectively. The median of survival was 42.6 months. The five-year survival rate for those patients who had received both surgical and chemotherapy treatments was %55.8. There was less mortality rate among the patients who had received both surgical and chemotherapy treatments compared to those who had not received any treatment (HR=0.57, 95% CI 0.24-0.93).

Conclusion: When CRC patients are treated using both surgical and chemotherapy treatments, they will have higher survival rate. Therefore, it is suggested to use both treatments for CRC patients.

Purpose

Colorectal cancer (CRC) is the second and the third kind of common cancer among women and men respectively and It's the fourth cause of mortality in the world. CRC incidence rate is different in various parts of the world, so that, It is the second cause of mortality among cancers in some countries (1–4). CRC is the third common cancer among women and the fifth among men in Iran and It is the fifth and sixth among women and men in Kurdistan province respectively (5, 6). Prognostic factors play an important role in the survival rate of the patients with this kind of cancer in its early and advanced stages. Moreover, demographic, socio-economic, pathologic factors and the type of treatment all affect the CRC patients' survival times. Despite the best available treatments, only 50% of patients survive for a long time.(7, 8).

Removing the tumor by surgery from the patient's body is the best therapeutic choice in this kind of cancer (9, 10). Chemotherapy seems to have a small role in the patients' survival time. Although chemotherapy effect size is not clear among different groups of patients, it mostly depends on the cancerous tumor stage (11, 12). CRC patients' prognosis depends directly on the diagnosis time and its stage (13, 14). CRC is curable through surgery if diagnosed in the early stages. A combination of various kinds of treatments is used in the advanced stages of the disease. Standard treating methods used for CRC patients are different based on the tumor size, location and type, and the patients physical characteristics as well (15– 17).

Common used treatments include surgery, chemotherapy or radiotherapy and a combination of these treatments together. Different surgical techniques, based on the therapeutic goals in various conditions and cancerous tissue removal, are used in different situations (18–20). In general, surgery is used in all stages of CRC except for those cases in metastatic stage which are less probable to be survived and their survival depend on the metastasis of cancer cells in their body (21, 22). Chemotherapy is also a type of treatment used in treating CRC cells and its effects on increasing the survival rate of these patients have been proven through clinical trials (21, 22). Chemotherapy is usually used in patients with metastatic cancer in their body and after the second stage of the tumor in a combination with surgery in order to decrease the death risk and to improve the patients' health condition(23). Radiotherapy, using high energy radiation for killing cancerous cells by damaging their DNA, is used before or after surgery. Although Radiotherapy might kill remnants of cancer cells, radiation can damage the healthy cells and produces side effects for the patients (24, 25). This treating method, like chemotherapy, is used in advanced stages and usually after the second stage of the disease. Treatment strategies in various stages of the disease are brought in therapeutic instructions. The effects of different types of treatments on CRC have been reported variably in different studies. The results of different studies on the stage, kind of treatment and the patients' survival times show improvement in treatment in all over the world in recent decades (21, 22, 26).

CRC treatment procedure including screening, surgery, chemotherapy and radiotherapy has improved in last decades, and the five-year survival for the patients through the last 30 years has, at least, increased from %51 to %65 (27, 28). Increasing evidence shows an increase in CRC patients' survival time in international level and this reveals that some changes in quality and the type of the treatments might have led to this increase in the survival rate (29, 30).

This study tries to investigate the effects of different types of treatments, with regard to other demographic and clinical factors, on estimating five-year survival rate of the CRC patients in Kurdistan province.

Methods

Data source

This is a retrospective Cohort study in which 335 CRC patients' data in Kurdistan province (the west of Iran) was investigated in a population-based study. Patients' data in five-years from first of March 2009 to 2014 were gathered using cancer registration system. Diagnosis and registration of the patient's data was encoded and extracted based on international classification diseases (ICD10), anatomic location of colon (C18), rectosigmoid (C19) and rectum (C20) cancers.

The survival rate was calculated from the time of diagnosis to the death time or the last follow up and the patients' basic data was provided through cancer registration system (cut-off date: October 2015). Then, demographic data of the patients including their age in the time of diagnosis, gender, address, insurance

status, history of smoking, socio-economic status (based on welfare status using principal component analysis) and cancer family history were gathered through patients medical records and going to the doors of their houses as well. Moreover, Pathologic and clinical data of the patients were gathered using their pathology reports, medical records and cancer registration system. The patients' treatment status was determined using their medical records and interviewing with the patient himself or one of his family members about the treatment procedure and their standard treatment procedure including surgery, chemotherapy and radiotherapy alone or in combination together was determined using the patients' medical records as well. They were assured that their demographic, pathological and clinical information as well as their medical records would remain confidential.

Statistical analysis

The initial outcome, studied here, was survival time which was defined as the interval time between the disease diagnosis to the patients' death or last follow up. The overall and specific survival rate were shown through Kaplan-Meier curve. Log-rank test was used to investigate survival time difference. One to five-year survival times for CRC patients were calculated and the median survival rate of the studied variables was determined. The significant level of this test was considered less than 5% ($P < 0.05$). Cox's proportional hazard regression models were used to estimate the hazard ratios (HR) for colorectal cancer specific mortality and overall mortality associated with demographic data. The correctness of the model fitted to the observations was determined using residual Martingale plot (31–33). The variables with the significant levels less than 0.1 ($P < 0.1$) were entered into the model and the Hazard Ratio (HR) and 95% confidence interval (CI) for estimating variables effect over the death risk resulting from CRC were determined. Stepwise multivariate regression method was used to analyze variables which independently had a significant relationship with the survival rate. Data Analysis was done using strata 12 (Stata Corp, College Station, TX).

Results

Studying 335 CRC patients in Kurdistan province showed that the incidence of this disease was higher among men (60.5%), men's age in the time of diagnosis is higher than women, age at diagnosis time in 137 patients (41%) were over 65 years and 82 (24.4%) were lower than 50 years old. Moreover, most of the patients used to live in cities (67.7%) and only 42 patients (12.5%) had a family history of developing this cancer. 307 patients (91.6%) had insurance and 24.4% were smokers. The results of the study, also, showed that, from the view point of the patients' clinical-pathologic status, 201 patients (60%) had colon cancer and 168 (50.1%) were diagnosed in the third III stage of the disease. Other prognostic factors are presented in the Table 1.

Table 1

Characteristics of the study population and 1, 3 and 5 year colorectal cancer cancer-specific survival [%], for Kurdistan province residents, diagnosed 2009–2014 (unadjusted). N = 335

CRC-survival (%)		N (%)	1 yr	3 yr	5 yr	<i>p-value</i>
Sex	Male	203 (60.5)	85.9	52.1	33.1	0.296
	Female	132 (39.5)	89.3	73.3	32	
Age at diagnosis	≤ 50 years	82 (24.4)	90.1	79.4	65.7	< 0.001
	51–64 years	116 (34.6)	85.2	63.7	45.4	
	≥ 65 years	137 (41)	78.4	49.9	14.6	
Residence	Rural	108 (32.3)	85	48.2	22.2	0.023
	Urban	227 (67.7)	88.3	60.3	39.3	
Insurance	No	28 (8.4)	61.7	38.2	34.1	0.125
	Yes	307 (91.6)	90.6	59.5	30.4	
Smoking	No	253 (75.5)	88	58.9	36.1	0.017
	Yes	82 (24.5)	85	47.6	23.8	
Socioeconomic status	Poor	105 (33.5)	90.7	70.8	44.7	0.002
	Moderate	104 (33.2)	89.4	51.9	30.6	
	Rich	104 (33.2)	72.7	54.3	8.4	
Family history of CRC	No	293 (87.5)	87.5	67.5	37.3	0.556
	Yes	42 (12.5)	85.4	54.3	32	
Comorbidity	No	205 (61.2)	87.2	59.1	41.6	0.026
	Yes	130 (38.8)	87.4	52	23.3	
Tumor location	Colon	201 (60)	87.5	54.6	34.3	0.717
	Rectum	94 (28.1)	84.6	58.7	35.4	
	Rectosigmoid	40 (11.9)	92.5	61	27.4	
TNM stage	II	68 (20.3)	89.7	74.3	40.4	0.085
	III	168 (50.1)	86.7	52.1	30.8	
Histologic type	Adenocarcinoma	308 (91.9)	86.8	56.5	32.4	0.599
	Mucinous\Other	27 (8.1)	92.5	51.4	41.3	
Tumor grade	Well differentiated	99 (29.5)	95.8	69.8	54.4	< 0.001

CRC-survival (%)		N (%)	1 yr	3 yr	5 yr	<i>p-value</i>
	Moderately differentiated	106 (31.6)	85.7	61.8	42.1	
	Poorly differentiated	86 (25.7)	81.2	51.2	23.5	
	Undifferentiated\anaplastic	44 (13.2)	83.7	28.4	4.1	
Treatment	None	10 (3)	53.2	33.2	-	< 0.001
	Surgery (S)	42 (12.5)	85.8	44.2	22.1	
	Chemotherapy(CH)	59 (17.5)	86	46.5	23.6	
	Radiotherapy (R)	23 (6.8)	85.2	62.1	24.1	
	S + R	86 (25.6)	88.1	73.2	46.5	
	S + CH	94 (28)	89.2	73.1	55.8	
	S + CH + R	21 (6.6)	81.3	41.2	30.4	
Abbreviations: HR, Hazard Rate; CRC, colorectal cancer; CI, confidence interval; TNM, tumor node metastasis; S, surgery; CH, chemotherapy; R, radiotherapy						

The one, three and five-year survival rate were %87, %57 and %33 respectively and the median survival time was 42.6 months (Fig. 1) and the median of survival is higher among women as well. Forty four patients (%13.3) were diagnosed with undifferentiated anaplastic tumor grade, for which Log-rank test showed a significant difference ($P < 0.001$). The median survival time for the patients diagnosed with poorly differentiated tumor grade was 36.2 months and the mortality rate was higher in this group (HR = 2.61, %95 CI 1.55–4.38). Moreover, the median survival time for the patients diagnosed with undifferentiated/anaplastic tumor grade was 25.4 months and the HR was 3.57 (HR = 3.57, 95% CI 2.10–6.22).

There was a significant statistical difference among the type of treatments, the patients have received ($P < 0.001$). The results showed that 3.6% of the patients had not received any kind of treatment and the survival rate was the least in this group (13.6 months). The five-year survival rate in patients who had received both surgery and chemotherapy was %55.8 and it was %46.5 for the patients received surgery and radiotherapy. (Table 1, Fig. 2).

Uni- and Multivariate Cox Regression analysis for the patients, based on the type of treatments they received, showed that HR and mortality rates for the patients who had received both surgery and chemotherapy were lower compared to the patients who had not received any treatment (HR = 0.57, %95 CI 0.24–0.93). However, univariate regression analysis showed that the patients, received surgery and radiotherapy, had a higher survival rate, but multivariate regression analysis did not show a significant difference in this group's survival time (HR = 0.64, %95 CI 0.22–1.33). There was not a significant

difference in the patients' survival rate who had received only surgery, chemotherapy or radiotherapy ($P > 0.05$) (Table 2).

Table 2
Univariate and Multivariate regression analysis for risk of CRC death, all CRC

Variables		Univariate	Multivariate	<i>p</i> -value
		HR (95%CI)	HR (95%CI)	
Sex	Female	1.0 (reference)	Not in model	-
	Male	1.18 (0.86–1.61)		
Age at diagnosis	≤ 50 years	1.0 (reference)	1.0 (reference)	-
	51–64 years	1.75 (1.03–2.98)	1.50 (0.80–2.82)	0.201
	≥ 65 years	3.60 (2.20–5.90)	2.78 (1.53–5.06)	0.001
Residence	Rural	1.0 (reference)	1.0 (reference)	
	Urban	0.69 (0.51–0.95)	0.98 (0.66–1.41)	0.113
Insurance	No	1.0 (reference)	Not in model	-
	Yes	0.96 (0.69–1.83)		
Smoking	No	1.0 (reference)	1.0 (reference)	-
	Yes	1.49 (1.07–2.09)	1.40 (0.95–2.07)	0.163
Socioeconomic status	Poor	1.0 (reference)	1.0 (reference)	-
	Moderate	0.70 (0.48–1.02)	0.82 (0.53–1.26)	0.808
	Rich	0.43 (0.29–0.65)	0.47 (0.29–0.78)	0.022
Family history of CRC	No	1.0 (reference)	Not in model	-
	Yes	0.87 (0.54–1.39)		
Comorbidity	No	1.0 (reference)	1	-
	Yes	1.41 (0.48–1.02)	1.14 (0.79–1.63)	0.549
Tumor location	Colon	1.0 (reference)	Not in model	-
	Rectum	1.05 (0.72–1.51)		

Variables		Univariate	Multivariate	
		HR (95%CI)	HR (95%CI)	<i>p</i> -value
	Rectosigmoid	0.84 (0.52–1.35)		
TNM stage	II	1.0 (reference)	1.0 (reference)	-
	III	1.44 (0.94–2.27)	1.22 (0.74–2.01)	0.317
Histologic type	Adenocarcinoma	1.0 (reference)	Not in model	-
	Mucinous\Other	0.84 (0.44–1.59)		
Tumor grade	Well differentiated	1.0 (reference)	1.0 (reference)	-
	Moderately differentiated	1.44 (0.91–2.29)	1.57 (0.93–2.66)	0.189
	Poorly differentiated	2.04 (1.30–3.20)	2.61 (1.55–4.38)	0.002
	Undifferentiated\ anaplastic	3.48 (2.14–5.67)	3.57 (2.10–6.22)	< 0.001
Treatment	None	1.0 (reference)	1.0 (reference)	-
	Surgery (S)	0.69 (0.52–1.14)	0.77 (0.63–1.55)	0.574
	Chemotherapy(CH)	0.58 (0.49–1.72)	0.76 (0.28–2.07)	0.612
	Radiotherapy (R)	0.64 (0.53–2.01)	0.75 (0.30–1.85)	0.534
	S + R	0.47 (0.41–0.96)	0.64 (0.22–1.33)	0.184
	S + CH	0.38 (0.22–0.69)	0.57 (0.24–0.93)	0.039
	S + CH + R*	0.91 (0.97–2.15)	0.99 (0.35–2.94)	0.397
Abbreviations: HR, Hazard Rate; CRC, colorectal cancer; CI, confidence interval; TNM, tumor node metastasis; S, surgery; CH, chemotherapy; R, radiotherapy				

Discussion

The results of this study showed that the patients' survival rate who had received both surgery and chemotherapy was higher than the patients with no treatment or only one type of treatment. Univariate regression analysis showed a lower HR in patients who had received surgery and radiotherapy, but multivariate regression analysis did not show any significant difference in this group. The median survival time for the patients who had not received any kind of treatments was lower compared to other patients.

The one, three and five-year survival rate were %87, %57 and %33 respectively and the median survival time was 42.6 months. In a systematic review study by Hoseini et al, (34) on the survival rate of the colorectal cancer patients, the results showed that 1, 3 and 5-year survival times were %85.9, %64.9 and %52.5 respectively and the survival median time was 52.2 months.

The type of treatment received and its effects on the survival rate of CRC patients have been investigated in other studies. Mehrabani et al, (35) found no significant relationship between the kind of received treatment by the patients (surgery, chemotherapy, radiotherapy, combination of them) and their survival times, but the mortality rate was higher in patients with no treatment (HR = 11.3, %95 CI 2.37–54.7).

Moreover, a study done by Asghari in Iran (36) showed that the mortality rate in patients who had received radiotherapy, chemotherapy and immunotherapy was 2.3 times more than the patients whose initial treatment had been surgery, which can be due to the tumor cells' characteristics. Lohavinij in Thailand (1) showed that chemotherapy after surgery indicates a good prognosis for CRC patients. Furthermore, Folkesson (37), in a study in Sweden, showed that patients' survival rate who had received both surgery and radiotherapy was higher compared to those who had only received surgery. Another study in Iran, also, showed that those patients who had received chemotherapy after surgery had a lower mortality rate (P = 0.018) (38).

Moreover, Simmonds et al, in a meta-analysis clinical trial study on the effects of chemotherapy on the patients' survival rate in advanced stages, showed that the death risk has significantly decreased in patients who had received chemotherapy (HR = 0.65, %95 CI 0.56–0.76). The survival median time was 8 months in the control group and 11.7 month for the trial group (11). In another meta-analysis clinical trial study by Buyes et al, it was shown that patients' survival rate who had received Fluoropyrimidines as an initial chemotherapy medicine was higher than those patients received Bolus Fluoropyrimidines (OR = 0.48, %95 CI 0.40–0.57) (39). Surgery is known to be the main and basic treatment for patients with CRC, and patients with emergency surgery seem to have a higher mortality rates compared to those with an elective surgery (40, 41). In a meta-analysis study, the results showed that a good follow up after surgery is influential on the patients' mortality rates (OR = 0.81, %95 CI 0.70–0.94) (42). Nevertheless, using other types of treatment including chemotherapy and radiotherapy can help decrease the disease relapse(43). Therefore, using chemotherapy or radiotherapy with surgery, in order to improve the patients' survival rate, is increasing nowadays. Radiotherapy is, recently, used with or without chemotherapy to kill the remaining cancerous cells after surgery or to decrease the tumor volume in order to facilitate the tumor surgery procedure. The standard treatment method is different for various patients based on the tumor

size and location and the patients' physical condition, and choosing the right kind of treatment by the physicians can enhance the likelihood of the treatment success.

One of the reasons for less survival rate in patients who only received chemotherapy or surgery in Kurdistan province can be that they were not able to pay for the high cost of chemotherapy and surgery. Moreover, Low economic status, low income because of low jobs and no supplementary insurance to cover all costs can be other reasons in this regard (44, 45). At the same time, patients who received both chemotherapy and surgery seem to have a better economic situation; therefore, they were able to go to private hospitals in larger cities with better treatment facilities that meet higher health standards.

The tumor diagnosis in those patients' who received combined treatment of radiotherapy, chemotherapy and surgery might have occurred in advanced stages and they might have had worse health conditions in that time. Although the time interval between chemotherapy and radiotherapy and surgery is a controversial issue, the common interval time from the last session of chemotherapy to surgery is about 4–6 weeks. There are contradictory results about the amount of interval time between radiotherapy and chemotherapy and surgery in various observational studies. The difference in survival rate might be between the patients received a combination of chemotherapy and surgery and those received only surgery, chemotherapy or radiotherapy which requires further investigation (46–49).

The increase of CRC incidence in older people can affect the survival rate of the patients too, so as the risk of death during 30 days after surgery has considerably increased in older patients. In a study in Netherlands, the mortality rate after surgery in 90–99 year-old patients had increased in comparison to 80–89 year-old ones, so as the mortality rate had increased %8 in 80–84 year-old, %13 in 85–90 year-old patients and %20 in patients more than 90 years old (50).

The results of this study, from the view point of age increase and the decrease in the survival rate is in line with other studies, however; worse prognosis in young patients have been reported in some other studies. The reason for this difference can be due to the type of treatment received by the patients and diagnosis of the cancer in advanced stages (51–53).

In older patients there might be some other diseases along with their cancer which make their physical condition worse and it prevents them to receive surgery (50). The survival rate in older patients with comorbidity was half compared to other patients based on Charlson Co-morbidity Index (54). In some other studies, the results showed that CRC in young people is more invasive, diagnosed in later and advanced stages and it has worse pathologic results and lower survival rate as well (13, 55–57). Yet, selection bias in choosing the proper and right treatments of surgery and/or chemotherapy in older patients and those with underlying diseases should not be neglected. The kind of hospital (public or private), treatment facilities, surgery and the surgeons' experience and skill might affect the survival rate of the patients too.

Better economic status is known to be influential on the patients' survival rate. Uni- and multivariate Cox regression analysis showed that patients with better economic status had higher survival times (HR =

0.47, %95 CI 0.29–0.78, P = 0.022). Some other studies have shown that economic status was an important and determinant factor in increasing the patients' survival rate (56). The results of those studies showed that the patients with a lower economic status had less access to medical facilities and their mortality rate was 1.2 times more than the patients with higher economic status (HR = 1.20, %95 CI 1.16–1.25)(55). Patients' lower economic status was related to their jobs and incomes, and to their less accessibility to medical facilities in rural areas and small towns which have led to the late diagnosis of the CRC in its advanced stages and an increase in the treatment costs and a decrease in their survival rate. However, the increase in the Spanish, Japanese and Chinese patients' mortality rate who live in the USA didn't show any significant difference with regard to their economic status (58). Early diagnosis, progressive and helping treatment in the early stages of the cancer and valid tumor grade classification are effective factors on the patients' survival rate.

Treatment quality and its availability, better economic status, diagnosis in the early stages of the disease alongside the type of the treatment are influential factors on the CRC patients' survival rate and clinical trials or meta-analysis studies can investigate the outcomes of the type of the treatment based on different stages of the disease well.

Conclusion

When CRC patients are treated using both surgical and chemotherapy treatments, they will have higher survival times. Therefore, it is suggested to use both treatments for CRC patients. A combination of surgery and chemotherapy can enhance the CRC patients' survival time and it is suggested to increase the patents' accessibility to these treatments.

Declarations

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Availability of data and materials

Available data set obtained from pathologic and clinical data of the patients were gathered using their pathology reports, medical records, cancer registration system records and going to the doors of their houses as well. The dataset supporting the conclusions is available upon request to the corresponding author.

Consent to publish

Not applicable

Declaration of Competing interest

The authors declare that they have no competing interests.

Author's contributions

DR, GM and MAR conceived, designed the study, analyzed, interpreted the data, and drafted the manuscript. GM, DR participated in the design of the study, composition of the study tool, supervision of the research process and critical revision of the manuscript. DR, GM and MAR participated in study design, composition of the study tool and critical review of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Approval for this study was obtained from Ethical Committee of the Kurdistan University of Medical Sciences (IR.MUK.REC.1394.36). A written informed consent was obtained from all patients. All patients were free to ask any questions and to withdraw if they did not wish to continue. All methods were carried out in accordance with relevant guidelines and regulations.

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Figures

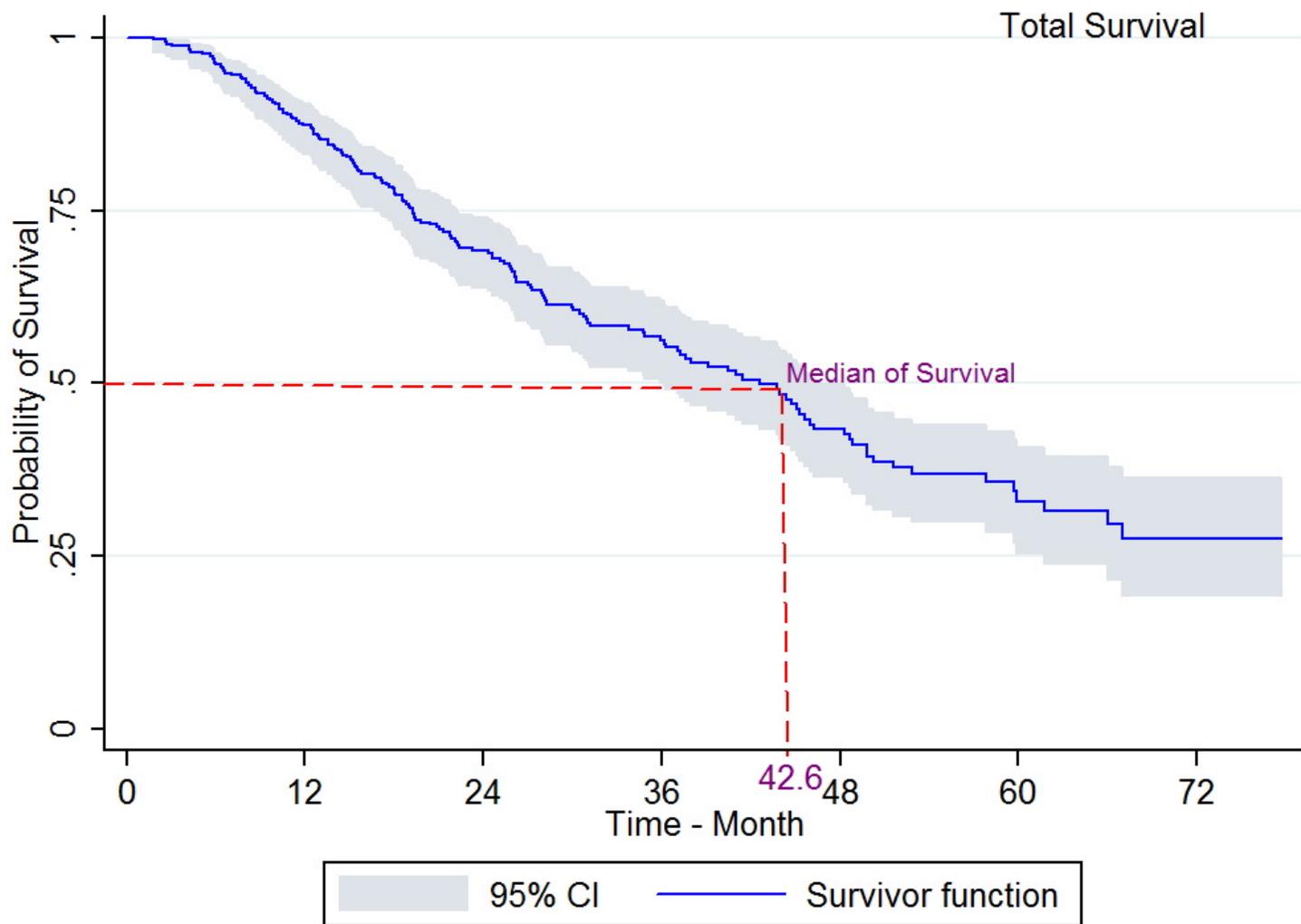


Figure 1

The one, three and five-year survival rate were %87, %57 and %33 respectively and the median survival time was 42.6 months (Figure) and the median of survival is higher among women as well.

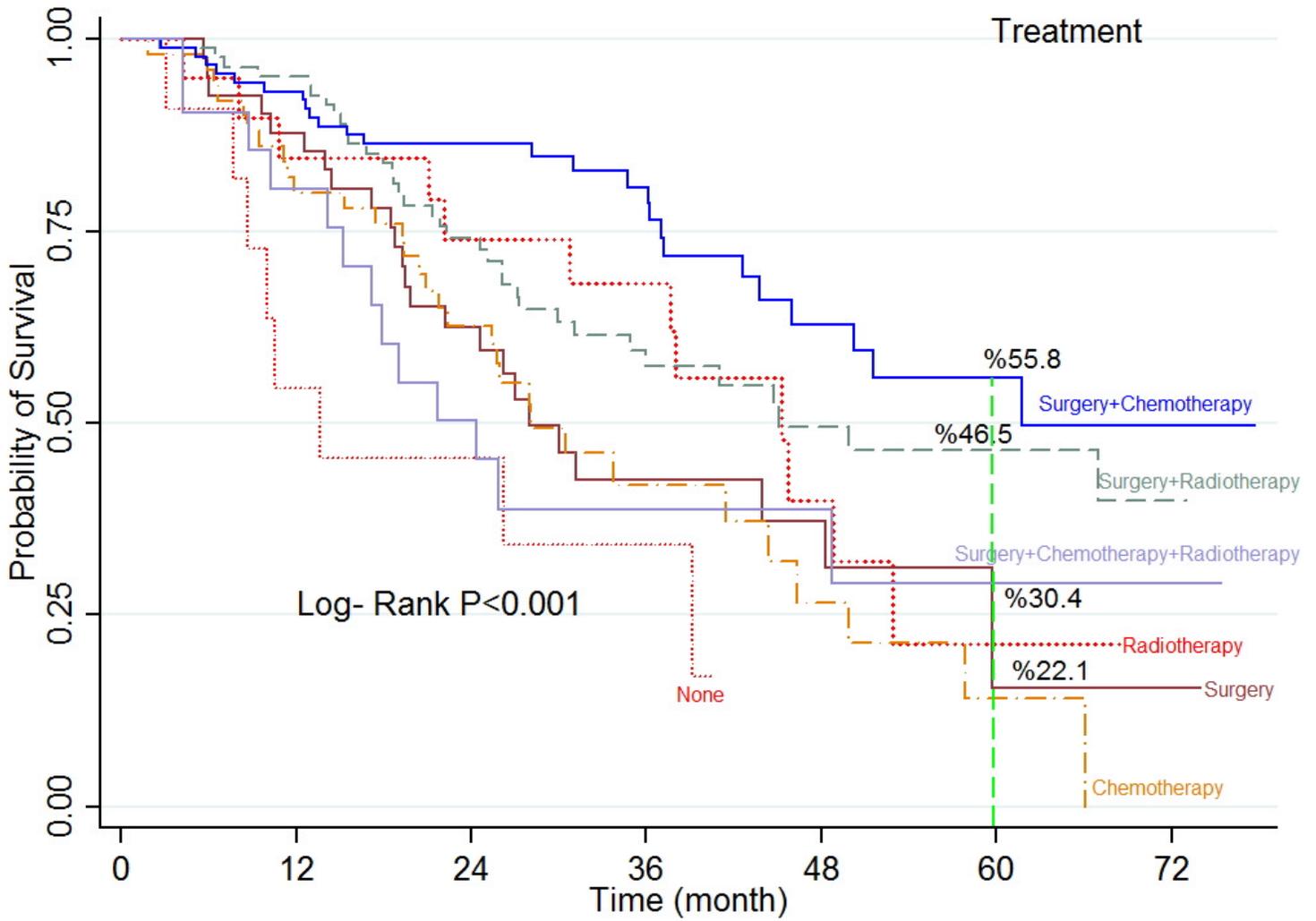


Figure 2

There was a significant statistical difference among the type of treatments, the patients have received ($P < 0.001$). The results showed that 3.6% of the patients had not received any kind of treatment and the survival rate was the least in this group (13.6 months). The five-year survival rate in patients who had received both surgery and chemotherapy was %55.8 and it was %46.5 for the patients received surgery and radiotherapy.