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First hospital contact via the Emergency Department is an independent predictor of overall survival and disease-free survival in patients with colorectal cancer

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ABSTRACT

Aims: the aim of this study was to examine the possible association between the type of hospital admission and subsequent survival of the patient, as well as the pathological features recorded in a large population of patients with colorectal cancer.

Methods: the study included 1,079 patients diagnosed with colon or rectal cancer in the Hospital Costa del Sol (Marbella, Spain). The relationship between patient survival rate and type of first admission to the hospital (elective or emergency admission) was assessed. The

following variables were studied: age, gender, tumor location, pathological stage, differentiation grade, chemotherapy before surgery and survival.

Results: colon tumors are more common in patients admitted to hospital for the first time via the emergency service (63.7%) and the tumors tend to be poorly differentiated (64.2%) and metastatic (70%). These patients also present a more aggressive disease and a poorer prognosis than patients with an elective admission. With regard to patients from the Emergency Department, a Cox regression analysis showed a risk-ratio (RR) of 1.36 (confidence interval [CI] 95%: 1.11-1.66) for disease-free survival and of 1.41 (95% CI: 1.14-1.76) for overall survival.

Conclusions: hospital admission via the Emergency Department is an indicator of aggressiveness and poorer prognosis compared to patients who enter via programmed routes.

Key words: Colorectal cancer. Prognosis. Admission. Emergency service. Survival.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, with nearly 1.4 million new cases diagnosed in 2012 (1). Apart from non-melanoma skin cancers, CRC is the third most common cancer among males and the second among females in Spain and accounts for 15% of all cancers. The incidence and mortality rates in Spain are expected to increase over the next few years (2). Despite these figures, scientific advances achieved in recent years have improved diagnostic methods and treatment strategies of this disease, resulting in a decrease in mortality rates (3). In this regard, the Organization for Economic Cooperation and Development (OECD) Health Report states that cancer mortality rates between 1990 and 2011 have decreased by 13%, particularly in Spain (4). Although this rate would be within the average of OECD countries, it is lower than the rate in other European countries or the United States (1).

Nowadays, low levels of formal education and the impossibility to modify particular risk factors (family history of tumors, genetic alterations, physical exercise, diet and smoking, etc.) hinder the primary prevention of this disease (5-7). Thus, justifying the need to improve secondary prevention strategies. In this respect, an appropriate reaction to the first

symptoms by the patient and an early detection of CRC by Primary Care physicians or screening programs contribute to treatment success and increase patient survival in over 90% of cases (8,9).

Numerous studies have determined useful prognostic parameters of CRC, such as age, gender, tumor localization and pathological tumor stage, which are among the most studied. Other factors such as the type of hospital admission have also been considered. Retrospective studies have found that emergency admissions account for 15-50% of the total hospital admissions (10-14). These studies have also examined the characteristics and prognosis of patients who required emergency surgery compared to those who underwent elective surgery, excluding the large percentage of patients who were not admitted on the same day (15,16). Porta et al. carried out the first study in this regard and examined the prognosis of digestive cancer patients in relation to the type of hospital admission. This study reported that 52% of patients admitted via an emergency procedure had a lower survival rate than those that underwent elective surgery (17). Similar correlations were reported for other digestive tumors, as well as for other types of malignancies such as breast cancer (18,19).

Both hospital-based and population-based cancer registries are useful sources of information and represent a fundamental tool to characterize malignancies. Data collected in population-based cancer registries are relatively limited and do not provide enough information about disease progression and patient survival. On the other hand, hospital-tumor registries provide valuable information about patients and disease course. They are also a valuable tool for all medical services dealing with cancer patients, as they help to improve their treatment and enable tracking and the evaluation of the use of hospital resources (12,19).

The concern about the use of the Emergency Department for undiagnosed patients is justified, especially when associated with a worse prognosis. For these reasons, this study examined the possible relationship between CRC patient survival and the type of initial contact with the hospital. Furthermore, its association with pathological features in a large series of colorectal carcinomas was also evaluated. Thus, all patients who visited the emergency service for the first time, regardless of whether they were finally admitted at that time or underwent emergency surgery, were considered for the study.

PATIENTS AND METHODS

Patients

A retrospective cohort study of 1,079 patients diagnosed with CRC at the Hospital Costa del Sol (HCS) (Marbella, Spain) was performed. The hospital serves a reference population of 372,964 inhabitants and does not have a screening program. Furthermore, almost all cases of carcinomas are attended by the HCS, which has the necessary services for the management of these patients. All symptomatic patients hospitalized and treated for the first time for CRC at the hospital were eligible for the study. The data in this study were obtained from January 1st 1996 to December 31st 2009 and follow-up was performed until January 31st 2014 (a minimum of five years follow-up). Carcinomas of the anal canal and tumors diagnosed by autopsy were excluded.

Methods

Information with regard to hospital admissions was obtained from the HCS Tumor Registry (19) (HCSTR), which was established in January 1995 as an initiative of the Tumor Commission using patient clinical records and the pathology department database as basic information resources. A fundamental requirement for these registries is their reliability and comparability with data from other registries. HCSTR operates in accordance with the World Health Organization (WHO) and the International Association of Cancer Registries (IACR) guidelines on case definitions, sources of information, recorded data and conditions applied. All personal information regarding diagnosis, therapeutic treatment and patient monitoring follow a systematic protocol that is anonymized in order to guarantee data confidentiality.

All patients who first attended the hospital via the emergency service, regardless of whether they were admitted or underwent immediate emergency surgery, were included in the study. The following variables were studied: age, gender, tumor localization, pathological stage and grade of differentiation, chemotherapy before surgery and patient survival (both disease-free and overall).

Patients were classified into two groups according to the type of hospital visit after the appearance of the first symptoms:

1. Elective group: patients who had visited their Primary Care physician and/or specialist.

2. Emergency Service group: patients who were initially treated in the emergency service. In this case, all patients who first visited the emergency service with tumor-related symptoms were studied, regardless of whether they were subsequently hospitalized or immediately underwent emergency surgery.

Survival rates were calculated from the date of diagnosis to recurrence or death. Data were censored for patients who were alive (recurrence-free) at the last monitoring visit and only cancer-specific survival was considered.

Statistical analysis

Means were compared by one-way analysis of the variance. The significance of the categorical variables was determined using the Chi-squared test. Univariate survival analysis was performed using the Kaplan-Meier method and Cox proportional hazards multivariate regression analysis was used to estimate the magnitude of the association and control for other factors. The statistical significance level was set at $p < 0.05$ and all statistical calculations were performed using the SPSS 15 software (Chicago, IL, USA).

RESULTS

The descriptive and bivariate data are shown by type of hospital admission in table 1. The average age of the study population was 68 (SD ± 11.8) years, 57.9% were male and 42.1% were female (data not shown). Also, 68.9% of patients had colon cancer and 31.1% had rectal cancer; 41.6% of cases corresponded to an elective admission, whereas 58.4% were admitted via emergency services.

Most patients admitted via the emergency services had colon cancer (63.7% *versus* 36.3% in programmed admission, $p < 0.001$) (Table 1) and belonged to the older age group ($p = 0.042$) (data not shown). In addition, 64.2% of these patients also had poorly differentiated tumors compared to 43% in the scheduled admission ($p < 0.01$). Admission via emergency services rather than elective admission was more frequent among female patients ($p = 0.054$) (Table 1). Type I was the most frequent pathological stage among scheduled patients, whereas types II to IV were more frequent in those admitted via the emergency services; 70% of the

emergency admissions had stage IV CRC (p < 0.001). These results highlight a statistical relationship between chemotherapy prior to surgery and emergency admissions (p = 0.072). Another important observation was that 52.6% of scheduled-treatment patients did have a recurrence *versus* only 35% of those admitted via the emergency service (p < 0.001). A similar pattern was observed with respect to mortality, as 65% of patients who first visited the hospital via the emergency service succumbed within the survival period, compared to 35% of the elective group. Survival of patients according to type of hospital admission, adjusted for age, differentiation and pathological stage is shown in figure 1. Weight loss was more frequent among patients with a first contact via the Emergency Department as opposed to patients from the scheduled admission, who presented blood in stool more frequently (p < 0.001). With regard to the survival rates of the population with respect to the type of hospital admission, the average disease-free survival period or overall survival was higher for the elective group (Table 2 and Fig. 1).

The hazard ratio (HR) for disease-free survival was 1.36 (CI 95%: 1.11-1.66) according to the Cox regression analysis for the emergency service group, which was adjusted for age, degree of differentiation and pathologic stage (Table 3). Therefore, we conclude that emergency service admission is an independent predictor of poor survival. The same multivariate model was used to assess overall survival and the HR obtained was 1.41 (CI 95%: 1.14-1.76) (Table 3).

DISCUSSION

This study estimates the clinical-pathological characteristics and specific survival rates of CRC associated with the type of admission to hospital, regardless of whether they were subsequently hospitalized or immediately underwent emergency surgery. It is important to determine the proportion of cancer patients who attend the emergency service for treatment without a prior diagnosis, as this substantially influences their prognosis. In our study population, 58.4% of patients had their first contact with the hospital via the Emergency Department. This value is higher than that reported by Polednak et al. (10) Manning et al. (11) and Mitchell et al. (20) but similar to that found by Agüero et al. (12). The reason for this discrepancy may be that we included all patients with a first contact with the emergency service, regardless of whether they were admitted on the same day. Whatever

the case, it seems clear that the high percentage of patients with a first contact with the emergency service may reflect the deficient attention paid to this problem beforehand by both the patient and primary healthcare services. Therefore, it seems apparent that action should be taken in this respect.

As previously described in other reports (14,17,20-22), our data show that those with a first contact via the emergency service are generally older and predominantly female. This trend is difficult to explain from our results and future additional studies considering cultural and sociologic factors are necessary to clarify this point. Patients who attend the emergency service more often have poorly-differentiated CRC tumors and are at an advanced stage of the disease. These results are consistent with those previously reported by other groups in patients undergoing emergency surgery (23-25). Likewise, as previously published in other series, constitutional symptoms such as weight loss are more frequent in this group, while rectal bleeding is more frequent in patients with a programmed admission (17).

Another interesting observation is the relationship between chemotherapy prior to surgery and the emergency service as a first contact with the hospital. This situation may arise as emergency hospital admissions are related to the presence of more advanced tumors and therefore, neoadjuvant chemotherapy prior to surgery is needed. This fact is evident as this variable was not an independent prognostic factor in the Cox regression analysis. In this respect, Porta et al. also reported that surgery is the first treatment more frequently required for elective-treatment tumors (17).

In the present study, the differences in the survival rates were evaluated of CRC patients whose first contact was via the emergency service compared to those with a scheduled visit. Previous studies have reported a poorer prognosis for patients who undergo emergency surgery (15,16,24). In this regard, Porta et al. also found a poorer prognosis in a study that included all patients whose hospital admission was via the emergency service, regardless of subsequent surgery (17).

Our study had a larger population than the above-mentioned studies and showed that initial hospital contact via the emergency service is an independent prognostic factor for survival. These differences in survival do not appear to be due to differences in the quality of care, in either case. Moreover, the hospital cancer registry is a very reliable tool for monitoring these patients.

With regard to the limitations of the study, this is a retrospective study in a specific area of the Spanish territory and our results may not be extrapolated to the rest of the population, especially if there is no implemented CRC screening program. On the other hand, it is not possible to determine whether our results are influenced by population variables (race, cultural level, pluripathology, etc.) (26,27) or by organizational variables in the health system where the study was conducted. Considering these limitations, we can conclude that CRC patients whose first contact with the hospital was via the Emergency Department present more advanced stages of the disease and independently predicted poorer survival rates than those with a scheduled visit. Thus, highlighting the need to implement a more generalized screening program for this type of tumor.

REFERENCES

1.   Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359-86. DOI: 10.1002/ijc.29210

2.   Arnold M, Sierra S, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66(4):683-91. DOI: 10.1136/gutjnl-2015-310912

3.   Mathoulin-Pelissier S, Bécouarn Y, Belleannée G, et al. Quality indicators for colorectal cancer surgery and care according to patient-tumor, and hospital related factors. BMC Cancer 2012;12:297. DOI: 10.1186/1471-2407-12-297

4.   OECD. Health at a glance 2013: OECD indicators. OECD Publishing; 2013. DOI: 10.1787/health_glance-2013-en

5.   Keighley MRB, O'Morain CO, Giacosa A. On behalf of the United European Grastroenterology Federation (UEGF) Public Affairs Committee. Public awareness of risk factors and screening for colorrectal cancer in Europe. Eur J Cancer Prev 2004;13:257-62. DOI: 10.1097/01.cej.0000136575.01493.9b

6.   Norat T, Bingham S, Ferrari P, et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst 2005;97(12):906-16. DOI: 10.1093/jnci/dji164

7.   Zarcos-Pedrinaci I, Fernández-López A, Téllez T, et al. Factors that influence treatment delay in patients with colorectal cancer. Oncotarget 2017;8(22):36728-42. DOI: 10.18632/oncotarget.13574

8.   Byles J, Redman S, Hennrikus D, et al. Delay in consulting a medical practitioner about rectal bleeding. J Epidemol Community Health 1992;46:241-4. DOI: 10.1136/jech.46.3.241

9.   Díaz Tasende J. Colorectal cancer screening and survival. Rev Esp Enferm Dig 2018;110(11):681-3. DOI: 10.17235/reed.2018.5870/2018

10.   Polednak AP. Inpatient hospital admission through an emergency department in relation to stage at diagnosis of colorectal cancer. Cancer Detect Prev 2000;24:283-9.

11.   Manning AT, Waldron R, Barry K. Poor awareness of colorectal cancer symptoms; a preventable cause of emergency and late stage presentation. Ir J Med Sci 2006;175:55-7. DOI: 10.1007/BF03167968

12.   Agüero F, Murta-Nascimento C, Gallén M, et al. Colorectal cancer survival: results from a hospital-based cancer registry. Rev Esp Enferm Dig 2012;104(11):572-7. DOI: 10.4321/S1130-01082012001100004

13.   Gunnarsson H, Jennische K, Forssell S, et al. Heterogeneity of colon cancer patients reported as emergencies. World J Surg 2014;38(7):1819-26. DOI: 10.1007/s00268-014-2449-7

14.   Hogan J, Samaha G, Burke J, et al. Emergency presenting colon cancer is an independent predictor of adverse disease-free survival. Int Surg 2015;100(1):77-86. DOI: 10.9738/INTSURG-D-13-00281.1

15.   Ghazi S, Berg E, Lindblom A, et al. Low-Risk Colorectal Cancer Study Group. Clinicopathological analysis of colorectal cancer: a comparison between emergency and elective surgical cases. World J Surg Onco 2013;11:133. DOI: 10.1186/1477-7819-11-133

16.   Wong SK, Jalaludin BB, Morgan MJ, et al. Tumor pathology and long-term survival in emergency colorectal cancer. Dis Colon Rectum 2008;51(2):223-30. DOI: 10.1007/s10350-007-9094-2

17.   Porta M, Fernández E, Belloc J, et al. Emergency admission for cancer: a matter of survival? Br J Cancer 1998;77(3):477-84. DOI: 10.1038/bjc.1998.76

18.   Redondo M, Rodrigo I, Pereda T, et al. Prognostic implications of emergency admission and delays in patients with breast cancer. Support Care Cancer 2009;17(5):595-9. DOI: 10.1007/s00520-008-0513-2

19.   Redondo M, Rivas-Ruiz F, Guzmán-Soler MC, et al. Monitoring indicators of health care quality by means of a hospital register of tumours. J Eval Clin Pract 2008;14(6):1026-30. DOI: 10.1111/j.1365-2753.2007.00937.x

20.   Mitchell Al D, Inglis KM, Murdoch JM, et al. Emergency Room presentation of colorectal cancer: a consecutive cohort study. Ann Surg Oncol 2007;14(3):1099-104. DOI: 10.1245/s10434-006-9245-z

21.   McPhail S, Elliss-Brookes L, Shelton J, et al. Emergency presentation of cancer and short-term mortality. Br J Cancer 2013;109:2027-34. DOI: 10.1038/bjc.2013.569

22.   Abel GA, Shelton J, Johnson S, et al. Cancer-specific variation in emergency presentation by sex, age and deprivation across 27 common and rarer cancers. Br J Cancer 2015;112(Suppl 1):S129-36. DOI: 10.1038/bjc.2015.52

23.   Bass G, Fleming C, Conneely J, et al. Emergency first presentation of colorectal cancer predicts significantly poorer outcomes: a review of 356 consecutive Irish patients. Dis Colon Rectum 2009;52(4):678-84. DOI: 10.1007/DCR.0b013e3181a1d8c9

24.   Lana A, Álvarez-Guerrero S, Herrero-Puente P, et al. Diagnóstico de sospecha del cáncer en los servicios de urgencia hospitalarios. An Sist Sanit Navar 2014;37(1):59-67. DOI: 10.4321/S1137-66272014000100007

25.   Amri R, Bordeianou LG, Sylla P, et al. Colon cancer surgery following emergency presentation: effects on admission and stage-adjusted outcomes. Am J Surg 2015;209(2):246-53. DOI: 10.1016/j.amjsurg.2014.07.014

26.   Weidner TK, Kidwell JT, Etzioni DA, et al. Factors associated with Emergency Department utilization and admission in patients with colorectal cancer. J Gastrointest Surg 2018;22(5):913-20. DOI: 10.1007/s11605-018-3707-z

27. Askari A, Malietzis G, Nachiappan S, et al. Defining characteristics of patients with colorectal cancer requiring emergency surgery. Int J Colorectal Dis 2015;30(10):1329-36. DOI: 10.1007/s00384-015-2313-8

Table 1. Bivariate and descriptive analysis, by type of hospital admission

Variables		All		Elective		Urgent		p
		Mean	SD	Mean	SD	Mean	SD	p
Age		68.0	11.8	67.1	11.4	68.6	12.1	0.042
		n	%	n	%	n	%	p
Type of admission	Elective	449	41.6					
	Urgent	630	58.4					
Sex	Male	625	57.9	276	44.2	349	55.8	0.054
	Female	454	42.1	173	38.1	281	61.9	
Location	Colon	743	68.9	270	36.3	473	63.7	< 0.001
	Rectum	336	31.1	179	53.3	157	46.7	
Pathological stage	I	172	15.9	107	62.2	65	37.8	< 0.001
	II	322	29.8	128	39.8	194	60.2	
	III	318	29.5	134	42.1	184	57.9	
	IV	267	24.7	80	30.0	187	70.0	
Basis for diagnosis	Histology	1,065	98.7	447	42.0	618	58.0	0.103
	Cytology	2	0.2	0	0.0	2	100.0	
	Other	12	1.1	2	16.7	10	83.3	
Chemotherapy prior to surgery	No	967	89.6	393	40.6	574	59.4	0.072
	Yes	112	10.4	56	50.0	56	50.0	
Differentiation	Well differentiated	276	28.4	138	50.0	138	50.0	0.002
	Moderately differentiated	575	59.2	231	40.2	344	59.8	
	Poorly differentiated	120	12.4	43	35.8	77	64.2	
DFS status	No relapse	576	53.4	273	47.4	303	52.6	< 0.001
	Relapse	503	46.6	176	35.0	327	65.0	
Overall survival status	Alive	659	61.1	302	45.8	357	54.2	0.001
	Deceased	420	38.9	147	35.0	273	65.0	

DFS: disease-free survival; SD: standard deviation.

Table 2. **Analysis of survival rates according to the type of hospital admission**

		Mean (months)	CI 95%		p
			Lower	Upper	
Disease-free survival	Elective	127.2	117.8	136.7	< 0.001
	Urgent	98.6	90.3	107.0	
	Overall	111.3	104.9	117.7	
Overall survival	Elective	139.0	129.7	148.3	< 0.001
	Urgent	112.8	104.3	121.4	
	Overall	124.9	118.4	131.3	

CI: confidence interval.

Table 3. Cox regression model to estimate disease-free survival and overall survival

Disease-free survival						
Variables		β	p	RR	CI 95%	
					Lower	Upper
Type of hospital admission	Elective			1.00		
	Urgent	0.31	< 0.01	1.36	1.11	1.66
Age		0.01	< 0.01	1.01	1.00	1.02
Differentiation	Well		< 0.01			
	Moderate	0.02		1.02	0.80	1.29
	Poor	0.53		1.70	1.25	2.31
Pathological stage	I-II			1.00		
	III-IV	1.59	< 0.01	4.90	3.85	6.24
Overall survival						
Variables		β	p	CR	CI 95%	
					Lower	Upper
Type of hospital admission	Scheduled			1.00		
	Emergency	0.35	< 0.01	1.41	1.14	1.76
Age		0.02	< 0.01	1.02	1.00	1.03
Differentiation	Well		< 0.01			
	Moderate	-0.08		0.92	0.71	1.20
	Poor	0.56		1.75	1.26	2.44
Pathological stage	I-II			1.00		
	III-IV	1.67	< 0.01	5.29	4.05	6.91

CI: confidence interval; RR: risk ratio.
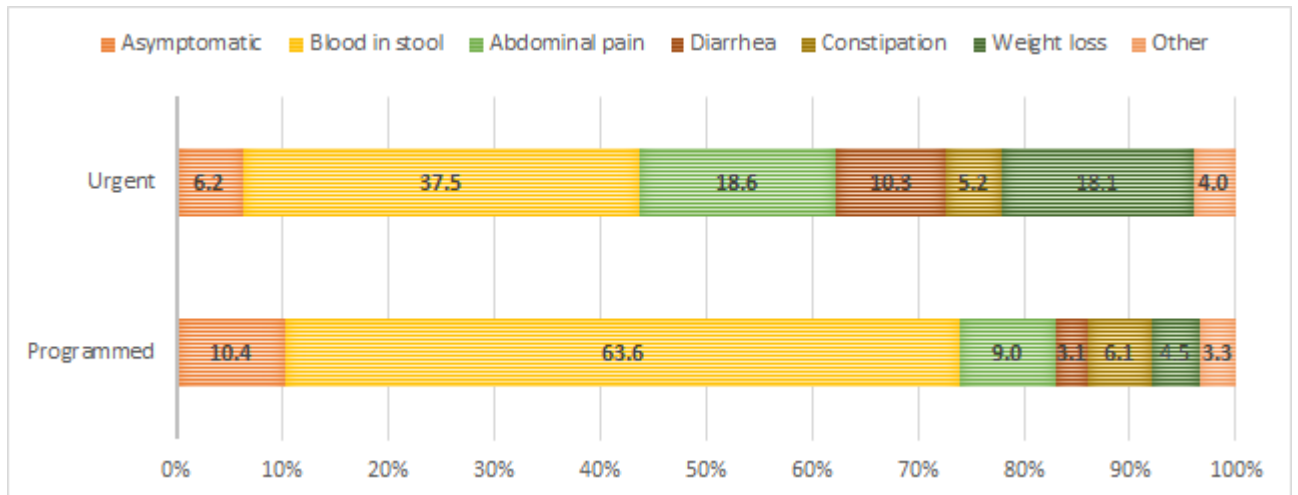
Fig. 1. Symptoms according to the type of first contact with the hospital.
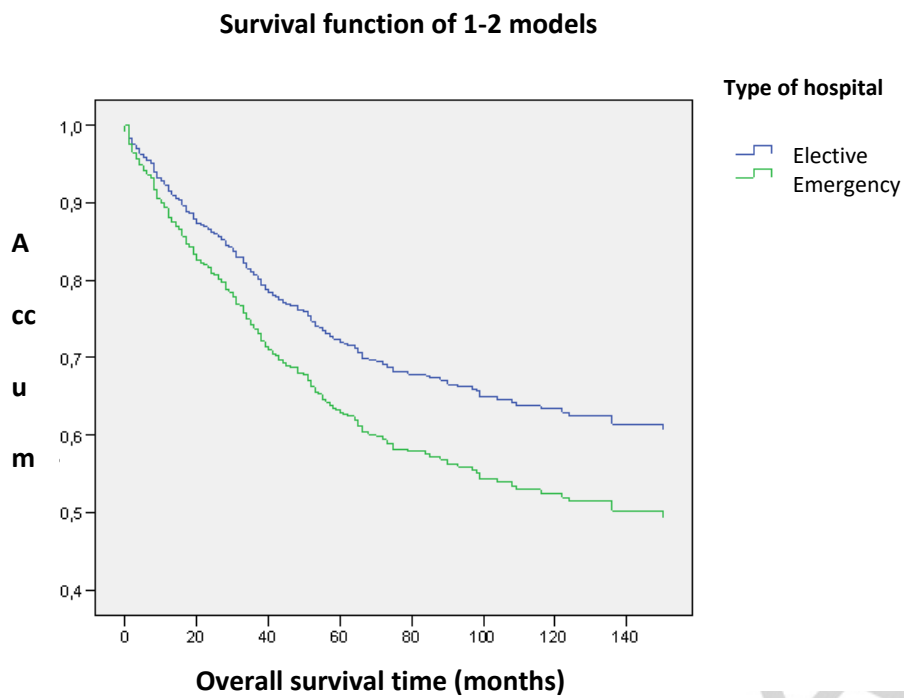
Survival function of 1-2 models

Fig. 2. Survival of patients according to type of hospital admission, adjusting for age, differentiation and pathological stage.