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Colon lymphomas: an analysis of our experience over the last 23 years

Verónica Martín-Domínguez[1], Jorge Mendoza[1], Ariel Díaz-Menéndez[2], Magdalena Adrados[2], José A. Moreno-Monteagudo[1] and Cecilio Santander[1]

[1]Digestive Diseases Service and La Princesa Health Research Institute (IIS-IP). Hospital Universitario de La Princesa. Madrid, Spain. [2]Anatomy Service. Hospital Universitario de La Princesa. Madrid, Spain

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Correspondence: Verónica Martín Domínguez. Digestive Diseases Service. Hospital Universitario de La Princesa. C/ Diego de León, 62. 28006 Madrid, Spain
e-mail: veronicamartin29@yahoo.es

ABSTRACT

Introduction: colon lymphoma (CL) is an uncommon variety of non-Hodgkin lymphoma (NHL) that represents less than 0.6% of all primary colonic neoplasms. Early diagnosis is challenging as clinical manifestations are non-specific. The goal of this review was to discuss our experience over the last few years regarding the clinical, endoscopic, histological, diagnostic, therapeutic and evolutionary characteristics of CL.

Patients and methods: a retrospective, descriptive analysis of patients with CL diagnosed from 1994 to 2016 at the Hospital Universitario de La Princesa (Madrid, Spain) was performed.

Results: a total of 29 patients with CL were identified, with a median age of 67 years; 18 were male (62%). The most common clinical manifestations included abdominal pain, constitutional syndrome, diarrhea and a palpable abdominal mass. Eight (27.6%) patients were asymptomatic and six (20.6%) initially presented with surgical complications. A colonoscopy was performed in 24 patients and the most common findings included diffuse infiltration and solid growth. The most common location was the descending and sigmoid

colon. The most common histological subtypes included mantle B-cell NHL and diffuse large B-cell lymphoma. Chemotherapy was administered to 28 patients (96.5%), surgery was performed in six (20.7%) and combined chemo-radiotherapy was administered to one patient. Median survival was 156 months. Survival was 100.0% at one year and 55.0% at ten years.

Conclusions: due to the variable aspects of CL on endoscopy, a histological study of all colonic segments is required. Chemotherapy is the treatment of choice and emergency surgery followed by chemotherapy is required for complications. Primary factors associated with poorer survival include age above 65 years, relapsing disease and partial or nil responses.

Key words: Non-Hodgkin lymphoma. Colon lymphoma. Mantle cell lymphoma. Bulky tumor. Burkitt's lymphoma. Chemotherapy.

INTRODUCTION

Lymphoproliferative diseases are classified by the World Health Organization (WHO) as (1) Hodgkin's lymphoma (HL) and non-Hodgkin lymphoma (NHL), the latter being more common. Gastrointestinal lymphoma (GIL) is the most common type of extranodal infiltration (2-4), with a rate of 15-20%, as mesenteric or retroperitoneal lymph nodes are common origins that may share lymphatic drainage with the gastrointestinal tract (5).

NHL may involve any gastrointestinal tract segment, either primarily or secondarily. However, the colon is a less common location and is affected in 10% to 20% of cases (6). Colon lymphoma (CL) only represents 0.2-1.2% of all colonic neoplasms (2,7). Few studies have been reported in Spain but some reviews and case series have reported an incidence of 1-2% of all colorectal cancers (6,8,9). It may be primary or secondary to systemic lymphoma. Thus, differentiation is key in order to determine prognosis and treatment. Hence, Dawson established a set of diagnostic criteria for primary colonic lymphoma in 1961 (10).

Computed tomography (CT) is used for lymphoma staging and diagnosis. Over the last 25 years, colonoscopy has played an increasingly relevant role as add-on procedure to rule out secondary colonic involvement, thus allowing diagnostic confirmation by histology studies. It

eventually replaced a barium enema as the procedure of choice for suspected colon neoplasms. Endoscopic findings may be multiple and non-specific with a normal-looking mucosa, hence histological confirmation with immunohistochemical testing must be the rule (11). The goal of our review was to report our 23-year-long experience regarding the clinical, endoscopic, histological, diagnostic and evolutionary characteristics of patients with CL.

MATERIALS AND METHODS

A retrospective, descriptive study that reviewed the medical records of all patients diagnosed with CL between January 1994 and December 2016 at the Hospital Universitario de La Princesa in Madrid, Spain, was performed. The clinical data analyzed included: age, sex, risk factors (immunosuppression status at diagnosis), symptoms and laboratory tests (lactate dehydrogenase, albumin, hemoglobin [Hb]). Endoscopic findings included: mucosal appearance, lesion location, involved colonic segment and endoscopic suspicion of lymphoma. A diagnosis was confirmed by histology of biopsy samples from colonoscopy or surgical specimens. Patients were categorized by the type of lymphoma (HL or NHL) according to the WHO classification. Patients were staged via CT as per the Ann Arbor classification, as modified by Musshoff (8,12). Lymphomas were classified as high-grade or low-grade by immunohistochemical testing.

Statistical analysis

The statistical analysis was performed using the SPSS 21.0 software package. For categorical variables, data were expressed as frequencies. The Student's t-test was used for independent data when comparing quantitative variables between study groups, with a $p < 0.05$ for statistical significance. Survival analysis was carried out using a Kaplan-Meier analysis and a Cox model; the resulting significant data were used as independent variables.

RESULTS

Patient characteristics

A total of 29 patients with CL, 18 (62%) males and eleven (38%) females were identified, with a median (interquartile range [IQR]) age at diagnosis of 67 years (54-82 years). Table 1

shows the clinical, epidemiological, endoscopic, histological and staging characteristics. The most common clinical manifestations included abdominal pain, constitutional syndrome and/or weight loss, diarrhea and a palpable abdominal mass. Eight patients (27.6%) were asymptomatic at the time of diagnosis. There were no patients with immunosuppression data. HIV infection, inflammatory bowel disease and the use of corticosteroids were ruled out. One patient had a chronic hepatitis C viral (HCV) infection at the time of diagnosis, without evidence of advanced disease, portal hypertension or decompensation. Four patients (13.8%) had anemia (Hb: 13-17 g/dl in males or 12-16 g/dl in females) at the time of diagnosis; one (3.4%) had hypoalbuminemia, and 2/13 (15.3%) had elevated serum levels of lactate dehydrogenase (LDH) (> 214 U/l).

Diagnostic testing

The diagnosis of CL was obtained via colonoscopy with biopsy sampling in 24 patients and a diagnostic yield of 95.8%. Colonoscopy was indicated in the presence of gastrointestinal (GI) symptoms in 16 patients and as an add-on procedure to rule out secondary infiltration from a nodal lymphoma in eight patients without GI complaints. In five patients, the diagnosis was reached via CT and/or emergency colectomy at disease onset. Lesions were located in the descending and sigmoid colon in 12 patients (41.4%); nine patients (31%) had two or more colonic segments involved, mainly including the ascending colon.

The most common endoscopic findings (n = 24) included diffuse mucosal infiltration in ten patients (41.7%) and the presence of a tumor or mass in eight patients (33.3%). In our series, three of 24 colonoscopies (12.5%) were normal (no mucosal lesions reported). However, lymphoid infiltration was found by histology. In six patients (25%), there was an endoscopic suspicion of lymphoma due to diffuse infiltration, whereas colonic adenocarcinoma was erroneously diagnosed in five (20.8%) cases. The most common radiographic finding was circumferential wall thickening or the presence of a tumor in 16 patients (55.1%). Fourteen patients (48.2%) had a bulky mass, with a diameter ≥ 10 cm in eight cases. Seven patients (24.1%) had a primary CL and 22 (75.9%) a secondary CL. Five patients (17.2%) had stage I/II lesions (one stage I, four stage II) and 22 (75.8%) had stage III/IV lesions (two stage III, 20 stage IV). The stage was not specified in two patients.

Histology

According to the WHO classification, 28 patients had B-cell NHL (96.6%) and only one patient had a classic HL of the mixed cellularity type (3.4%). Histologic NHL types included low-grade NHL in 19 patients (67.9%), high-grade NHL in eight patients (28.5%) and indeterminate NHL in one patient (3.6%). The most common histologic subtypes included mantle cell lymphoma in 16 patients (57.1%) and diffuse large B-cell lymphoma (DLBCL) in six patients (21.4%).

Treatment and outcome

Treatment strategies included surgery and/or radiotherapy and/or chemotherapy, which were selected according to clinical stage and histological subtype. Six patients (20.6%) underwent surgery due to complications; this included three emergency surgical procedures (sigmoid perforation, ileocolic intussusception and ileocolic obstruction) and three elective surgical procedures (subacute ileocolic intussusception, cecal tumor with enterovesical fistula and stenosing tumor). A total of 5/6 patients underwent a right hemicolectomy. Twenty eight patients received chemotherapy; 23 (82.1%) as monotherapy and five (17.9) after surgery. Only one patient in the whole series did not receive chemotherapy due to an adverse postoperative outcome and death. One patient (3.6%) received radiotherapy after chemotherapy and surgery.

Response to treatment was nil in three patients (10.7%), partial (PR) in two patients (7.1%) and complete (CR) in 23 patients (82.1%). No relapses occurred in eleven patients (39.3%); relapses did occur in 15 patients (53.6%) and the relapse status was unknown in two patients.

Survival analysis

Survival analysis was performed based on all 28 patients who underwent chemotherapy. Median survival was estimated as 156 months (95% CI: 95-217 months). One-year survival was 100.0% (28 patients) and 85.7% (24 patients) at three years, 75.0% (21 patients) at five years and 55.0% at ten years (eleven of 20 patients with ten-year follow-up). A total of 14 patients died (50.0%) and 14 (50.0%) remained alive at the end of follow-up. Table 2 lists and compares the characteristics of the patients who died and those that were alive at the

end of follow-up. Relapse was the only variable significantly associated with an outcome of death. The relapse rate was higher for patients who died (10 of 12, 83.3%) as compared with those who survived (5 of 14, 35.7%) (p = 0.014).

Survival was analyzed using the Kaplan-Meier approach. Fourteen patients died (50.0%) and 14 remained alive at the end of follow-up (50.0%). The median survival time was estimated to be 156 months (95% CI: 95-217 months).

The following variables were assessed as related to survival:

1. Treatment: chemotherapy *vs* chemotherapy + surgery.
2. Tumor size: < 10 cm *vs* ≥ 10 cm.
3. Response: nil + PR *vs* CR.
4. Histology: low-grade NHL *vs* high-grade NHL.
5. Sex: male *vs* female.
6. Age: < 65 years *vs* ≥ 65 years.
7. Relapse: no *vs* yes.

Survival was higher for patients with a complete response (median survival, 180 [95% CI: 124.8-235.1] months) *versus* patients with a partial or nil response (median survival, 36 [95% CI: 0-87.5] months) (log-rank p = 0.006) (Fig. 1). Furthermore, survival was longer for patients younger than 65 years (median survival, 216 months) than for patients older than 65 years (median survival, 108 [95% CI: 31-184.7] months) (p = 0.004) (Fig. 2). According to the multivariate Cox model analysis, the probability of death per time unit (month) was also 8.912 times greater for patients above 65 years of age compared to those below 65 years, with a HR of 10.266 (95% CI: 1.333-79.064). There were no significant changes according to death rate and survival with regard to the remaining study variables of treatment, tumor size, histology and sex.

DISCUSSION

CL is an uncommon type of NHL and represents a minor percentage of colon malignancies. The mean age of cases in our series was 67 years and the condition was twice as common in males as females (ratio, 2:1). The highest incidence was found between the 5th and 7th decades of life, consistent with that reported in the literature (13-15). Clinical manifestations are non-specific and abdominal pain, weight loss and diarrhea are the most

common symptoms. Ten percent of patients remained asymptomatic and then presented with acute abdomen that required an emergency hemicolectomy, which is also similar to that reported in the literature (14,15).

The cecum is the most common site of primary lymphoma, with involvement of the ileocecal valve due to the abundant lymphoid tissue present in this area (2,16). In our series, the most commonly involved area was the descending and sigmoid colon (41%), likely due to the fact that both primary and secondary lymphomas were included in the analysis. When the primary lymphoma group was broken down and analyzed, the cecum and ileocecal valve were found to be the most commonly involved area, again consistent with the literature (14,17).

The endoscopic appearance of CL is non-specific, the findings ranging from a normal-looking or minimally irregular mucosa to large tumors that are indistinguishable from adenocarcinoma. In our series, 12.5% of colonoscopies were normal but had lymphoid infiltration when studied histologically. Hence, we believe that colon lymphomas may be underdiagnosed in patients with apparently normal colonoscopies and no histologic study. Furthermore, lymphoma was suspected in 25% of colonoscopies and adenocarcinoma was erroneously diagnosed in 20.8% of patients (16).

GILs are usually of the diffuse B-cell subtype and the most common histological subtype is the diffuse large B-cell lymphoma, followed by MALT lymphoma (2). In our series, the most common histological subtype was mantle cell lymphoma (64%) and most were high-grade (67%). Overall, better survival and lower death rates were observed for primary lymphomas as compared to secondary lymphomas. However, the difference was not statistically significant and perhaps resulted from the fact that 4/7 patients with primary CL required surgery for complications. In all, 76% of patients were diagnosed with advanced disease stage (III and IV) and most had low-grade lymphomas (70%), which is in contrast to previous studies (11). Traditionally, immunosuppression, HIV infection and inflammatory bowel disease were considered as major risk factors (17). However, in our series, as well as in other recent studies, no such association was found (6).

CL treatment includes surgery, chemotherapy and radiotherapy, or any combination of these treatment strategies. Most series reported until 20 years ago were consistent in that primary CL should be managed with surgery during early stages and with chemotherapy in

the case of advanced disease (13,16,18). However, in the past few years and following the advent of newer, highly effective chemotherapy agents such as monoclonal antibodies, the role of surgery is under debate. There is a tendency to resort to surgery for complications or indolent tumors (resistant to standard chemotherapy regimens), whereas radiotherapy is reserved for unresectable or incompletely resected lesions (15). In our review, chemotherapy was the backbone therapy for most patients and this is the first-line treatment for NHL with nodal involvement (6,13). Surgery was indicated for complications, such as perforation, ileocolic intussusception, obstruction and enterovesical fistula, and was followed by chemotherapy.

The prognosis of CL is worse compared to other gastrointestinal lymphomas. Variables related to poorer prognosis include primarily sex (male), clinical stage (III and IV) and size (< 5 cm) (2,16,19,20). Gou et al. (21) found that impaired functional status, hypoproteinemia, intestinal perforation, T-cell type, advanced stage (III/IV), absence of radical surgery and the absence of chemotherapy were all factors associated with a relatively poor prognosis. Bailey described histologic type and grade (diffuse worse than MALT lymphoma) and the need for emergency surgery as primary factors that affect survival (6,14). In our series, we found that variables associated with poorer survival included age above 65 years and a nil or partial response. Moreover, death risk was associated with relapse rate. The remaining study variables such as treatment, tumor size, histological type and sex were not significantly modified by death rate. This is likely due to the low number of patients in our series and the absence of long-term follow-up for more recently diagnosed cases.

CONCLUSIONS

CL clinical manifestations are non-specific and the endoscopic appearance is highly variable, with mainly infiltration and/or diffuse nodularity and also normal mucosa. This renders histology a must, regardless of endoscopic appearance. The treatment of choice is chemotherapy and in the case of complications such as intestinal perforation, emergency surgery with subsequent chemotherapy. There is a high rate of morbidity and mortality. Primary factors associated with poorer survival and death include age above 65 years, relapse and nil or partial response. However, prospective studies are needed to compare the various chemotherapy regimens available with or without surgery, over a longer follow-

up period.

REFERENCES

1. Muller-Hermelink HK, Chott A, Gascoyne RD, et al. B-cell lymphoma of the colon and rectum. In: Hamilton SR, Asltonen eds. WHO Classification of tumours. Pathology and genetics of tumours of the digestive system. Ryon: IARC press; 2000. pp. 139-41.

2. Times M. Colorectal lymphoma. Clin Colon Rectal Surg 2011;24(3):135-41. DOI: 10.1055/s-0031-1285997

3. Koch P, Del Valle F, Berdel WE, et al. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92. J Clin Oncol 2001;19(18):3861-73. DOI: 10.1200/JCO.2001.19.18.3861

4. Terada T. Gastrointestinal malignant lymphoma: a pathologic study of 37 cases in a single Japanese institution. Am J Blood Res 2012;2(3):194-200.

5. Aledavood A, Nasiri MRG, Memar B, et al. Primary gastrointestinal lymphoma. J Res Med Sci 2012;17(5):487-90.

6. Pascual M, Sánchez-González B, García M, et al. Primary lymphoma of the colon. Rev Esp Enferm Dig 2013;105(2):74-8. DOI: 10.4321/S1130-01082013000200003

7. Barbaryan A, Ali AM, Kwatra SG, et al. Primary diffuse large B-cell lymphoma of the ascending colon. Rare Tumors 2013;5(2):85-8. DOI: 10.4081/rt.2013.e23

8. Aragón Sánchez FJ, García Molina FJ, Rodríguez Fernández A, et al. Primary colorectal lymphoma. Rev Esp Enferm Dig 1997;89(12):903-18.

9. Moya Sanz A1, Gómez Codina J, Prieto Rodríguez M, et al. Toxic megacolon: a rare presentation of primary lymphoma of the colon. Eur J Gastroenterol Hepatol 2000;12(5):583-6. DOI: 10.1097/00042737-200012050-00019

10. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg 1961;49:80-9. DOI: 10.1002/bjs.18004921319

11. Gurney KA, Cartwright, Gilman EA. Descriptive epidemiology of gastrointestinal non-Hodgkin's lymphoma in a population-based registry. Br J Cancer 1999;79:1929-34. DOI: 10.1038/sj.bjc.6690307

12. Musshoff K, Schmidt-Vollmer H. Proceedings: prognosis of non-Hodgkin's lymphomas with special emphasis on the staging classification. Z Krebsforsch Klin Onkol Cancer Res Clin Oncol 1975;83(4):323-41. DOI: 10.1007/BF00573019

13. Tauro LF, Furtado HW, Aithala PS, et al. Primary lymphoma of the colon. Saudi J Gastroenterol 2009;15(4):279-82. DOI: 10.4103/1319-3767.56095

14. Bairey O, Ruchlemer R, Shpilberg O. Non-Hodgkin's lymphomas of the colon. Isr Med Assoc J 2006;8(12):832-5.

15. Wong MT, Eu KW. Primary colorectal lymphomas. Colorectal Dis 2006;8(7):586-91. DOI: 10.1111/j.1463-1318.2006.01021.x

16. Dionigi G, Annoni M, Rovera F, et al. Primary colorectal lymphomas: review of the literature. Surg Oncol 2007;16(Suppl 1):S169-71. DOI: 10.1016/j.suronc.2007.10.021

17. Martínez-Ramos D, Gibert-Gerez J, Miralles-Tena JM, et al. Laparoscopic colectomy for primary colonic lymphoma. Rev Esp Enferm Dig 2005;97(10):744-9. DOI: 10.4321/S1130-01082005001000007

18. Ding D, Pei W, Chen W, et al. Analysis of clinical characteristics, diagnosis, treatment and prognosis of 46 patients with primary gastrointestinal non-Hodgkin lymphoma. Mol Clin Oncol 2014;2(2):259-64. DOI: 10.3892/mco.2013.224

19. Lee J, Kim WS, Kim K, et al. Intestinal lymphoma: exploration of the prognostic factors and the optimal treatment. Leuk Lymphoma 2004;45(2):339-44. DOI: 10.1080/10428190310001593111

20. Gou HF, Zang J, Jiang M, et al. Clinical prognostic analysis of 116 patients with primary intestinal non-Hodgkin lymphoma. Med Oncol 2012;29(1):227-34. DOI: 10.1007/s12032-010-9783-x

Table 1. Clinical, endoscopic and histological characteristics of patients

Characteristics	*n = 29 (%)*
Age at diagnosis (years)	
Mean	67 years
Range	54-82 years
Sex	
Male	18 (62)
Female	11 (37.9)
*Clinical manifestations**	
Abdominal pain	8 (27.5)
Constitutional syndrome and/or weight loss	7 (24.1)
Diarrhea	4 (13.7)
Constipation	3 (10.3)
Lower gastrointestinal bleeding	3 (10.3)
Rectal tenesmus	1 (3.44)
Palpable abdominal mass	3 (10.3)
Asymptomatic	8 (27.5)
Location	
Ascending colon	7 (24.1)
Transverse colon	1 (3.4)
Descending-sigmoid colon	12 (41.4)
Multiple segments	9 (31)
Endoscopic findings	*n = 24*
Diffuse infiltration	10 (41.7)
Tumor or mass	8 (33.3)
Polyps	3 (12.5)
Normal mucosa	3 (12.5)
Histology	
Classic HL	1 (3.4)
NHL	28 (96.5)
NHL subtype	
Mantle cell lymphoma	16/28 (57.1)
Diffuse large B-cell lymphoma	6/28 (21.4)
MALT lymphoma	2/28 (7.1)
Follicular lymphoma	2/28 (7.1)

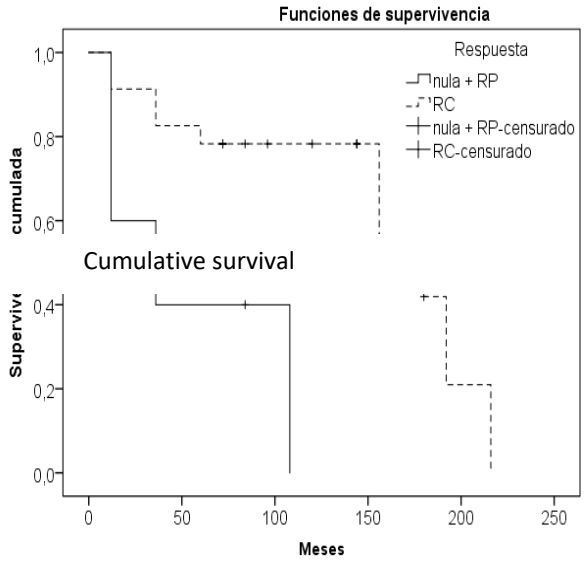
*Some patients exhibited multiple clinical manifestations.

Table 2. A comparison of the characteristics of patients that died and remained alive at the end of follow-up

			Death				
			No (n = 14)		Yes (n = 14)		
Variable	Category	n	n	%	n	%	p
Sex	Male	18	10	55.6%	8	44.4%	0.430
	Female	10	4	40.0%	6	60.0%	
Age. Median (IQR)		28	58.5 (56.0-71.3)		71.0 (65.8-82.0)		0.027
Histology	Low-grade NHL	19	10	52.6%	9	47.4%	1.000[§]
	High-grade NHL	7	4	57.1%	3	42.9%	
	NHL	1	0	0.0%	1	100.0%	
	Classic HL	1	0	0.0%	1	100.0%	
Stage	I and II	5	3	60.0%	2	40.0%	1.000
	III and IV	21	11	52.4%	10	47.6%	
Size. Median (IQR)		13*	6.5 (1.9-10.8)		10.0 (4.5-10.0)		0.710
Origin	Secondary	22	11	50.0%	11	50.0%	1.000
	Primary	6	3	50.0%	3	50.0%	
Surgery[†]	No	23	11	47.8%	12	52.2%	1.000
	Yes	5	3	60.0%	2	40.0%	
Radiotherapy[‡]	No	27	13	48.1%	14	51.9%	1.000
	Yes	1	1	100.0%	0	0.0%	
Response	Nil	3	1	33.3%	2	66.7%	0.326 [‖]
	PR	2	0	0.0%	2	100.0%	
	CR	23	13	56.5%	10	43.5%	
Relapse	No	11	9	81.8%	2	18.2%	0.014
	Yes	15	5	33.3%	10	66.7%	

*No death: 4 and death: 9. [†]Surgery combined with chemotherapy. [‡]Radiotherapy combined with surgery and chemotherapy. [§]The low-grade NHL and high-grade NHL categories were considered for comparison purposes. [‖]The nil response and PR categories were grouped

together for comparison purposes.



Response
nil + PR
--- CR
nil + PR-censored
CR-censored

Fig. 1. Survival according to type of response using the Kaplan-Meier method. Complete response (CR), partial response (PR) or nil response.

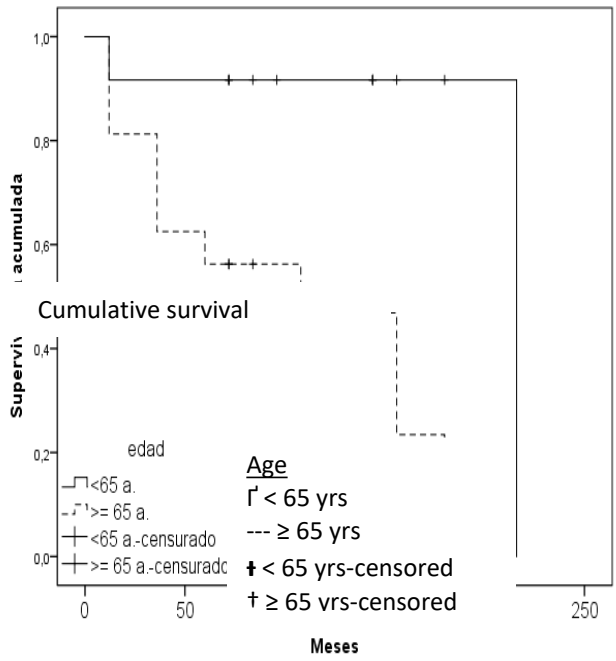


Fig. 2. Survival according to age: ≥ 65 years or < 65 years.