Revista Española de Enfermedades Digestivas
THE SPANISH JOURNAL OF GASTROENTEROLOGY

Title:
Screening-detected colorectal cancers show better long-term survival compared with stage-matched symptomatic cancers

Authors:
Javier A. Cienfuegos, Jorge Baixauli , Patricia Martínez Ortega, Víctor Valentí , Fernando Martínez Regueira, Pablo Martí-Cruchaga, Gabriel Zozaya, José Luis Hernández Lizoain

DOI: 10.17235/reed.2018.5509/2018
Link: PubMed (Epub ahead of print)

Please cite this article as:
A. Cienfuegos Javier, Baixauli Jorge, Martínez Ortega Patricia, Valentí Víctor, Martínez Regueira Fernando, Martí-Cruchaga Pablo, Zozaya Gabriel, Hernández Lizoain José Luis. Screening-detected colorectal cancers show better long-term survival compared with stage-matched symptomatic cancers. Rev Esp Enferm Dig 2018. doi: 10.17235/reed.2018.5509/2018.

Revista Española de Enfermedades Digestivas
THE SPANISH JOURNAL OF GASTROENTEROLOGY

OR 5509

Screening-detected colorectal cancers show better long-term survival compared with stage-matched symptomatic cancers

Javier A. Cienfuegos[1,2,3], Jorge Baixauli[1,2], Patricia Martínez-Ortega[1,2], Víctor Valentí[1,2,3], Fernando M. Regueira[1,2], P. Martí-Cruchaga[1,2], Gabriel Zozaya[1,2] and José Luis Hernández-Lizoáin[1,2]

[1]Department of General Surgery. Navarra University Clinic. School of Medicine. University of Navarra. Pamplona, Spain. [2]Institute of Health Research of Navarra (IdisNA). Pamplona, Spain. [3]CIBER Physiopathology of Obesity and Nutrition (CIBERobn). Instituto de Salud Carlos III. Pamplona, Spain

Received: 5/02/2018

Accepted: 25/05/2018

Correspondence: Javier A. Cienfuegos. Department of General Surgery. Clínica Universidad de Navarra. University of Navarra. Av. Pío XII, 36. 31008 Pamplona, Spain
e-mail: fjacien@unav.es
Nº ORCID: http://orcid.org/0000-0002-6767-0573

ABSTRACT

Purpose: the aim of this study was to compare overall and disease-free survival among patients with colorectal cancer detected via a screening program as compared to those with symptomatic cancer.

Material and methods: patients diagnosed via colonoscopy (screening group) and those with clinical symptoms (non-screening) were identified from 1995 to 2014. Demographic, clinical, surgical and pathologic variables were recorded. Stage I, II and III cancers were included. Overall and disease-free survival were calculated at five and ten years after tumor resection and survival was calculated by matching both groups for cancers at stage I, II and III.

Results: two hundred and fifty patients were identified as a result of screening procedures and 1,330 patients presented with symptomatic cancers. There were no significant differences in the baseline characteristics between the two groups. Pathologic stage, degree of differentiation, perineural invasion and lymphovascular invasion were lower in the screening group ($p < 0.01$). Overall and disease-free survival at five and ten years were higher in the screening group ($p < 0.01$). However, when the subjects were matched for pathologic stage, significant differences were found between the two groups with regard to stage I and III tumors. Disease-free survival in stage III at five years (79.1 *vs* 61.7%; $p < 0.001$) and ten years (79.1% *vs* 58.5%; $p < 0.001$) were significantly higher in the screening group.

Conclusions: patients with stage I and III tumors that were diagnosed via a screening program have a higher overall and disease-free survival at five and ten years.

Key words: Screening. Colonoscopy. Colorectal cancer. Survival. Outcome.

INTRODUCTION

Colorectal cancer (CRC) is the most frequent tumor and the second leading cause of cancer related death in Spain and the Western world (1-3). The progressive sequence from adenoma to carcinoma in the pathogenesis of CRC was first described by Fearon y Vogelstein (4). Since then, CRC has been one of the paradigms of the efficacy of screening programs in the general population (5,6). Apart from the reduction in incidence, several randomized trials and a meta-analysis have confirmed that CRC screening reduces specific cancer mortality by between 20% and 35% at five and eight years, respectively (7-11).

Full colonoscopy has the highest sensitivity and specificity of all the screening procedures applied. However, a major limitation is its invasive nature, which is not always readily accepted by the general population (12,13). Several studies have reported differences in the histologic phenotype and survival in patients whose tumors were diagnosed via a screening program as opposed to those diagnosed as a result of clinical symptoms (10,14-18).

The aims of the present study were to analyze the clinical and pathologic features of the tumors and compare the long-term oncologic outcome between patients in a screening program via colonoscopy and those diagnosed as a result of the development of CRC symptoms (non-screening group).

MATERIALS AND METHODS

All patients undergoing surgery for CRC with a curative intent with stage I, II, and III tumors as defined by the American Joint Commission on Cancer (AJCC) (19) between 2004 and 2014 were identified from a prospective database of patients, maintained since 1995. Colon cancer was defined as a tumor located between the cecum and the rectosigmoid junction at < 15 cm from the anal verge. Cases of stage IV disease were excluded as these require a different therapeutic approach. Cases of hereditary colon cancer and those associated with inflammatory bowel disease were also excluded.

Patients diagnosed via the colonoscopy screening program (6) of the center and those diagnosed as a consequence of clinical symptom presentation were identified. The following data were collected: demographic data (age and sex), ASA (American Society of Anesthesiologists) functional status (20), body mass index (weight in kilograms divided by height in meters squared) and data related to the surgical procedure (duration, type of operation [e.g., open *vs* laparoscopic], the use of blood products, overall incidence of complications and the number of severe complications defined as those equal or greater than class IIIb according to the Clavien-Dindo classification) (21). Colectomies were performed with proximal ligation of the mesenteric vessels and rectal excisions via full resection of the mesorectum (22,23). From 2008 onwards, most of the resections were performed laparoscopically (24).

Pre-operative anemia was defined according to the World Health Organization (WHO) criteria for adults over the age of 15 years as a hemoglobin level < 130 g/dl in males and 120 g/dl in females (25). Dehiscence of anastomoses was defined according to the criteria of the International Group of Rectal Cancer (26) and hospital mortality was defined as that occurring during the first 30 days after surgery or during hospital admission for the surgery.

Histopathologic analyses were performed according to the norms of the American College of Pathologists and pathologic staging (TNM) using the criteria of the American Joint Committee on Cancer Staging, 7th edition (19,27). Perineural and lymphovascular invasion were classified according to the Batsakis and Sato criteria, respectively (28,29). The degree of tumor differentiation was assessed using the WHO classification (30).

Adjuvant chemotherapy for colon cancer was administered according to the norms of the American Society of Clinical Oncology (ASCO) and the Spanish Society of Medical Oncology (SEOM) (31,32). Locally advanced rectal cancers (at stages cT3-4 or cN1) and clinically bulky tumors received external radiotherapy (45 Gy to 54 Gy) neoadjuvant treatment over four weeks in combination with 5-fluorocil-based chemotherapy, according to a regimen described previously (33). All patients were monitored according to the guidelines established by the SEOM (32,34).

The diagnosis of local recurrence was made on the basis of histologic or radiologic confirmation and supportive laboratory findings. Disease-free survival (DFS) was defined as the time elapsed between surgery and the first recurrence or loss to follow-up. The screening and non-screened groups of patients were compared for the primary outcomes described above. The groups were matched for survival analysis according to the pathologic stage of the tumor (I, II and III) to determine if this feature affected the long-term outcome at each stage.

The study was approved by the Research Ethics Committee of the center. All the authors contributed to the drafting of the manuscript.

Statistical analysis

Descriptive statistics were calculated for the screening and non-screened groups. Continuous variables are described using the mean and standard deviation and the difference between these variables was analyzed using the Student's t-test. Categorical variables are described using frequencies and percentages and the difference between groups was measured using the Chi-squared test, or the Fisher's exact test when the number of cases was less than 5. A two-tailed p value of < 0.5 was considered to be

statistically significant.

A Kaplan-Meier analysis was performed to assess overall and disease-free survival. The analysis was performed according to tumor stage and the results were compared using the log rank test in order to calculate the p value of the difference between the groups. Univariate Cox regression was used to assess the association between type of diagnosis and survival. All analyses were performed using the SPSS statistical package (SPSS, Inc., Chicago, IL). Differences were considered significant at p = 0.05.

RESULTS

Of a total of 2,903 patients that underwent surgery for colorectal cancer, 1,580 met the inclusion criteria; 950 patients had colon cancer and 630 had rectal cancer (Fig. 1). Colon cancer was more frequently diagnosed than rectal cancer in the screening program (80% *vs* 56.4%; p < 0.01). There were no differences with regard to right sided colon cancer in the screening and non-screening group (50% *vs* 44.1%; OR 1.26; 95% CI 0.92-1.73; p = 0.139) (Table 1). Demographic data and those related to surgical risk, the surgical procedure, post-operative complications, histologic parameters and pattern of recurrence are summarized in table 1. There were no differences between the two cohorts with regard to gender, BMI and ASA functional status. The patients with symptomatic tumors had significantly lower baseline levels of hemoglobin (p < 0.01).

With regard to surgical parameters, there were no differences in the time taken for the procedure. Although laparoscopic techniques were used more frequently in the screening group as opposed to the non-screened group (44.4% *vs* 20.5%; OR = 3.08, 95% CI = 2.32-4.09; p < 0.01). Patients with symptomatic tumors required more blood products but there were no significant differences between the two groups with regard to the incidence of operative complications, the rate of severe complications (Clavien-Dindo ≥ IIIb), dehiscence of anastomoses or operative mortality (Table 1). There was a significantly higher prevalence of adenocarcinomas, larger and poorly differentiated tumors in the symptomatic group. There was also a lower prevalence of carcinoma *in situ,* with more advanced pathologic stage and a greater incidence of perineural and lymphovascular invasion (p < 0.01 for all values) (Table 1).

Two hundred and twelve patients died from colorectal cancer during a median follow-up of 85 months; eleven and 201 in the screening and non-screening group, respectively. There was a significantly greater incidence of recurrences during follow-up in patients with symptomatic tumors than in the screening group, 7.2% *vs* 20.9% respectively (OR = 0.294; 95% CI: 0.17-0.48, p < 0.01). Distant recurrences were more frequent than local recurrences in both groups (Table 1). Disease-free survival at five and ten years was significantly higher in the screening program as compared to those that presented clinical symptoms (HR 2.93, 95% CI 1.82-4.72; p < 0.01) (Fig. 2). However, there were differences between patients with stage I, II and III tumors in both groups with regard to disease-free survival by pathologic stage (Fig. 2). Disease-free survival at five years was significantly higher in the screening group as compared to the symptomatic patients group; 98.4% and 91.5% for stage I (HR 4.03; 95% CI 1.24-13.07; p = 0.02) and 79.1% *vs* 61.7% for stage III (HR 2.14; 95% CI 1.09-4.19; p = 0.02) (Fig. 3C).

DISCUSSION

Colorectal cancer is the second leading cause of cancer death in Spain and the Western world (1-3,35). Its growth pattern follows an adenoma to carcinoma sequence and screening programs have shown their efficacy in reducing the incidence and specific mortality from cancer (4,7,8,10-12). The main objective of this study was to compare the long-term oncologic outcome of stage I, II and III colorectal tumors diagnosed via a screening program using full colonoscopy as opposed to those diagnosed due to the appearance of symptoms. Stage IV tumors were excluded as they require a different therapeutic approach (36).

In our study, there were no significant differences in the demographic variables, baseline physiologic status (ASA, BMI) and degree of severity of post-operative complications between the screening and symptomatic patient groups. The only noteworthy parameters were significantly lower hemoglobin levels in the symptomatic patients and more laparoscopic colectomies in the screening group. The similarity in age between the two groups is striking, as the average age of the screening group would be expected to be lower as clinical guidelines recommend screening from the

age of 50. This difference was reported by other studies (5,10,16,37). However, similar survival rates (non-significant p) between both groups for stage I and II tumors was observed when survival was analyzed independently according to pathologic stage. In contrast, overall and disease-free survival for stage III disease were significantly higher in the screening group. These differences are consistent with those reported by other studies (10,16,38). However, the reasons for such differences have been a matter of debate, as in our study. There were no differences in age, preoperative risk factors or post-operative complications in these subpopulations of patients (stage III), which is consistent with other studies (10,16,17). As a possible explanation, it has been proposed that symptomatic tumors express a more aggressive biological phenotype and grow more rapidly than the "silent" tumors that are diagnosed incidentally via a screening program (10,16,39,40).

Several studies have linked these differences to lead time bias and length time bias. Lead time bias occurs as a result of early diagnosis, in such a way that survival is additionally and artificially prolonged. In theory, both cohorts would have the same survival time if they had been diagnosed due to the presence of symptoms (17,41,42). Length time bias is produced due to the slower growth of tumors identified via screening programs, which have a longer latent or pre-symptomatic phase. Thus, these tumors are more likely to be diagnosed in screening programs and therefore, survival is also artificially overestimated in these patients (17,41,42).

Although pathologic stage (TNM) and histologic parameters are the most important prognostic factors to determine long-term outcomes in CRC, there are other factors related to the host and surgical treatment which may have some bearing on our findings (14,15). Most authors agree that the subjects that voluntarily enroll in a screening program are more responsible, more health conscious, more likely to follow health care recommendations and usually have a better prognosis due to their habits and lifestyle. The symptomatic patients presented tumors at more advanced stages and with a greater number of histological factors indicative of a poor prognosis (presence of perineural invasion, positive lymphovascular invasion and poorly differentiated tumors) than those diagnosed incidentally. This has also been reported by other studies (10,16-18). Furthermore, lower T stage and more stage I tumors and

less rectal tumors were found in the screening group (Table 1). Logically, these findings were associated with a lower overall and disease-free survival in symptomatic patients as compared to the screening group (16-18). Due to all of these reasons, it is considered that screening could bias survival outcome (43-45).

In our study, the patients from the screening group required fewer blood products and had significantly higher baseline hemoglobin levels. It is well known that blood transfusion leads to a decrease in the cellular adaptive immune response, which in turn is associated with an increase in tumor recurrence. However, there were no differences in operative time or the incidence of severe post-operative complications in our series. These factors are also associated with a reduction in survival time in colorectal cancer (46-48).

Our study suffers from the limitations inherent to retrospective studies, which cover a wide period of time, 20 years in this case. There may have been variations in the therapeutic approaches throughout this period. Although it is true that all the patients underwent surgery performed by colorectal surgeons with standardized criteria and all the data were collected prospectively. Furthermore, as our center is specialized in the treatment of these patients, the delay between cancer diagnosis and surgery was relatively brief.

Our results confirm the positive effect of colorectal cancer screening on survival in patients with potentially curable tumors (stages I and III) that are treated with surgery. Such findings support the efficacy of screening programs in CRC and serve as an argument in favor of implementing preventive measures in the general population.

ACKNOWLEDGEMENTS

The authors would like to thank Paul Miller Ph.D. for the English version and Mrs. Lydia Munárriz for manuscript editing.

DISCLOSURE STATEMENT

All authors have read and approved the manuscript and it is not under consideration elsewhere. The authors are not aware of any affiliations, memberships, funding or financial holdings that might be perceived as affecting the objectivity of the

manuscript.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67(1):7-30. DOI: 10.3322/caac.21387

2. Arnold M, Sierra MS, 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. Galceran J, Ameijide A, Carulla M, et al. Cancer incidence in Spain, 2015. Clin Transl Oncol 2017;19(7):799-825. DOI: 10.1007/s12094-016-1607-9

4. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61(5):759-67. DOI: 10.1016/0092-8674(90)90186-I

5. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64(10):1637-49. DOI: 10.1136/gutjnl-2014-309086

6. Betés M, Muñoz-Navas MA, Duque JM, et al. Use of colonoscopy as a primary screening test for colorectal cancer in average risk people. Am J Gastroenterol 2003;98(12):2648-54.

7. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London) 2010;375(9726):1624-33. DOI: 10.1016/S0140-6736(10)60551-X

8. Hewitson P, Glasziou P, Irwig L, et al. Screening for colorectal cancer using the faecal occult blood test, hemoccult. Cochrane Database Syst Rev 2007;(1):CD001216. DOI: 10.1002/14651858.CD001216.pub2

9. Zauber AG. The impact of screening on colorectal cancer mortality and incidence: has it really made a difference? Dig Dis Sci 2015;60(3):681-91. DOI: 10.1007/s10620-015-3600-5

10. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ 2014;348:g2467. DOI: 10.1136/bmj.g2467

11. Chen C, Hoffmeister M, Brenner H. The toll of not screening for colorectal cancer. Expert Rev Gastroenterol Hepatol 2017;11(1):1-3. DOI: 10.1080/17474124.2017.1264269

12. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366(8):697-706. DOI: 10.1056/NEJMoa1108895

13. Inadomi JM. Screening for colorectal neoplasia. N Engl J Med 2017;376(16):1599-600. DOI: 10.1056/NEJMcp1512286

14. Sebastian E, Courtier R, Macià F, et al. The impact of screening on short-term outcome after surgery for colorectal cancer. Rev Esp Enferm Dig 2017;109(7):485-90. DOI: 10.17235/reed.2017.4569/2016

15. Mansouri D. Lower morbidity and improved outcomes in patients with screen-detected colorectal cancer. Rev Esp Enferm Dig 2017;109:483-4. DOI: 10.17235/reed.2017.5107/2017

16. Amri R, Bordeianou LG, Sylla P, et al. Impact of screening colonoscopy on outcomes in colon cancer surgery. JAMA Surg 2013;148(8):747-54. DOI: 10.1001/jamasurg.2013.8

17. Gill MD, Bramble MG, Hull MA, et al. Screen-detected colorectal cancers are associated with an improved outcome compared with stage-matched interval cancers. Br J Cancer 2014;111(11):2076-81. DOI: 10.1038/bjc.2014.498

18. Morris EJA, Whitehouse LE, Farrell T, et al. A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. Br J Cancer 2012;107(5):757-64. DOI: 10.1038/bjc.2012.331

19. American Joint Committee on Cancer, ed. Colon and rectum. In: AJCC cancer staging manual. 7th ed. New York; 2010. pp. 145-66.

20. Keats AS. The ASA classification of physical status - A recapitulation. Anesthesiology 1978;49(4):233-6. DOI: 10.1097/00000542-197810000-00001

21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205-13. DOI: 10.1097/01.sla.0000133083.54934.ae

22. Chang GJ, Kaiser AM, Mills S, et al. Practice parameters for the management of colon cancer. Dis Colon Rectum 2012;55(8):831-43. DOI: 10.1097/DCR.0b013e3182567e13

23. Heald R, MacFarlane JK. Surgical management of rectal cancer. Br J Surg 1995;82(12):1704-5. DOI: 10.1002/bjs.1800821249

24. Milsom JW, De Oliveira O, Trencheva KI, et al. Long-term outcomes of patients undergoing curative laparoscopic surgery for mid and low rectal cancer. Dis Colon Rectum 2009;52(7):1215-22. DOI: 10.1007/DCR0b013e3181a73e81

25. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: WHO. Cited 2017 Mar 22. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf

26. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010;147(3):339-51. DOI: 10.1016/j.surg.2009.10.012

27. Washington MK, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Arch Pathol Lab Med 2009;133(10):1539-51.

28. Batsakis JG. Nerves and neurotropic carcinomas. Ann Otol Rhinol Laryngol 1985;94(4 Pt 1):426-7.

29. Sato T, Ueno H, Mochizuki H, et al. Objective criteria for the grading of venous invasion in colorectal cancer. Am J Surg Pathol 2010;34(4):454-62. DOI: 10.1097/PAS.0b013e3181d296ef

30. Hamilton SR, Bosman FT, Boffetta P, et al. Carcinoma of the colon and rectum. In: WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer; 2010. pp. 134-46.

31. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005;352(5):476-87. DOI: 10.1056/NEJMra040958

32. Grávalos Castro C, Maurel Santasusana J, Rivera Herrero F, et al. SEOM clinical guidelines for the adjuvant treatment of colorectal cancer. Clin Transl Oncol 2010;12(11):724-8. DOI: 10.1007/s12094-010-0586-5

33. Arredondo J, Baixauli J, Beorlegui C, et al. Prognosis factors for recurrence in patients with locally advanced rectal cancer preoperatively treated with chemoradiotherapy and adjuvant chemotherapy. Dis Colon Rectum 2013;56(4):416-21. DOI: 10.1097/DCR.0b013e318274d9c6

34. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi64-72. DOI: 10.1093/annonc/mdt354

35. GLOBOCAN Cancer Fact Sheets: colorectal cancers. Cited 2018 Jan 9. Available from: http://globocan.iarc.fr/old/FactSheets/cancers/colorectal-new.asp

36. Benson AB, Venook AP, Cederquist L, et al. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15(3):370-98. DOI: 10.6004/jnccn.2017.0036

37. Pande R, Froggatt P, Baragwanath P, et al. Survival outcome of patients with screening versus symptomatically detected colorectal cancers. Colorectal Dis 2013;15(1):74-9. DOI: 10.1111/j.1463-1318.2012.03120.x

38. McClements PL, Madurasinghe V, Thomson CS, et al. Impact of the UK colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends. Cancer Epidemiol 2012;36(4):e232-42. DOI: 10.1016/j.canep.2012.02.006

39. Nagtegaal ID, Allgood PC, Duffy SW, et al. Prognosis and pathology of screen-detected carcinomas: how different are they? Cancer 2011;117(7):1360-8. DOI: 10.1002/cncr.25613

40. Chang DT, Pai RK, Rybicki LA, et al. Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. Mod Pathol 2012;25(8):1128-39. DOI: 10.1038/modpathol.2012.61

41. Kay BR, Witte DL. The impact of cancer biology, lead time bias, and length bias in the debate about cancer screening tests. J Insur Med 1991;23(2):102-4.

42. Duffy SW, Nagtegaal ID, Wallis M, et al. Correcting for lead time and length bias in estimating the effect of screen detection on cancer survival. Am J Epidemiol 2008;168(1):98-104. DOI: 10.1093/aje/kwn120

43. Mansouri D, McMillan DC, Crighton EM, et al. Screening for colorectal cancer: what is the impact on the determinants of outcome? Crit Rev Oncol Hematol 2013;85(3):342-9. DOI: 10.1016/j.critrevonc.2012.08.006

44. Fletcher RH. Colorectal cancer screening on stronger footing. N Engl J Med 2008;359(12):1285-7. DOI: 10.1056/NEJMe0806029

45. Delgado-Rodríguez M, Llorca J. Bias. J Epidemiol Community Health 2004;58(8):635-41. DOI: 10.1136/jech.2003.008466

46. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev 2006;(1)(1):CD005033.

47. Horowitz M, Neeman E, Sharon E, et al. Exploiting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Oncol 2015;12(4):213-26. DOI: 10.1038/nrclinonc.2014.224

48. Richards CH, Platt JJ, Anderson JH, et al. The impact of perioperative risk, tumor pathology and surgical complications on disease recurrence following potentially curative resection of colorectal cancer. Ann Surg 2011;254(1):83-9. DOI: 10.1097/SLA.0b013e31821fd469

Revista Española de Enfermedades Digestivas
THE SPANISH JOURNAL OF GASTROENTEROLOGY

Table 1. Patient demographics, tumor characteristics, treatment and outcome of screening and symptomatic patients

Characteristics (nº, %)	*Screening (n = 250)*	*Non screening (n = 1,330)*	*OR*	*95%CI*	*p value*
Age, mean (SD) year	63.8 (19.9)	62.4 (4.6)	0.990	0.97-1.0	0.08
Male	160 (64)	828 (62.3)	1.078	0.81-1.42	0.601
ASA					
- I-II	127 (54.7)	702 (61)	1 ref.		
- III	96 (41.4)	398 (34.6)	1.333	0.99-1.76	0.054
- IV-V	9 (3.9)	51 (4.4)	0.975	0.46-2.03	0.947
BMI, mean (SD)	26.4 (3.8)	26.3 (3.9)	0.994	0.96-1.02	0.724
Hemoglobin, mean (SD) g/dl	13.3 (1.85)	12.5 (2.06)	0.823	0.76-0.88	< 0.01
Overall tumor location					
- Colon	200 (80%)	750 (56.45%)	3.093	2.22-4.29	< 0.01
- Rectum	50 (20%)	580 (43.6%)			
Tumor location in colon					
- Right colon	100 (50%)	331 (44.1%)	1.266	0.92-1.73	0.139
- Left colon	100 (50%)	419 (55.9%)			
Laparoscopic surgery	111 (44.4)	273 (20.5)	3.089	2.32-4.09	< 0.01
Transfusion	23 (9.7)	240 (18.8)	0.565	0.31-0.99	0.05
Postoperative complications	64 (25.6)	360 (27.1)	0.927	0.68-1.26	0.631
Severe complications Clavien-Dindo ≥ IIIb	11 (4.4)	86 (6.5)	0.666	0.35-1.26	0.215
Anastomosis dehiscence	5 (2)	35 (2.6)	0.755	0.29-1.94	0.561
30-day mortality	1 (0.4)	8 (0.6)	0.666	0.08-5.33	0.700
T stage					
- pT1	100 (40.8)	229 (17.2)	1 ref.		
- pT2	65 (26)	292 (22)	0.5	0.35-0.713	< 0.01
- pT3	73 (29.2)	722 (54.3)	0.227	0.16-0.31	< 0.01

- pT4	10 (4)	87 (6.5)	0.258	0.12-0.51	< 0.01
N stage					
- N0	202 (80.8)	923 (69.4)	1 ref.		
- N1	42 (16.8)	282 (21.2)	0.681	0.47-0.97	0.035
- N2	6 (2.4)	125 (9.4)	0.219	0.09-0.50	< 0.01
Pathologic stage (AJCC)					
- I	153 (61.2)	450 (33.8)	1 Ref.		
- II	49 (19.6)	473 (35.6)	0.305	0.21-0.43	< 0.01
- III	48 (19.2)	407 (30.6)	0.347	0.24-0.49	< 0.01
Tumor size cm, mean (SD)	3.26 (1.95)	3.79 (2.2)	1.136	1.05-1.22	< 0.01
Perineural invasion	14 (5.6)	248 (18.7)	0.333	0.18-0.59	< 0.01
Lymphovascular invasion	24 (9.6)	291 (21.9)	0.53	0.33-0.84	0.007
Adjuvant chemotherapy	65 (27.3)	684 (55.8)	0.298	0.21-0.40	< 0.01
Recurrence rate (%)	18 (7.2%)	278 (20.9%)	0.294	0.17-0.48	< 0.01
Systemic recurrence	16 (6.4)	260 (19.5)	0.281	0.16-0.47	< 0.01
Local recurrence	3 (1.2)	58 (4.4)	0.266	0.08-0.85	0.026
Histologic type					
- Adenocarcinoma	218 (87.2)	1207 (90.8)	1 ref.		
- Mucinous adenocarcinoma	15 (6)	106 (8)	0.783	0.44-1.37	0.393
- Signet-ring cell carcinoma	2 (0.8)	5 (0.4)	2.21	0.42-11.4	0.344
- Carcinoma *in situ,* pTis	15 (6)	12 (0.9)	6.91	3.19-14.9	< 0.01
Tumor grade					
- Well differentiated	61 (27.5%)	142 (13.2%)	1 Ref.		
- Moderately differentiated	141 (63.5%)	816 (75.7%)	1.33	0.95-1.78	0.054
- Undifferentiated	20 (9%)	120 (11.1%)	0.975	0.46-2.03	0.947
- Unknown (262)					

ASA: American Society Score for the enumeration of mortality and morbidity; AJCC: American Joint Commission on Cancer; OR: odds ratio; CI: confidence interval; BMI: body mass index. Data are expressed as the mean and standard deviation (SD) or number of patients (%).

Revista Española de Enfermedades Digestivas
THE SPANISH JOURNAL OF GASTROENTEROLOGY

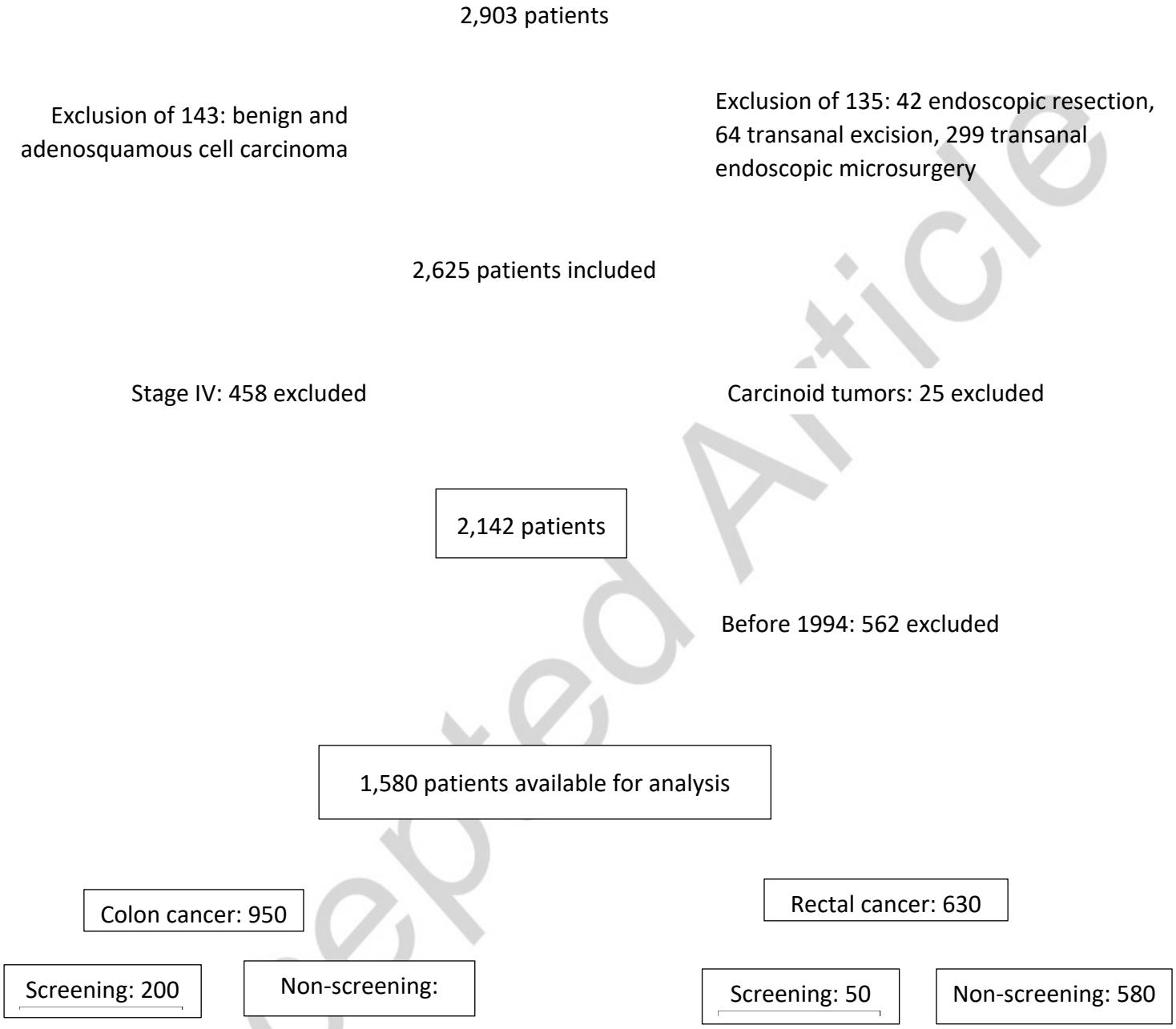

Fig. 1. Flowchart of the total population. All cases of colorectal cancers surgically treated from 1995 to 2014.

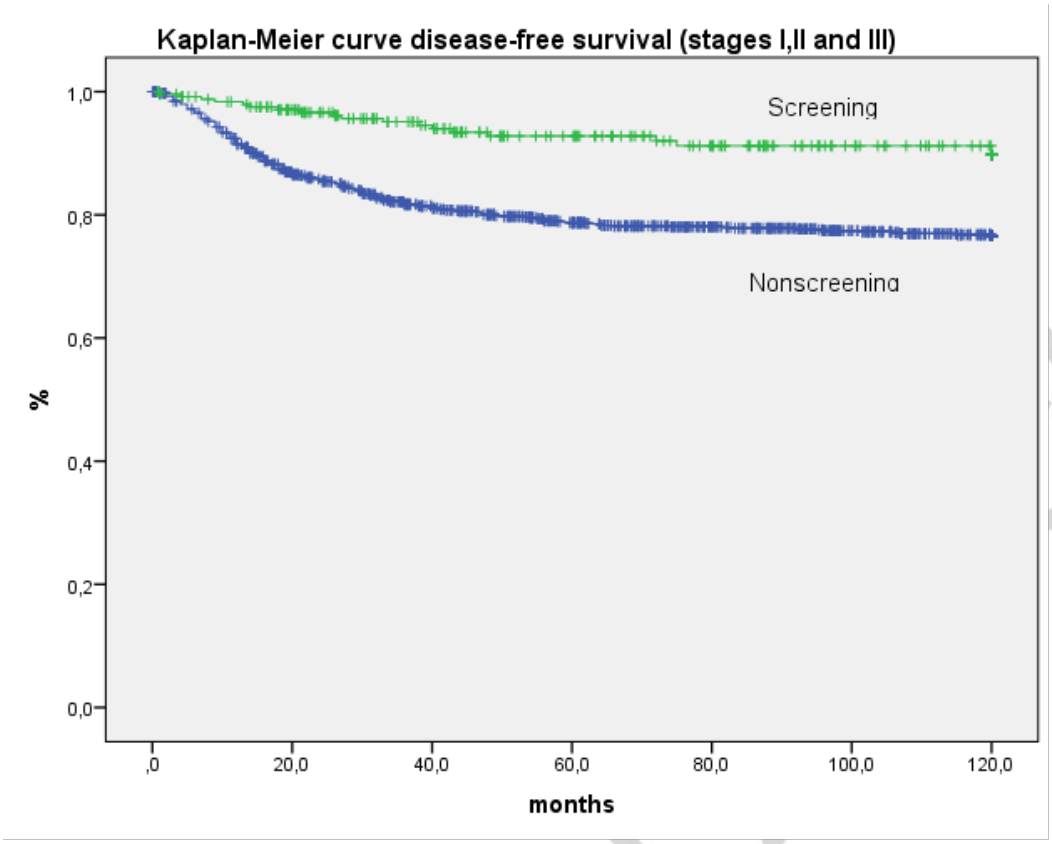

Fig. 2. Kaplan-Meier disease-free curves for the screening and non-screening groups. R: hazard ratio; CI: confidence interval.

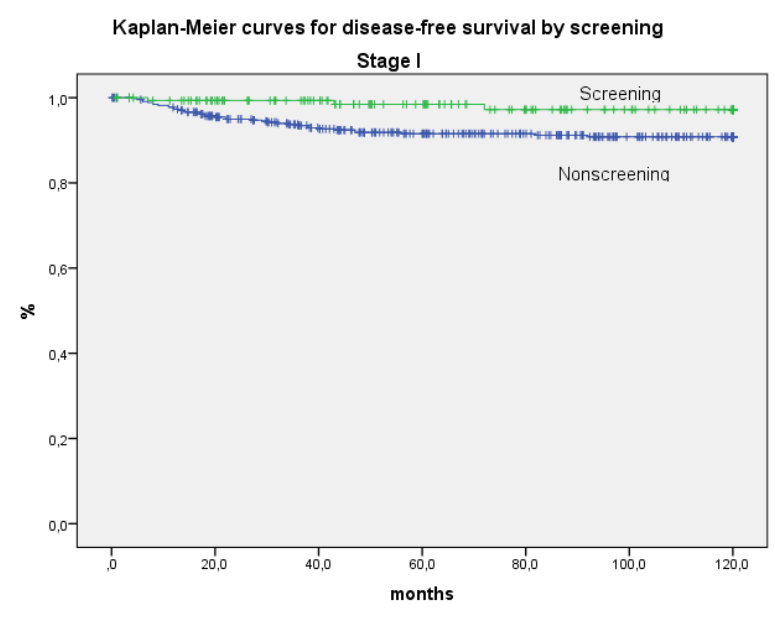

Fig. 3. Kaplan-Meier curves showing disease-free survival stage by stage of the screening and non-screening groups. HR: hazard ratio; CI: confidence interval.