Possible better long-term survival in left versus right-sided colon cancer – a systematic review

Iben Onsberg Hansen[1] & Per Jess[1, 2]

ABSTRACT

INTRODUCTION: Colon cancer is one of the most frequent types of cancer in Denmark and the western world. Recent studies indicate that there are differences between right- and left-sided colon cancer with regard to epidemiology, clinical manifestation, pathology and prognosis. The present systematic literature review focusses on this subject.

METHOD: PubMed, the Ovid Database and the Cochrane Library of Systematic Reviews were searched for relevant literature in October 2011. Only 17 studies fulfilled the inclusion criteria, which were 1) literature published after 1998, 2) written in Danish or English, and 3) peer-reviewed publication.

RESULTS: We found that patients with right-sided colon cancer were older, more often females, possibly had more co-morbidities, had more advanced tumour stages, increased tumour sizes, more poorly differentiated tumours, different molecular biological tumour patterns and a poorer prognosis than patients with left-sided colon cancer. Multivariate analyses showed that age, gender, mode of presentation (emergency/elective), co-morbidity and stage had significant influence on survival, but it was uncertain whether tumour location itself had such an effect, though the different molecular biological patterns indicate this.

CONCLUSION: The findings potentially have consequences for the planning of screening and treatment of colon cancer, but further research in the area is needed.

! TEXT BOX

Patients with right-sided colon cancer are older and more often females than patients with left-sided colon cancer.

Patients with right-sided colon cancer have more co-morbidities, but show less acute presentation than patients with left-sided colon cancer.

Right-sided colon cancers are often in a more advanced stage at diagnosis than left-sided colon cancers and have different molecular biological patterns.

Patients with right-sided colon cancer have a worse prognosis than patients with left-sided colon cancer.

SYSTEMATIC REVIEW

1) Faculty of Health Sciences, University of Copenhagen
2) Department of Surgery, Roskilde Hospital

Dan Med J 2012;59(6):A4444

Colon cancer (CC) is one of the most frequent types of cancer in Denmark and the Western World. In 1990, Bufill was the first to propose that CC found in the distal and proximal location of the colon may follow different biological pathways [1]. It has subsequently been suggested that there are differences in epidemiology, perioperative course, pathology and prognosis between patients with cancers in the right and the left side of the colon [2]. The reason for this is uncertain, but it could partly be due to the different embryologic development of the two segments of the colon which may result in different molecular biological patterns of the tumours, which therefore represent two separate disease entities [3, 4]. Any such differences might have consequences for the planning of screening as well as for the treatment of patients with colorectal cancer (CRC). The aim of the present study was to perform a systematic review of the literature with a view to elucidating the subject.

METHOD

The PubMed and the Ovid databases were searched during October 2011 for literature on right- versus left-sided colon cancer. The following MeSH terms "Colonic neoplasms" and "Prognosis" were combined with "Left OR Left-sided OR left sided" and "Right OR Right sided OR Right sided". Right-sided colon cancer (RCC) is defined as malignant neoplasms in the caecum, ascending colon or transverse colon. Left-sided colon cancers (LCC) are located from the splenic flexure to the sigmoid colon, both included. The search identified 290 publications. The following inclusion criteria were then applied: 1) papers addressing the subject: right-sided versus left-sided colon cancer, 2) research papers published after 1998, 3) research papers published in English or Danish and 4) peer-reviewed publication. Additional searches were performed from the reference lists of the selected literature. After this procedure, a total of 17 studies were selected for the review (see a PRISMA flow diagram in **Figure 1**). Seven of these studies were prospective and ten were retrospective (**Table 1**) [2, 4, 6-20]. Finally, the Cochrane Database of Systematic Reviews was searched, but no relevant publications were identified. The PRISMA guidelines were followed [5].

RESULTS

The results from this systematic review are presented under the following subheadings: epidemiology, clinical manifestation, pathology and prognosis.

Epidemiology

Age and gender

The distribution of age and gender in the respective studies is shown in **Table 2**. Nine of the studies gave information about age, and it was found that the median age of patients with RCC was 71-74 years, while it was 66-71 years for LCC. Ten studies found RCC patients to be females more often than LCC patients.

Clinical manifestation

Comorbidity and emergency presentation

Limited data were available to determine the distribution of co-morbidity and presentation as acute versus elective operations among RCC and LCC patients. Only two articles addressed co-morbidity. One recorded co-morbidities in 85.3% of RCC patients and 82.7% of LCC patients ($p < 0.01$) [9]. The other study used a co-morbidity-related risk score and found that co-morbidity was significantly higher in RCC patients in stage I and III, but lower in RCC with stage II colon cancer. The risk score was found to be an independent variable for overall five-year mortality [20]. Two articles addressed presentation as an emergency and found 14% emergency presentations in RCC and 16% in LCC ($p = 0.003$) [10] and 12% in RCC and 15% in LCC ($p = 0.014$) [11], respectively.

Pathology

Union for International Cancer Control (UICC) stage, tumour-node-metastasis (TNM) status, tumour size and differentiation, and molecular biological pattern.

RCC patients were found to be in more advanced UICC stages (Stage III/IV) than LCC patients at diagnosis; and in accordance with this, RCC showed locally advanced tumour growth significantly more often (pT3/4) than LCC [2, 9, 10, 13-16, 18-20]. A larger number of lymph nodes were also harvested in RCC patients than in LCC patients, and more of the lymph nodes were cancer-positive in RCC than in LCC [2, 13, 14, 19, 20]. However, a single study painted a more complex picture with the highest proportion of lymph node-positive disease found for tumours in the caecum and at the splenic flexure [9]. One study showed that tumors in RCC were larger in size than in LCC [13], and six studies showed that tumours were more poorly differentiated in RCC than in LCC [2, 9, 13, 14, 19, 20]. Four studies found RCC to be mucinous more often than LCC [2, 6, 9, 18]. A recent study found that carcinoma of the caecum and splenic flexure had the highest proportion of lymphatic invasion, while tumours of descending colon had the lowest [9]. Further, this study showed a difference in metastatic spread between the colonic subsites, irrespective of right or left side of colon. Synchronous hepatic metastases were less frequently diagnosed in ascending and descending colon carcinoma. Metastatic spread to the lungs was most often seen in carcinoma of the caecum and sigmoid colon, whereas caecal tumours had the highest incidence of peritoneal carcinomatosis [9]. The molecular biological tumour patterns differed between RCC and LCC with more frequent C-KI-RAS mutations [3], defective DNA mismatch repair genes [4], expression of a non-functional p53 protein and a p53 gene mutation [6] and microsatellite instability [21] in RCC than in LCC.

Prognosis

Survival data

Patients with RCC were found to have a worse overall prognosis than patients with LCC (**Table 3**). However, when prognosis was viewed in relation to stage, the results were a little more complex. RCC patients showed a worse prognosis in stages I and III, but not in stage II in two of the studies [2, 15]; and in three other studies [6, 13, 14], the prognosis in stage II was even better than in LCC patients. One study showed an equal prognosis in the different stages [19].

Some of the studies had further subdivided RCC and LCC, and one of these studies found that patients with cancers of the sigmoid had a better cancer-specific survival than patients with cancer in the rest of the colon [19], while patients with transverse colonic cancer seemed to have the worst prognosis of all [13, 16].

Four of the studies had performed multivariate analysis to eliminate the influence of differences in pa-

FIGURE 1

PRISMA flow diagram of the literature search of the study. Source: [5].

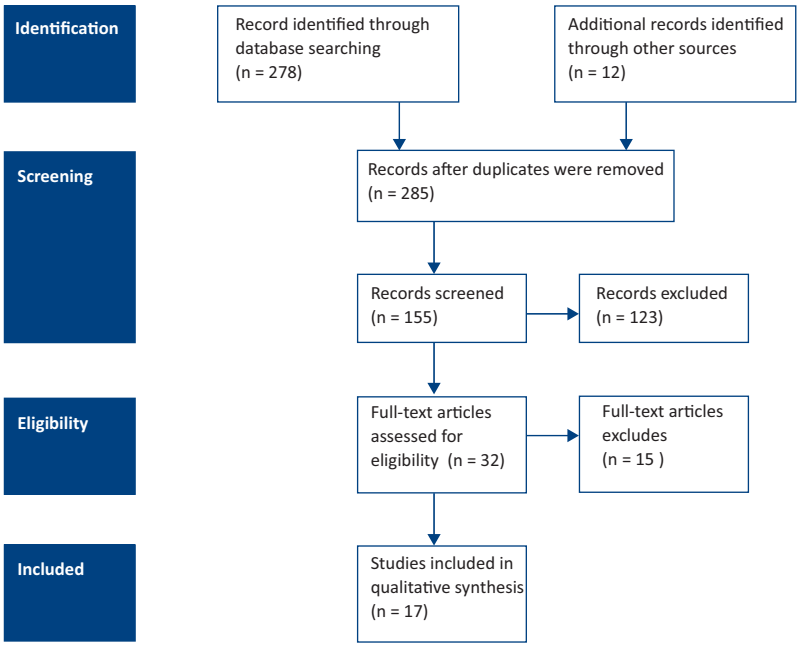


TABLE 1

Identified literature in the present systematic review of right- versus left-sided colon cancer.

Reference	Country	Study type	Patients, n	Right-sided, %	Epi-demi-ology	Clinical mani-festation	Path-ology	Prog-nosis
Prospective								
Gervaz et al, 2001 [6]	Switzerland	Observational single-center study	122	31			×	×
Gatta et al, 2003 [7]	Europe/USA	Registries study: EUROCARE/SEER	11,183	Europe: 51 USA: 55				×
Nawa et al, 2008 [8]	Japan	Regional register study	3,552	32			×	
Benedix et al, 2010 [2]	Germany	Observational multi-center study	17,641	47	×	×	×	×
Benedix et al, 2011 [9]	Germany	Observational multi-center study	29,568	47	×			
Hutchins et al, 2011 [4]	United Kingdom	Observational multi-center study	1,913					×
Suttie et al, 2011 [10]	United Kingdom	Observational multi-center study	613	46	×	×	×	×
Retrospective								
Faivre-Finn et al, 2002 [11]	France	Regional register study	3,368	44		×		×
Angell-Andersen et al, 2004 [12]	Norway	Nationwide register study	32,450	51	×			×
Meguid et al, 2008 [13]	USA	Regional register study	77,978	57	×		×	×
Wray et al, 2009 [14]	USA	Regional register study	82,926	58	×		×	×
Christodoulidis et al, 2010 [15]	Greece	Observational single center study	453	55	×		×	×
Hemminki et al, 2010 [16]	Sweden	Regional register study	6,353	59	×		×	x
Meza et al, 2010 [17]	UK/USA	Registries study ONS/SEER	795,680	UK: 52 USA: 56	×			
Snaebjornsson et al, 2010 [18]	Iceland	Nationwide register study	2,133	50	×		×	
Derwinger et al, 2011 [19]	Sweden	Observational single center study	1,558	53	×		×	×
Weis et al, 2011 [20]	USA	Regional register study	53,801	67	×	×	×	×

x = the subject is dealt with in the respective publication.

tient and tumour characteristics on the prognosis. With this approach, Suttie et al [10] showed that age, stage and mode of presentation, but not tumour location, had a significant impact on survival, while Faivre-Finn et al [11] found that stage, emergency presentation, age, as well as tumor location were significant predictors of prognosis. A third study found that location was no longer a significant factor for survival after adjusting for covariates [20]. However, in the largest prospective study included in the present review, both location, age, gender, tumour differentiation and co-morbidity were significantly related to decreased survival, but the effect of right-sided location on prognosis was found only to have an odds ratio of 1.12 (95% confidence limits: 1.018-1.226, p = 0.02) [2]. Consequently, the impact of tumour location itself on survival remains uncertain, though the different patterns in molecular biology in RCC and LCC discussed below indicate that an impact exists [4].

DISCUSSION

In an epidemiological study by Saltzstein and colleagues, increasing age was associated with a shift of anatomic site of origin of CRC from the left to right side of the colon [22]. This is in accordance with the results of the present review, where the median age at diagnosis of RCC was 71-74 years versus 66-71 years in LCC (Table 2). A report from The Danish National Board of Health stated that 40% of the patients were 75 years or older at diagnosis of CRC in Denmark (2007) [23]. In the same report, the age interval for screening was recommended to be 50-74 years. The argumentation for this was the small risk of CRC together with a reduced compliance to screening with increasing age. With this strategy, nearly half of all RCC patients and 40% of all CRC patients will not be offered screening and the accompanying advantage of early diagnosis of potential cancer, but this shall, naturally, be viewed in relation to a life expectancy in Denmark in 2008/2009 of 80.75 years for women and 76.52 years for men.

TABLE 2

Distribution of age and gender among patients with right- and left-sided colon cancer.

	Median age, years		Gender, female/male, %	
Reference	right-sided	left-sided	right-sided	left-sided
Benedix et al, 2010 [2]	71	69	55/45	46/54
Suttie et al, 2011 [10]	74	71	56/44	45/55
Angell-Andersen et al, 2004 [12]	–	–	57/43	49/51
Meguid et al, 2008 [13]	73	69	56/44	48/52
Wray et al, 2009 [14]	74	70	55/45	47/53
Christodoulidis et al, 2010 [15]	74	66	59/41	25/75
Meza et al, 2010 [17]	72	70	56/44	49/51
Snaebjornsson et al, 2010 [18]	73	71	51/49	47/53
Derwinger et al, 2011 [19]	71	67	60/40	46/54
Weiss et al, 2011 [20][a]	69% > 75 years	61% > 75 years	62/38	52/48

a) Only patients older than 65 years were included in the study.

In most of the studies, a larger percentage of RCC patients than LCC patients were women (Table 2). The correlation between RCC, increased age and female gender may partly be explained by hormonal and genetic factors. The use of postmenopausal hormones may halve the risk of CRC among women [24, 25], and lifestyle and dietary habits may differ between women and men as investigated in relation to the development of serrated polyps in the right and left colon [26].

It has previously been shown that emergency resection is associated with an increased morbidity and postoperative mortality compared with elective resection [27]. This was confirmed by the findings of Suttie et al [10] and Faivre-Finn et al [11], though no difference in postoperative mortality between patients with RCC and LCC was observed in the last study. This was probably so because the differences in acute and elective operations between the two groups were relatively small.

Benedix [2] and Weiss [20] found RCC patients to have more co-morbidity than LCC patients. The significance of co-morbidity was described in a report from the Danish Cancer Research Forum from 2011 [28], where colon cancer patients diagnosed between 2007 and 2009 had a 1-year survival rate of 76% when no co-morbidity was registered, while the 1-year survival rate was only 44% in patients with a high degree of co-morbidity. These findings were confirmed by Iversen et al [29].

According to Hemminki et al [16], patients with RCC had more advanced stages at diagnosis than patients with LCC, and Snaebjornsson et al [18] found that the more advanced stages of RCC were due to tumour (T) and lymph node (N) stages, but not to metastases (M stage). RCC was associated with a larger number of harvested lymph nodes and a larger amount of positive lymph nodes among these than LCC [2, 13, 14, 19, 20]. The number of resected and positive lymph nodes is a quality parameter, as lymph node metastases are of imperative significance to prognosis and treatment [30, 31]. With regard to metastases, Benedix and colleagues [2] found that LCC more frequently spread to the liver and pulmonary systems than RCC, whereas RCC more often spread to the peritoneum, probably due to the increased prevalence of mucinous adenocarcinoma among RCC cases [2, 6, 9, 18]. There was no difference in the frequency of metastases to brain, bone, skin and/or ovaries [2]. Furthermore, several studies have shown that RCC was more poorly differentiated than LCC [2, 9, 13, 14, 19, 20] and had increased tumor size [13].

In a more recent study, Benedix and colleagues [9] found a need for a further subdivision of RCC and LCC. The study indicated that age and tumour differentiation support the common segregation into RCC and LCC, but with regard to gender, UICC stage, metastases, T- and N-status and lymphatic invasion, a subdivision into the caecum, ascending, transverse, descending and sigmoid colon is necessary. Cancers of the caecum and splenic flexure seemed more advanced (stage III/IV in the UICC classification) and more often had lymphatic invasion than cancers of the ascending and descending colon. Still, the overall picture from the present systematic literature review is that RCCs are more advanced than LCCs. Beside the hormonal and genetic factors earlier mentioned, the reason for this could be the weaker symptoms in patients with RCC than in patients with LCC. RCC is often associated with unnoticed bleeding, whereas LCC is associated with changes in bowel habits, passage trouble and obstruction [15, 20]. This may cause RCC patients to seek medical assistance later than LCC patients. Another factor that may delay the diagnosis in RCC is connected to colonoscopy and the documented inferior rate of success in the detection of RCC [32]. This is due to incomplete examinations in 3-13% of the patients and is thought to be responsible for half of all missed cancers [33]. The problem is most severe in older patients and especially in women [34], which may pos-

TABLE 3

Survival data in patients with right-sided versus left-sided colon cancer.

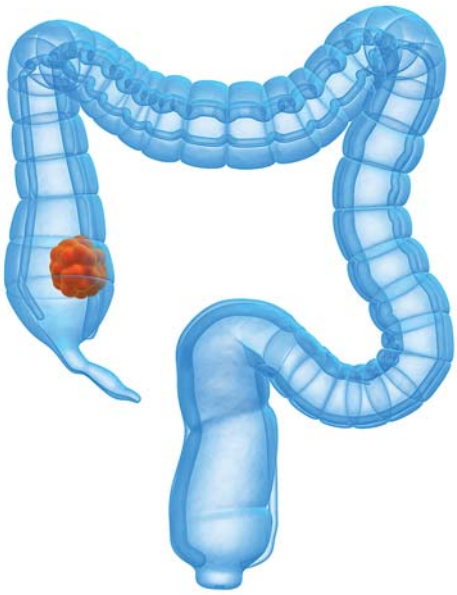
Reference	Survival data
Endpoint: 5-year survival rate, %	
Benedix et al, 2010 [2]	RCC 67 versus LCC 71 (p < 0.01)
Gatta et al, 2003 [7]	USA: RCC 59 versus LCC 65 Europe: RCC 44 versus LCC 48
Christodoulidis et al, 2010 [15]	RCC 56 versus LCC 66 (p < 0.0001)
Endpoint: overall median survival, months	
Suttie et al, 2011 [10]	RCC 54.4 versus LCC 59.8 (p < 0.01)
Meguid et al, 2008 [13]	RCC 78 versus LCC 89 (p < 0.001)
Wray et al, 2009 [14]	RCC (transverse-proximal) 59-60 versus LCC (descending-sigmoid) 66-83 (p < 0.0001)
Endpoint: overall survival	
Gervaz et al, 2001 [6]	Dukes B tumours: RCC higher than LCC (p = 0.045)
Derwinger et al, 2011 [19]	RCC lower than LCC (p < 0.037)
Endpoint: relative 5-year survival, %	
Gatta et al, 2003 [7]	Europe: RCC 44 versus LCC 48 USA: RCC 59 versus LCC 65
Endpoint: relative risk of death, multivariate relative survival model	
Faivre-Finn et al, 2002 [11]	RCC 1.24 versus LCC 1.00 (p < 0.0001)
Endpoint: adjusted relative risk for cancer-specific mortality	
Angell-Andersen et al, 2004 [12]	RCC 1.00 versus LCC 0.97 (95% confidence interval: 0.93-1.00)
Endpoint: hazard ratio adjusted for covariates for 5-year mortality	
Weiss et al, 2011 [20]	RCC 1.01 versus LCC 1.00 (p = 0.6)
Hemminki et al, 2010 [16]	RCC 1.16 versus LCC 1.04 (p < 0.01)

LCC = left-sided colon cancer; RCC = right-sided colon cancer.

sibly explain part of the increased prevalence of poorly differentiated cancers in advanced stages of RCC among older females.

Overall, most of the studies found a poorer survival in RCC than in LCC. Multivariate analyses indicated that other factors than tumour location contribute to the higher mortality in RCC [2, 10, 11, 20]. These factors include age, gender, acute/elective surgery and co-morbidity, which were shown to influence the prognosis, while Benedix et al only found little impact of location itself [2]. This was supported by Weiss et al [20] who found no difference in prognosis between RCC and LCC after adjustment for age, gender, co-morbidity and post-operative adjuvant chemotherapy treatment, and by Suttie et al [10] who found age, operative intent, mode of presentation and stage to be the only variables with a significant impact on survival in multivariate analysis. However, molecular biological investigation have shown differences between RCC and LCC with more mutations of the C-KI-RAS proto-oncogene in RCC, which, in turn, was associated with a significantly poorer prognosis, thereby indicating an impact of location itself [3].
A more recent molecular biological study found that defective DNA mismatch repair (dMMR) genes were also predominantly seen in parts of the colon located orally to the splenic flexure, which, as earlier mentioned, is a part of the embryologically derived midgut (more precisely orally from the transition between the oral two-thirds and anal one-third of the transverse colon), whereas dMMR genes were rare in the hindgut-derived descending, sigmoid colon and the rectum [4]. However, patients with dMMR had a reduced recurrence rate [4]. Microsatellite instability (MSI), has also been observed more often among RCC patients than among LCC patients [21], and is similarly related to a better overall survival [35, 36] despite the fact that the effect of adjuvant chemotherapy, especially 5-fluouracil, is reduced in patients with MSI [37]. Further, Weiss et al found that a lower percentage of patients with RCC than patients with LCC completed a course of adjuvant chemotherapy, probably because of their more advanced age, which, in turn, could contribute to the lower survival rate in RCC [20].

In summary, several factors may have an impact on survival in RCC and LCC and this complex issue demands further research. The molecular biology behind RCC and LCC and potential differences in the effect of adjuvant and palliative chemotherapy and biologically targeted therapies [38] will be studied further, and the relevance of an upper limit of 74 years in the Danish screening programme needs reconsideration, as does the future potential to detect RCCs at earlier and more favourable stages. A recently initiated study on ten-year data from the nationwide Danish Colorectal Cancer database (DCCG) with a focus on differences in epidemiology, pathology and survival between RCC and LCC will hopefully further elucidate the subject.



Drawing of the colon.

CONCLUSION

The present review confirmed that there are clinical, pathological and prognostic differences between RCC and LCC. Patients with RCC were shown to be older, more often females, and they had more co-morbidities, more advanced tumour stages, a larger amount of harvested lymph nodes, increased tumour size, more poorly differentiated tumors, and different molecular biological tumour patterns than patients with LCC. In line with this, RCC patients were found to have a worse prognosis than LCC patients, but the reason for this seems rather complex and further research in the area is therefore needed.

CORRESPONDENCE: *Per Jess,* Kirurgisk Afdeling, Roskilde Sygehus, 4000 Roskilde, Denmark. E-mail: pjss@regionsjaelland.dk
ACCEPTED: 27 March 2012
CONFLICTS OF INTEREST: none

LITERATURE

1. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal location. Ann Int Med 1990;113:779-88.
2. Benedix F, Kube R, Meyer F et al. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum 2010;53:57-64.
3. Elnatan J, Gosh HS, Smith DR. C-KI-RAS activation and the biological behaviour of proximal and distal colonic adenocarcinomas. Eur J Cancer 1996;32A:491-7.
4. Hutchins G, Southward K, Handley K et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. J Clin Oncol 2011;29:1261-70.
5. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses. The PRISMA statement. PLoS Med 2009;6:e1000097.
6. Gervaz P, Bouzourene H, Certtini JP et al. Distinct genetic categories and clinical outcome based on proximal or distal tumor location. Dis Colon and Rectum 2001;44:363-73.
7. Gatta G, Ciccolallo L, Capocaccia R et al. Differences in colorectal cancer

survival between European and US populations: the importance of sub-site and morphology. Eur J Cancer 2003;39:2214-22.
8. Nawa T, Kato J, Kawamoto H et al. Differences between right- and left-sided colon cancer in patient characteristics, cancer morphology and histology. J Gastroenterol Hepatol 2008;23:418-23.
9. Benedix F, Schmidt U, Mroczkowski P et al. Colon carcinoma – classification into right and left-sided cancer or according to colonic subsite? Analysis of 29,568 patients. Eur J Surg Oncol 2011;37:134-9.
10. Suttie SA, Shaikh I, Mullen R et al. Outcome of right-and left-sided colonic and rectal cancer following surgical resection. Colorectal Dis 2011;13: 884-9.
11. Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM et al. Colon cancer in France: evidence for improvement in management and survival. Gut 2002;51:60-4.
12. Angell-Andersen E, Tretli S, Coleman MP et al. Colorectal cancer survival trends in Norway 1958-1997. Eur J Cancer 2004;40:734-42.
13. Meguid RA, Slidell MB, Wolfgang CL et al. Is there a difference in survival between right-versus left-sided colon cancers? Ann Surg Oncol 2008;15:2388-94.
14. Wray CM, Ziogas A, Hinojosa MW et al. Tumor subsite location within the colon is prognostic for survival after colon cancer diagnosis. Dis Colon Rectum 2009;52:1359-66.
15. Christodoulidis G, Spyridakis M, Symeonidis D et al. Clinicopathological differences between right- and left-sided colonic tumors and impact upon survival. Tech Coloproctol 2010;14:45-7.
16. Hemminki K, Santi I, Weires M et al. Tumor location and patient characteristics of colon and rectal adenocarcinomas in relation to survival and TNM classes. BMC Cancer 2010;10:688.
17. Meza R, Jeon J, Renehan AG et al. Colorectal cancer incidence trends in the United States and United Kingdom: Evidence of right- to left sided biological gradients with implications for screening. Cancer Res 2010;70:5419-29.
18. Snaebjornsson P, Jonasson L, Jonsson T et al. Colon cancer in Iceland – a nationwide comparative study on various pathology parameters with respect to right and left tumor location and patients age. Int J Cancer 2010;127:2645-53.
19. Derwinger K, Gustavsson B. Variations in demography and prognosis by colon cancer location. Anticancer Res 2011;31:2347-50.
20. Weiss JM, Pfau PR, O'Connor ES et al. Mortality by stage for right- vesus left-sided colon cancer: analysis of surveillance, epidemiology, and end result-medicare data. J Clin Oncol 2011;29:4401-9.
21. Iacopetta B. Are there two sides to colorectal cancer? Int J Cancer 2002;101:403-8.
22. Saltzstein SL, Behling CA. Age and time as factors in the left–to-right shift of the subsite of colorectal adenocarcinoma: a study of 213,383 cases from the California Cancer Registry. J Clin Gastroenterol 2007;41:173-7.
23. Danish National Board of Health. Recommendations for screening for colorectal cancer. Copenhagen: Danish National Board of Health, 2010.
24. La Vecchia C, Brinton LA, McTiernan A. Menopause, hormone replacement therapy and cancer. Maturitas 2001;39:97-115.
25. Newcomb PA, Zheng Y, Chia VM et al. Estrogen plus progestin use, microsatellite instability, and the risk of colorectal cancer in women. Cancer Res 2007;67:7534-9.
26. Wallace K, Grau MV, Ahnen D. The association of lifestyle and dietary factors with risk for serrated polyps of the colorectum. Cancer Epidemiol Biomarkers Prev 2009;18:2310-7.
27. Kim J, Mittal R, Konyalian V et al. Outcome analysis of patients undergoing colorectal resection for emergent and elective indications. Am Surg 2007;73:991-3.
28. Theme report II: Comorbidity and older cancer patients. 2011. www.DMCG.dk (1 Feb 2012).
29. Iversen LH, Norgaard M, Jacobsen J et al. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006 – a population-based cohort study. Dis Colon Rectum 2009;52:71-8.
30. Pheby DF, Levine DF, Pitcher RW et al. Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. J Clin Pathology 2004;57:43-7.
31. Ratto C, Sofo L, Ippoliti M et al. Accurate lymph-node detection in colorectal specimens resected for cancer is of prognostic significance. Dis Colon Rectum 1999;42:143-54.
32. Bressler B, Pazrat LF, Chen Z et al. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology 2007; 132:96-102.
33. Leaper M, Johnston MJ, Barclay M et al. Reasons for failure to diagnose colorectal carcinoma at colonoscopy. Endoscopy 2004;36:499-503.
34. Shah HA, Paszat LF, Saskin R et al. Factors associated with incomplete colonoscopy: a population-based study. Gastroenterology 2007;132:2297-303.
35. Samowitz WS, Curtin K, Ma KN et al. Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. Cancer Epidemiol Biomarkes Prev 2001;10:917-23.
36. Hemminki A, Mecklin JP, Jarvinen H et al. Miscrosatellite instability is a favorable prognostic indicator in patients with colorectal cancer receiving chemotherapy. Gastroenterology 2000;119:921-8.
37. Vasen HF, Moslein G, Alonso A et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genetics 2007;44:353-62.
38. Van Cutsem E, Dicato M, Arber N et al. Molecular markers and biological targeted therapies in metastatic colorectal cancer: expert opinion and recommendations derived from the 11th ESMO/World congress on gastrointestinal cancer, Barcelona 2009. Ann Oncol 2010; 21 Suppl 6:v1-10.