APPENDIX C.3 GENERAL SURGERY: COLORECTAL CANCER LITERATURE REVIEW

Western Canada Waiting List Project

Literature Review – General Surgery: Colorectal Cancer

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1. Introduction

This literature review summarizes recent study-based data concerning the outcomes of colorectal cancer (CRC), with special regard to the impact of treatment delay on clinical outcomes. This review was conducted under the auspices of the Western Canada Waiting List Project to assist the General Surgery Panel in its task of developing tools for managing surgical waiting lists. In particular, the review was designed to inform the development of priority criteria across all general surgical procedures. Panelists will be [were] asked to assess the extent to which the review provided meaningful assistance in this regard. [See separate report.]

This review focuses on four major questions: (1) what impact does delay in treatment – especially surgery – have on outcomes of CRC and the effectiveness of its treatments; (2) how much suffering and disability do patients with CRC experience pre-operatively; (3) how effective are treatments for CRC in improving outcomes, including suffering, disability, and mortality rates; and (4) which pre-operative variables best predict the degree of benefit likely to be experienced by patients undergoing treatments for CRC.

2. Search Strategy

A comprehensive search was completed to obtain relevant literature. The search consisted of the following:

- References were searched for with the use of the electronic databases Medline, Best Evidence, Cochrane Library, LegalTrac, HealthSTAR, and CancerLit;
- Recent review articles, practice guidelines, and consensus reports were searched for on the web by professional organizations such as the National Cancer Institute and the Society of Surgical Oncology;
- In an ancestry analysis, references were obtained from bibliographies of articles retrieved through the computerized searches;
- Informal consultation with Western Canada Waiting List Project surgical panelists to request more information and ask whether they knew of additional data of which we should be aware;
- Key references were checked using the Science Reference Index (1994-2000) for related articles.

Appendix A lists the search terms used to obtain references, as well as a list of the web sites accessed. Articles were limited to those published between 1989 and 2000, written in English or containing an English abstract. Approximately 3,600 references were obtained initially; abstracts for all articles were screened for relevance, particularly their ability to address the four research questions listed above. A total of 507 references were further reviewed, with key articles obtained and analyzed for inclusion in this report. Of these, 129 were selected for citation in this report.

3. Condition and Treatment Description

3.1 Prevalence and incidence

Cancer of the colon and rectum is the fourth most common cause of cancer death in Canada, with lung, breast, and prostate cancer being more common. An estimated 16,600 new cases were

diagnosed in Canada for 1999, with 3,400 men and 3,000 women dying of colorectal cancer (CRC) last year. The lifetime risk of dying from this disease is 2.8% and 2.6% for men and women.[1]

The incidence and mortality rates in the Canada and the United States are decreasing, probably due to improved cancer screening, better surgical and adjuvant therapies (e.g., radiation and chemotherapy), and salutary dietary changes. CRC generally occurs in patients over 50 years of age, with only 3-9 percent of cases occurring in patients less than 40 years old.[2, 3] Peak incidence occurs between the ages of 60 - 79, then gradually declines.[4] Age-adjusted incidence rates are slightly higher in men compared to women; this difference is more pronounced for rectal cancer (1.73 relative risk) than for colon cancer (1.34).[5]

3.2 Risk factors

CRC results from a complex interaction between inherited susceptibility and environmental or lifestyle factors. A diet high in natural fiber and calcium-rich, low-fat dairy products, and vigorous physical activity decreases the risk of CRC, whereas a diet high in animal fat, sedentary lifestyle, and being overweight increases risk.[6]

About 10-15% of all colorectal cancer occurs in high risk groups, including patients with:

- chronic inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease);
- previous malignant disease;
- hereditary conditions such as familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer (HNPCC), Lynch I Syndrome, and Lynch II Syndrome (up to 50% incidence).[7]
-

Other conditions associated with an increased risk of CRC include a history with adenomas or first degree family history of CRC or adenomas diagnosed before 60 years of age, and a personal history of ovarian, endometrial, or breast cancer.[8]

Evidence has accrued in support of the view that CRC develops from benign adenomatous polyps, a process that can take up to ten years. In a non-randomized controlled trial, detection and removal of these polyps significantly reduced the incidence of colorectal cancer.[9] The prevalence of adenomas in the general population is about 25-60 percent, and increases with age. Of these, about 95 percent are small (< 1cm), with a 1 percent probability of becoming cancerous; the remaining 5 percent are relatively large (> 1cm), and carry a 10 percent probability of becoming malignant. A 1997 guideline on colorectal screening suggested that measures used to reduce the incidence and prevalence of adenomas may reduce the risk of developing colorectal cancer.[10]

3.3 Survival

3.3.1 Staging

This review uses the tumor/nodes/metastases (TNM) staging system developed by the American Joint Commission on Cancer (AJCC). References to disease stages obtained from articles using other systems were converted to the TNM system for ease of comparison (see Appendix B). The AJCC staging system combines three main variables: (T) the degree of penetration of primary

lesion; (N) the presence or absence of lymph node involvement and the number of involved nodes; and (M) the presence or absence of metastasis. The combination of the T, N, and M classification indicates the extent of the disease. Systems of grouping patients have been developed to ensure, as far as possible, that each group is relatively homogeneous in respect of survival. A further explication and comparison of cancer staging systems is provided in Appendix B.

About half of all patients diagnosed with CRC present with an advanced stage of disease (III/IV), indicated by nodal involvement or metastases.[11-19] For example, the Surveillance, Epidemiology, and End Results (SEER) database shows that 51 percent of new cases present at stage III/IV for rectal cancer; the corresponding figure for colon cancer was 59 percent.[20] The rate of advanced disease at diagnosis appears to be higher in younger patients, with 68 - 78 percent presenting in stage III/IV.[3, 4, 21-23]

3.3.2 Tumor types and associated progressions

Most colorectal tumors (90-95 percent) are adenocarcinomas and carry a more favorable prognosis than the less common colloid or mucinous tumors, which occur in 5-17 percent of cases.[5] Poorly differentiated or mucus producing tumors, or those with advanced histological grade, are associated with rapid progression of the disease process. Adenocarcinomas are considered slow growing, following normal polyp dwell time. Younger patients tend to have a higher incidence of poorly differentiated or mucinous tumors, which are associated with more rapidly progressive disease.[2, 3, 24, 25] In a 1990 review article, 28 percent of the younger patients had mucinous tumors (3-60 percent), and 25 percent had poorly differentiated tumors (12.5-48 percent).[4]

3.3.3 Polyp dwell time

The amount of time it takes for an adenoma to progress from a benign state to a period of clinical significance is referred to as the "polyp dwell time." Only larger polyps are at significant risk for progression to malignancy[10]; this rarely occurs in less than three years[9], and more often between 4.5 to 10 years. A study analyzing autopsy specimens reported that initial malignant cells take 4.8 years to double in number and begin to produce symptoms among patients.[26] In a 1993 non-randomized controlled trial of patients who had polyps removed, only five cases of colorectal cancer were reported out of the 1,418 patients who had been screened with baseline and periodic colonoscopy for 6 years.[9] All cases were asymptomatic prior to surgical treatment and all were early stage I disease (well differentiated adenocarcinomas). Two other studies, an observational study of biopsied polyps[27], and a case-control study on screening[28], support the view that about 10 years is likely to elapse before benign polyps become malignant.

3.3.4 Survival rates

About 90 percent of patients whose CRC has not spread through the bowel wall will live five years after diagnosis (see Table 1). Of patients with lymph node involvement, only 65 percent will survive five years. Stage IV metastatic disease has the poorest prognosis, with 8 percent surviving in five years. Overall five year survival from CRC is about 60 percent, and this figure does not vary substantially by sex, age of incidence, or ethnicity.

Table 1: SEER relative* 5-year survival rates 1989 - 1996 (%) [20]			
	Colon	Rectal	Colorectal
Overall	62%	60	61
Stage I/II (Localized)	92	87	90
Stage III (Regional)	68	57	65
Stage IV (Distant)	9	7	8
Males overall	62	59	61
Females overall	61	61	61
< 45	57	60	58
45-54	62	65	63
55-64	63	63	63
Table 1: SEER relative* 5-year survival rates 1989 - 1996 (%) [20] (cont.)			
	Colon	Rectal	Colorectal
65-74	64	62	64
> 75	60	52	58
Caucasian (overall)	63	61	62
Afro-American (overall)	52	52	52

*The relative survival rate refers to the ratio of the observed survival rate to the expected rate for a group of people in the general population. It tends to be higher than observed survival rates.

3.3.5 Recurrence rates

Recurrence rates are associated with the tumor stage, the treatment regimen, and the presence or absence of clear margins.[29] In a multivariate analysis, lymph node status was independently associated with recurrence-free survival.[30] About 5-10 percent of stage I/II colon and stage I rectal cancers recur within 5 years of surgery[31]; stage II rectal cancers have a 25-30 percent rate of recurrence[32], and stage III colorectal cancers recur about 50 percent of the time.[31, 32] In a randomized controlled trial, preoperative radiation treatment resulted in a 8-20 percent decrease in five-year local/regional recurrence of rectal cancer, with a recurrence rate of 11 percent with radiation therapy compared to 27 percent in patients receiving surgery alone.[33] Similarly the addition of chemotherapy to surgery improved recurrence rates by 17 percent, with a further 5 percent reduction in five-year local or regional recurrence rates when postoperative radiation was added (8 percent recurrence with adjuvant chemo-radiation therapy vs. 13 percent recurrence with adjuvant chemotherapy).[30]

3.4 Diagnosis and symptoms

3.4.1Diagnosis and screening

CRC may be diagnosed based on presenting symptoms or as the results of a screening program. Except for patients with obstructing or perforating cancers, the duration of symptoms is not correlated with prognosis.[5] Because early colorectal cancer often produces no symptoms, and because many of the symptoms are nonspecific, aggressive efforts at detection through screening programs have been promoted.

To diagnose presymptomatic patients, screening guidelines endorsed by such organizations as the American Cancer Society and the American College of Radiology recommend various schedules

for screening, depending on the person's risk factors.[8, 10, 34] It is commonly recommended that people over the age of 50 have annual fecal occult blood testing and an annual digital examination, as well as a more definitive imaging test (e.g. flexible sigmoidoscopy, colonoscopy, or double contrast barium enema) every five or ten years. Although not recommended for routine staging of primary colorectal rumors, a CT-scan may be performed to determine the presence or extent of metastasis in the abdomen and retroperitoneum[35], or to obtain a core needle biopsy sample of the suspect mass. Transrectal ultrasound may be used to evaluate rectal tumors.[36].

3.4.2 Symptoms

Up to 20 percent of all colorectal patients are virtually asymptomatic at diagnosis. Presenting symptoms among the remaining 80 percent of patients occur secondary to bleeding, obstruction or perforation. The following symptoms are the most common in patients later diagnosed with CRC: rectal bleeding, abdominal pain, and change in bowel habits such as constipation and diarrhea. Other symptoms include mucus discharge, anemia, weight loss, weakness, fatigue, or jaundice.

Symptoms are correlated with tumor location and age, however the relationship between stage and symptoms remain poorly defined.[37] One study of 53 patients found that the likelihood of the cancer being late stage (stage III/IV) was decreased if the presenting symptoms were low energy and diarrhea, and increased if symptoms included rectal bleeding, heartburn, and lack of appetite.[38]

Patients with rectal cancer tend to present with more rectal bleeding and bowel habit changes, and less abdominal pain, compared to colon cancer, whereas patients with colon cancer generally present with more abdominal pain and anemia than patients with rectal tumors.[15, 17-19, 37, 39, 40] Right colon cancer has a higher incidence of abdominal pain, bowel habit changes, anemia and abdominal distention, and less rectal bleeding.[41, 42]

More often younger patients, particularly those younger than 20, present with multiple symptoms.[3, 21, 22, 43, 44] Partial or total obstruction can occur in up to one quarter of all cases of colorectal cancer.[12, 15, 17, 18, 45] Obstruction often presents more insidiously, with intermittent and progressive abdominal distention and bowel habit changes, rather than an acute episode. Obstruction is associated with distal disease.[37]

3.4.3 Duration of symptoms

Depending on the manner in which CRC is diagnosed, between one-quarter and one-half of diagnosed patients will be asymptomatic or have had symptoms less than 4 months. Another 20 percent will have symptoms of 4-6 months duration; 15-35 percent will have had symptoms for between 6 months and one year, and about 10-20 percent will have had symptoms for over one year.[11, 12, 17, 19, 24, 39, 46-51]

Delays between the onset of symptoms and the definitive diagnosis and treatment of CRC can be attributed either to patients or to doctors and hospitals. Some studies have shown that these two sources are roughly comparable in their relative contribution to delay[39, 46, 52], while others have observed that patient-attributable delays are longer than doctor/hospital-attributable

delays.[37, 41] Table 2 lists several documented reasons for delay in diagnosis and treatment of CRC. Prolonged medical work-up for anemia and lack of routine digital rectal examination are the two most commonly cited reasons for delay in diagnosis.

Table 2: Causes for medical delays in diagnosis and treatment

Reason	Reference
Anemia, prolonged medical work-up	[11, 16, 39, 41, 53]
Lack of routine digital rectal examination	[40, 52, 54, 55]
Hospital waiting times for investigative studies	[52]
Poor quality or false-negative barium enema, or inadequate or false-negative sigmoidoscopy	[40, 52]
Referral time to a non-surgical specialty	[55]

3.5 Treatment

Surgery is the most commonly used treatment for localized cancer of the colon or rectum, resulting in cure in about 50 percent of patients.[7] A right or left hemi-colectomy is performed to resect the cancerous tissues; generally resulting in a temporary colostomy. Resection of cancer of the rectum may result in a permanent colostomy depending on the location of the cancer to the anal canal and sphincter muscles. Local excision is used in some stage I colorectal cancer, and is currently under study in stage II rectal cancer patients.[56, 57] It has the benefit of preserving anal continence and both bladder and sexual function, but there are concerns about higher rates of local failure with this technique.[58]

Adjuvant chemotherapy and radiation are often used in advanced CRC in an attempt to prolong survival and reduce risk of recurrence. Chemotherapy is used in the treatment of both rectal and colon cancer[7, 59-62], whereas radiotherapy is used only in rectal and anal tumors. Recent evidence from a randomized controlled trial reported no survival benefits or reduction in recurrence rates with the addition of postoperative radiation compared to surgery alone or surgery and chemotherapy alone.[30, 32]

Hepatic resection for metastases can improve survival, particularly when patient selection is refined by presurgical staging investigations such as intraoperative ultrasound.[7, 63, 64] However, for most patients with stage IV disease, treatment is directed towards improving quality of life by reducing symptoms.

Surveillance after treatment is generally considered necessary because death is often the result of recurrence of the tumor. However, the use of standard surveillance has been criticized. In a review article, Kievit concluded that follow-up in most cases will lead only to significant increases in cost, without an increase in quality-adjusted life expectancy.[65]

See Appendix C for detailed treatment recommendations.

4. Effect of Waiting for Treatment

4.1 Practice guidelines

Clinical practice guidelines have been developed to assist management of patients with CRC rarely address the question of appropriate timing of surgery or adjuvant therapy. For example, the National Comprehensive Cancer Network (US) Colon and Rectal Cancer Treatment Guidelines for Patients (March 2000) makes no mention of when treatment should be undertaken in relation to the diagnosis.[66] Nor do any of the following guidelines discuss appropriate timing of surgery or consequences of delay:

- National Cancer Institute, CancerNet Physician Desk Query "Colon Cancer";[7]
- National Cancer Institute, CancerNet Physician Desk Query "Rectal Cancer";[59]
- The NIH Consensus Statement "Adjuvant Therapy for Patients with Colon and Rectum Cancer"[31]
- Society of Surgical Oncology Practice Guidelines, "Colorectal Cancer Surgical Practice Guidelines";[67]
- American Society of Colon and Rectal Surgeons, "Core Subjects: Colon and Rectal Cancer";[68]
- American Society of Clinical Oncology, "Outcomes of Cancer Treatment for Technology Assessment and Cancer Treatment Guidelines"[69];
- American College of Radiology, Appropriateness Criteria: Gastrointestinal Imaging, Pre-Treatment Staging of Colorectal Cancer.[34]

Some CRC screening guidelines do address the issue of treatment timing in relation to diagnosis and prognosis, although not in definitive terms.[10, 34] For example, Winawer et al. stress the importance of treating colorectal cancer tumors before they produce symptoms as a means of reducing mortality and the morbidity associated with progressing disease.[10] This sentiment is provided in light of the fact that over half of the symptomatic patients treated for colorectal cancer present with advanced disease and have relatively poor prognoses. Moreover, it seems clear that clinical prognosis is generally fixed by the time the CRC results in symptoms. Therefore, earlier diagnosis and subsequent treatment of slow growing tumors may not affect the time of death, and any observed differences in survival may be explained by a lead time or length time bias. Length time bias results because screening tends to preferentially detect slower growing neoplasms, and lead-time bias arises when the follow-up of groups does not begin at comparable stages in the natural history of a condition.[70] Because screening detects many slow growing neoplasms, the apparent effectiveness of an intervention may be due not to delay of death but because the diagnosis was made earlier in the course of the disease.

4.2 Definition of acceptable delay

Twenty five articles were reviewed that directly addressed the duration of symptoms before surgical treatment (see Appendix D). Many studies used the word "delay" to describe the duration of symptoms before presentation to their physician, diagnosis, or treatment, although most did not define what would constitute an acceptable duration of symptoms before surgery is instituted. The most commonly articulated standard was a delay between a clinical history and surgery of no more than 12 weeks regardless of the source of delay (i.e. patient vs. system).[11, 16, 48] Others have confined their definitions to system delays only, suggesting that any delays of more than 3 months from initial clinical presentation to treatment are unacceptable.[40, 55] The latter definition accepts longer intervals between the onset of symptoms and surgery as

acceptable, because the three month "clock" begins "ticking" later in the clinical course than in the former definition.

4.3 Influence of symptom duration on survival

Fourteen original studies and two review articles, reported that duration of symptoms was not significantly correlated with survival.[4, 11, 14-16, 18, 47, 48, 50, 70-76] Eight studies reported that shorter duration of symptoms (< 3-6 months) was associated with a poorer survival although none of these studies controlled for the effect of stage on survival.[17, 19, 24, 46, 51, 77-79]. Three older studies found that shorter duration of symptoms (less than 3-4 months) was associated with *better* survival, but again none of these studies controlled for the effects of stage.[22, 42, 80] In general, stage of cancer on diagnosis and duration of symptoms do not appear to be closely correlated.[12, 13, 17, 37, 40, 42, 46, 48, 49, 73, 74, 80]

These findings have lead to a consensus, evident as early as 1978 that the timing of diagnosis and treatment in patients who present with symptoms likely does not have a major impact on prognosis[81] For this reason, improvements in survival are more likely to be obtained in identifying and treating presymptomatic patients through public screening programs.[12, 17, 19, 41, 42, 46, 48, 49, 52]

In summary, there is little evidence to guide the timing of surgery in patients who present with symptoms. In addition, the survival value of surgery in patients whose CRC is detected by screening is likewise uncertain in view of the lead- and length-time biases inherent in screening, as described above.

5. Baseline Health Status

A significant part of the evaluation of treatment effectiveness in CRC concerns the extent to which patients experience functional problems and unpleasant symptoms, in addition to the impacts of this condition on survival. In this section we will examine the extent of such problems and symptoms in preoperative patients.

5.1 Function

Functional or physical status is commonly measured preoperatively in cancer studies. A variety of instruments are used, including the Eastern Co-operative Oncology Group Performance Status Rating (ECOG-PSR), the Karnosfsky Performance Scale (KPS), and the Nottingham Health Profile (NHP). See Appendix E for a full description of these measures, and others discussed below.

In the analyses that follow, we have standardized scores on these various instruments on a 0-100 (worst-best) scale for ease of comparison.

The ECOG-PSR is a generic measure of physical function usually assessed by a clinician and reported as a percentage of the study population. Its scale has five points, ranging from 0 (pre-disease state) to 4 (completely bedridden, incapable of self care). In a study of 882 patients with colorectal cancer, patients older than 75 had worse physical status preoperatively (ECOG-PSR), compared to patients age 65-75 and patients under 65 (see Table 3).[82]

Table3: Proportion (%) ECOG-Performance Status Rating: Preoperative						
Study focus	CRC	CRC	CRC	Cancer **	Cancer **	Non-cancer
Age groups	< 65	65-75	> 75	<70	> 70	> 70
n =	361	279	242	174	133	278
0 - 1 (ambulatory, capable of light work - capable of self care, not able to work, with or without symptoms)	82* 0=52 1=30	68* 0=30 1=38	46* 0=16 1=30	97	82	41
2 - 4 (Bed rest 50%, limited self-care - completely bedridden, incapable of self-care)	18*	37*	53*	2	16	59
Reference	[82]	[82]	[82]	[83]	[83]	[83]

*Values derived from graph
**Includes colorectal cancer, breast cancer, and prostate cancer

In this retrospective review, over half of the patients older than 75 were unable to carry out physical work and were only capable of limited self-care. Repetto et al. studied the performance status and comorbidity of people with neoplasms, in which over one quarter were patients with colorectal cancer. In comparison with older people without neoplasms, it was evident that the non-neoplasm group had significantly worse physical status compared to patients with cancer.[83]

The study results suggest that in this population, cancer is more likely to be diagnosed in healthier elderly people. This finding may suggest that primary care providers were reluctant to refer patients for cancer work up who were in poor general health. Table 3 lists preoperative results obtained in two studies using the ECOG-Performance Status Rating scale.

The Karnosfsky Performance Scale (KPS) is a cancer specific measure of function that is also completed by the clinician. It has been used extensively in clinical trials, particularly those looking at metastatic colorectal cancer. Most studies that reported a KPS, however, were postoperative scores, used as the baseline for measuring benefits in a study of adjuvant therapy. One study, however, did provide KPS scores for 117 patients with colorectal cancer, with the mean KPS score preoperatively being 79 (13 SD, range 40-100).[84] As in many other studies, over half of the respondents presented with advanced disease.

The Nottingham Health Profile (NHP) is a well-validated indicator of departure from health with six dimensions. Whynes provided baseline scores for the NHP from two different studies of quality of life in colorectal cancer patients (see Table 4).[38, 85]. Both studies identified sleep, low energy and emotional reactions (nervousness, worry and anxiety) as the most disrupted areas of general health. Pain and social isolation were the least disrupted areas. Using the modified Rotterdam Symptom Checklist, Whynes et al. also showed the following areas were “quite a bit” or “very much” a problem in more than 12 percent of the study group (highest to lowest): decreased sexual interest, flatulence, lack of appetite, nervousness/anxiety, heartburn, urgency in bowel movement, and lack of energy.[38]

Table 4: Nottingham Health Profile, preoperative, 0-100 (worst-best)*		
Reference	[85]	[38]
n =	33	53
Emotional reactions	83	89
Energy	73	83
Pain	87	92
Physical mobility	85	92
Sleep	73	77
Social Isolation	89	93

*Results transformed from 100-0 (worst-best) scale, values estimated from graph

5.2 Pain
Preoperative pain in colorectal cancer was studied as part of the subscales of the NHP and as part of the quality of life measurement tool, the EORTC-QLQ-C30. As noted in Table 4, preoperative pain scores were 87 and 92 with a score of 100 considered as pain-free. These scores are consistent with Ulander et al. who studied 86 patients undergoing surgery for colorectal cancer using the EORTC-QLQ-C30, and reported a mean preoperative pain score of 89 (SD 23).[86]

5.3 Psychological
Like pain, psychological well being can be measured as part of the NHP, or solely using a mood or depression-specific tool. In the studies by Whynes using the NHP, more than 80 percent of the study group reported the presence of anxiety, worry and nervousness of some degree preoperatively.[38] Similarly, the most frequently cited problem in a study of 66 patients using the Bipolar Profile of Mood States (POMS) and the Beck Depression Inventory (BDI) was a general emotional disturbance, with anxiety and depression being most common psychological symptom.[87] Almost 50 percent of these patients met the criteria for a psychiatric disorder. The most common psychiatric disorders present in colorectal cancer patients include depression, and adjustment disorder with depression and anxiety.[87]

6. Surgical Outcomes
Despite the benefits of surgical and adjuvant therapy, patients who survive colorectal cancer do not return to their pre-disease health state.[88, 89] The five-year survival rate is the most common endpoint used in the literature to measure treatment outcome. To a lesser extent, studies refer to disease-free survival and quality of life as outcome measures. Outcomes are typically assessed at one month, three months, one year, three years, five years, and 10-years post-diagnosis (or post-surgery).

6.1 Function
No of the studies we reviewed provided both preoperative and postoperative performance status scores (ECOG-PSR) for colorectal cancer patients. When a postoperative score was provided, it was usually a baseline measurement as part of a study of adjuvant therapy. Although not specifically stated, it was assumed that this represented the physical status of the patient about six weeks after surgery. In a prospective study of 497 patients with stage IV colorectal cancer, almost three quarters of the study population were ambulatory with or without symptoms, and over a quarter reported being bedridden some or part of the day.[90] Similar performance status

scores were obtained in another study where 12-28 percent of the patients had a PSR score of 2, 3, or 4, while 71-88 percent with a score of 0 or 1; mean age of the study population was 62 years.[91].

Although no preoperative scores were provided in the article, Sullivan reported significant improvements in the KPS scores among 27-37 percent of patients (n = 210) with stage IV colorectal cancer being treated with adjuvant chemotherapy.[92] A 10-point increment improvement on the KPS was reported in 23 percent of the study population, whereas 37 percent remained about the same. Using the Functional Living Index-Cancer (FLIC), Sullivan also reported improvements in global function with 27 percent of the study population improving 8 points (converted scores; n = 181), while function remained stable in 62 percent, with improvements in symptoms in 19-49 percent.[92] See Table 5 for KPS scores. In a cross sectional study of survivals of lung, colon and prostate cancer, Schag et al. concluded that KPS is the best predictor of post-treatment quality of life.[88]

Table 5: Mean and distribution (%)* Karnosfsky Performance Scale 0-100 (worst-best) scores

Study focus	Stage IV CRC	Colon and Rectal	Stage IV CRC**
n =	44	117	209
Mean	80	93	90
91 - 100	23%		35%
81 - 90			35%
71 - 80	43%		30%
< 60	34%		
Reference	[93]	[88]	[92]

* Study population distribution based on KPS scores reported in 10-point increments.
**Study excluded patients with KPS > 80

Patients tend to have a higher functional dependency if an ostomy is placed, or if the patient was experiencing depressive symptoms before surgery.[87] Colo-anal straight anastomosis has poorer functional outcome in the first year post operatively (with more diarrhea and incontinence) than J-pouch anastomosis, however at two years the functional status was comparable.[94]

In a prospective study of 53 patients, Whynes et al. found that most variables on the Rotterdam Symptom Checklist (27 of 30 variables) failed to show a significant difference between pre and post symptoms at three months, including physical distress and colorectal specific symptoms.[38] Statistically significant improvements were noted in only three areas: appetite, rectal bleeding, and urgency of bowel movements. Furthermore, no differences were noted in postoperative symptoms between stages, suggesting that at three months postoperation, the symptom pattern is more common to all stages.

In the same study significant improvements were reported on the emotional reactions dimension of the NHP (worry, nervousness, anxiety).[38] See Table 6 for the reported postoperative NHP scores. Surgical treatment did not exert a significant impact on the patients' energy, pain,

physical mobility and social isolation. Whynes et al. concluded that preoperative worry, nervousness and anxiety arise more from anticipating the treatment rather then from the disease.

Table 6: Nottingham Health Profile, 3 month postoperative, 0 - 100 (worst-best)*

	Study group by presentation mode			Net Benefit (p <)	
	Screen detected	Symptomatic	CRC		
n =	226	182	33	33	49
Emotional reactions	92	91	90	7 (0.05)	6 (0.02)
Energy	81	82	83	10 (0.05)	3 (0.59)
Pain	90	92	90	3 (NS)	3 (0.41)
Physical mobility	90	89	97	3 (NS)	0.01 (0.28)
Sleep	87	85	85	12 (0.06)	6 (0.07)
Social isolation	96	94	94	5 (NS)	2 (0.92)
Reference	[85]	[85]	[85]	[85]	[38]

*Results transformed from 100-0 (worst-best), values estimated from graph
NS = Not significant

6.2. Pain

In prospective study of 181 patients with colon and lung cancer, Portenoy et al. concluded that pain is prevalent among ambulatory, well-functioning patients with colorectal cancer.[95] Both the intensity and the frequency of abdominal pain had an impact on the patient's health state. About 90 percent of patients experienced pain more than 25 percent of the time. The median pain duration was 4 weeks, and average pain intensity was moderate. Over one third of the patients had more than one discrete pain. Pain moderately interfered with general activity and work in approximately half of the patients. Similarly, more than half the patients that reported pain or moderate or greater intensity reported disruption in their sleep, mood, and enjoyment of life.

In two studies, the net benefit of surgery on pain appeared to be modest at best. Whynes et al. demonstrated a three-point improvement that was not considered statistically significant.[38] Ulander et al. reported a net change of *minus* three points on the QLQ-C30, suggesting that pain was slightly worse 5-6 months postoperatively, and in particular, colon cancer patients had less pain compared to rectal cancer patients.[86] However these studies are not sufficient to establish a clear indication of the effect of surgery on pain in patients with CRC.

6.3 Psychological

Barsevick et al. studied 66 patients to describe the nature and degree of psychological distress and functional dependency of persons with CRC.[87] Depressive symptoms changed substantially over time in relation to the events of diagnosis and treatment. Using the Profile of Mood States (POMS), preoperative scores improved only slightly with surgery, increasing four points (converted) on a 0-100 worst-best scale. This was the only study we were able to find on this topic.

6.4 Quality of life

Using a cancer specific measure EORTC-QLQ-C30, Ulander et al. reported moderate improvements in overall quality of life, as well as on the emotional functioning dimension (see

Table 7). Significant improvements were noted in global QOL, emotions, and appetite. Concerns with the financial impact of the disease was the only subscale that significantly worsened after surgery and adjuvant therapy. Rectal cancer patients had less functional gains in physical, role and social function compared to colon cancer patients. Ulander et al. also report that colon cancer patients experienced less pain and constipation six months after surgery, and rectal patients has less diarrhea.

Table 7: EORTC QLQ-C30, postoperative, 0-100 (worst-best), [86]

Dimension (n = 86)	Subscale	Mean (SD)	Net Benefit	p <
Function	Cognitive	85 (19)	3	0.09
	Emotional	82 (22)	10	0.0001
	Global	74 (25)	8	0.03
	Physical	77 (29)	- 5	0.06
	Role	79 (30)	- 5	0.06
	Social	82 (25)	1	0.67
Symptom*	Fatigue	72 (28)	2	0.27
	Pain	86 (22)	- 3	0.06
	Nausea/Vomiting	96 (14)	2	0.17
	Dyspnea	83 (24)	1	0.24
	Sleep Disturbance	82 (27)	1	0.86
	Appetite Loss	90 (23)	6	0.05
	Constipation	87 (21)	7	0.09
	Diarrhea	86 (27)	8	0.11
	Financial Impact	94 (19)	-4	0.05

*Scores transformed from 100-0 (worst-best)

The EORTC QLQ-CR38 is a quality of life measure specifically designed for use in colorectal cancer. It consists of 38 questions, and provides a number of subscales within dimensions of function and symptoms including the effects of radiation, chemotherapy, stoma, sexual dysfunction, and gastrointestinal symptoms. Spranger et al. studied 117 patients using this tool and reported post surgical scores as outlined in Table 8. Areas of most concern postoperatively included sexual function, sexual enjoyment, and future perspective, with men having more problems than women. Slight improvements were noted in weight gain, female sexual symptoms, future outlook and sexual enjoyment, with no improvement or worsening in areas of male sexual symptoms, defecation symptoms, chemotherapy side effects, gastrointestinal symptoms, micturition.[84]

Table 8: EORTC QLQ-CR38, postoperative, 0-100 (worst-best), [84]					
Dimension	Subscale		Mean (SD)		Net Benefit of adjuvant chemotherapy
		n =	Before adjuvant	After adjuvant	
Function	Body image	108	84 (21)	82 (21)	- 2
	Sexual function	92	23 (25)	21 (24)	- 2
	Sexual enjoyment	461	56 (27)	50 (30)	- 6
	Future perspectives	108	56 (29)	64 (30)	8
Symptoms*	Micturition	106	74 (21)	66 (23)	- 8
	GI Tract	108	88 (17)	73 (17)	- 15
	Chemotherapy side effects	108	89 (15)	82 (19)	- 7
	Defecation	72	81 (17)	73 (19)	- 8
	Stoma	38	77 (17)	79 (18)	2
	Male sexual problems	63	58 (40)	57 (40)	- 1
	Female sexual problems	12	82 (20)	83 (26)	1
	Weight loss	107	86 (29)	89 (20)	3

*Scores transformed from 100-0 (worst-best) severity of symptoms

7. Prognostic Indicators of Treatment Benefit

The following section discusses the preoperative variables associated with the outcomes in colorectal cancer. Studies of this nature often use overall survival as their endpoint using analytical methods such as the Kaplan- Meier, and life table. Multivariate analysis using Cox's regression determines the degree of independence for prognostic values by controlling for other variables that would otherwise affect the outcome result. Appendix F (Prognostic Indicators) contain a summary of studies that report on prognostic variables.

7.1 Independent predictors of survival

7.1.1 Tumor stage

The stage of the tumor in colorectal cancer is the most consistently reported independent prognostic factor. Prospective trials using multiple regression analysis have shown that the more advanced the stage, the less likely the survival at five years. This strong independent association necessitates controlling for stage when looking at other prognostic variables.[14, 15, 18, 70, 79, 96] Variables within the tumor staging system have also been shown to be independent prognostic indicators. These will be described individually below.

7.1.2 Depth of wall invasion

In four separate studies looking at 4,682 patients, the depth of the bowel wall invasion directly and independently associated with poor survival, even when controlled for stage in multivariate analysis.[15, 18, 75, 78, 97]

7.1.3 Lymph node involvement

Lymph node involvement has been shown to be an independent prognostic indicator for survival, leading to poor survival rates.[15, 18, 23, 75] Only one study showed that lymph node involvement was not an independent prognostic factor of colorectal cancer, with statistical significance being lost when the data set was controlled for the effects of stage.[78]

Park et al. studied 2,230 patients and found nodal involvement exceeded overall stage in statistical significance in a multivariate analysis.[15] Similar findings were reported by Heys in a 1994 UK study.[23] Furthermore, Park et al. found that patients with rectal cancer and nodal involvement had a worse survival than colon cancer patients with nodal involvement.[15]

7.1.4 Histopathologic grade

The histopathologic grade or differentiation refers to the extent to which a tumor resembles the normal tissue at the cancer site. Well-differentiated tumors have better survival rates than moderately differentiated tumors, which have better survival than poorly differentiated tumors, as reported in two studies (total n = 1935) using a multivariate analysis to control for the effects of stage.[18, 96] These studies also confirmed that mucus-secreting tumors have worse five-year survival than non-mucinous tumors (26 percent vs. 56 percent; n= 489)[96] and (44 percent vs. 73 percent; n = 1446)[18]. The histologic type and grade are therefore independent prognostic indicators. These findings are supported by with earlier studies, though the data was less statistical significance.[42, 75, 77, 79]

Similarly, Park et al. in a study of 2,230 patients found that pathology affected prognosis more in rectal cancer than in colon, with the level of statistical significance retained during Cox regression analysis only in the rectal cancer data set.[15]

7.1.5 Obstruction/perforation

Four prospective studies (total n = 2,646) using multivariate analysis showed that obstruction was an independent indicator of poor prognosis.[11, 18, 70, 78] These findings are consistent with earlier results of an investigation of 1,217 patients which showed obstruction to uniformly carry a poorer prognosis when compared to absolute survival rates of the group as a whole (24 percent vs. 38 percent).[77] In contrast, however, a study of 219 patients showed that the presence of preoperative obstruction lost statistical significance once stage was controlled for.[14]

7.2 Possible predictors of survival

7.2.1 Elevated CEA level

Although less studied than other variables reported thus far, an elevated carcinoembryonic antigen (CEA) level has been found to be a significant prognostic indicator, particularly in early disease. Advantages of preoperative CEA focus primarily on its role in the pre-therapeutic assessment of prognosis, for example in estimating the potential benefit of preoperative radiotherapy in stage II rectal cancer. Postoperative CEA (recommended to be tested every 3 months as routine surveillance) has a role in the detection of tumor recurrence and monitoring response of adjuvant therapy and some palliative treatments.[98]

In 1990, the NIH Consensus Conference statement identified an elevated preoperative CEA (> 5ng/ml) that remained elevated for more than 6 weeks postoperatively has an increased risk for recurrence.[31] In a 1998 review of tumor markers, Hunerbein concluded that CEA is the marker of choice for colorectal cancer, although it should not be used for screening purposes, or alone for postoperative surveillance. In four recent studies (total n = 4,381) using Cox regression analysis, a preoperative CEA level > 5 ng/ml was shown to have worse survival rates compared

to patients with normal CEA.[15, 18, 99, 100] In contrast, Slentz et al. studied the difference in pre and post operative CEA levels, and showed that an elevated preoperative CEA, particularly one that failed to decrease to normal postoperatively following curative resection, represented a poor prognostic factor ($p < 0.05$).

Harrison et al. studied outcomes in node-negative colon cancer patients to determine if they could predict which patients might experience recurrence. In this study of 572 patients with stage I and stage II colon cancer, preoperative CEA and overall stage was found to predict survival by multivariate analysis, and therefore could be used to identify a subset of stage II colon cancer that may benefit from postoperative chemotherapy.[101]

7.2.2 Symptoms

The lack of correlation between duration of symptoms and survival was discussed above in section 3.4.2. Similarly, two studies of colon cancer using multivariate analysis showed a lack of correlation between symptoms (e.g. change in bowel habit, rectal bleeding, anemia, or abdominal pain) and survival.[14, 78] Goh et al. studied 219 patients with colon cancer and found no significant influence of clinical variables such as change in bowel habit and rectal bleeding on three year survival.[14] Chapius et al. studied 709 colon cancer patients and found no association between survival and bowel habit changes or anemia. This same study found rectal bleeding or the absence of abdominal pain significantly associated with better survival but the significance was lost in the multivariate analysis when controlled for stage.[78]

Goh et al. found that abdominal distension had a significant influence on three-year survival in a multivariate analysis of 219 colon cancer patients. In this population, almost all patients with abdominal distention had some degree of obstruction and therefore a poorer prognosis.

In a study conducted by Polissar et al., the presence or absence of any single specific symptom was not found to be a significant predictor of survival, however patients with two or more symptoms had significantly worse three-year survival in a multivariate analysis.[47]

Goodman et al. conducted a study on 152 patients with right colon cancer and showed improved survival rates for patients with no abdominal symptoms and anemia, compared with patients with abdominal symptoms (48 percent vs. 17 percent).[16] Similar findings were documented earlier by Fegiz et al., in their study of 195 patients which showed improved survival rates for right colon cancer patients presenting with no abdominal symptoms and either anemia or positive fecal occult, compared to patients with abdominal symptoms (88 percent vs. 50 percent).[42] Asymptomatic patients (with anemia, fecal occult, and no abdominal symptoms) were less likely to have stage III tumors (25 percent) compared to other symptomatic groups (49 percent - 57 percent).[42] Goodman suggested that asymptomatic patients had a better prognosis due to the slow-growing nature of the tumor with low potential for spread.[16]

Anemia has been identified as a prognostic indicator[77], particularly when combined with other symptoms such as a positive fecal occult test[42], or the absence of abdominal pain or distension[16]. More recently, in a study of 219 older patients aged > 75, preoperative anemia in itself or as one of a multiple symptoms was found to be significantly correlated with better

survival compared to patients with no anemia (54 percent vs. 29 percent).[76] An earlier study (1985), however, disputes the prognostic value of anemia[78].

The presence of bloody stools at presentation has also showed improved survival rates for older patients. Hessman found that older patients who experienced preoperative weight loss > 5 kg were associated with worse survival (25 percent vs. 56 percent) when compared to patients with < 5 kg weight loss.[76] Additionally, older patients with an ASA score of 2 (mild systemic disease) had better five-year survival rates compared to patients with an ASA of 3 (severe systemic disease, not incapacitated).[76]

7.2.3 Age

The association of age and survival has been frequently studied; results have been mixed. There is some evidence to support age as an independent prognostic indicator.[14, 78, 96, 102] For example, analyses have consistently shown that patients younger than 40 and older than 70 tend to have worse survival rates than patients age 41-69. Similarly, in a retrospective review of 517 patients treated with locally curative intent surgery, patients aged under 50 or over 70 had significantly worse five-year survival.[96]

In two different studies using univariate analysis, patients under 40 years of age exhibited a significant association towards poorer prognosis than did older patients[14, 102], however, once multivariate analysis modeling was applied, the significance was lost[14]. Goh et al. also showed worse survival rates for patients older than 70, though again, the significance was lost when analyses controlled for stage. In contrast, an earlier multivariate analysis by Chapuis et al. showed age as a significant predictive indicator of survival, with patients younger than 70 having better survival rates than patients older than 70 (38-47 percent vs. 20-30 percent).[78]

Conversely, there are numerous studies that call into question the predictive value of age.[3, 15, 18, 23, 76, 79, 103] Significant correlations between age and five-year survival were not found in a series of studies using Cox multiple regression analysis.[2, 47, 70, 72, 104]

7.2.4 Performance status

Performance status is a reflection of the patient's functional capacity or general fitness. In Kingston's retrospective study of elderly patients, the major age-related determinant in the prognosis of CRC was the general fitness of the patient. Patients older than 75, fit for surgery, and who survived for more than 30 days after a curative resection, had a similar five-year survival rate as those patients in the younger age groups (< 65 years and age 65-75).[82]

This finding was supported by a study that measured general fitness with a performance status tool. The ECOG PS was used to compare palliative and adjuvant therapy among patients over 70. It was found that elderly patients with a good performance status (ECOG PS of 0 or 1) had similar one year survival rates as those younger patients with good performance status (44 percent vs. 48 percent).[105] However, Repetto suggested that the ECOG PS is inadequate to predict the prognosis of older cancer patients because it reflects concomitant chronic illness more than the cancer itself.[83]

Graf et al. studied 198 patients and concluded that preoperative KPS scores had a significant relationship to survival in both univariate and multivariate analyses.[106] Sullivan et al. obtained similar results.[92]

7.2.5 Gender

Generally gender has not been shown to hold good prognostic value. Five studies (total n = 3,536) did not find significant differences in five-year survival rates.[15, 70, 79, 96, 102] These studies confirmed the results of an earlier (1981) large eight-year study of 1,115 patients investigating gender and survival rates.[107] Park et al. studied (1999) patients with rectal cancer and found significant differences between women's survival compared to men's survival in a univariate analysis (73 percent vs. 64percent). However, significance was lost when the data was controlled for stage and other factors.[18] An earlier study (1981) of 709 patients found woman had slightly better survival rates than men (34 percent vs. 39 percent), whereas a small study (n = 154) showed significantly better three-year survival rates among men than women (71 percent vs. 50 percent).[47]

7.2.6 Location of primary tumor

Although SEER data shows slightly worse survival rates for rectal cancer than colon cancer, most studies do not support a consistently significant prognostic correlation between location of primary tumor (colon vs. rectal) and five-year survival.[46, 107] This holds true particularly when controlling for the effects of stage.[14, 15, 18, 70, 78, 79, 97, 102] Only one study found better survival rates in rectal cancer patients compared with colon cancer patients (77 percent vs. 49 percent), using a Cox regression analysis.[47]

In a univariate analysis of 161 patients, Pescatori et al. showed better surgical results and improved survival in patients with right colon tumors than patients with left colon tumors. In this study population, right colon tumors tended to have longer clinical history, and more localized disease, whereas left colon tumors incurred more emergency surgery.[46]

8. Conclusion

Practice guidelines for management of CRC do not provide clarification on the appropriate timing of surgical treatment. The literature addressing the duration of symptoms before surgical treatment suggests that three months might be an acceptable time between first reporting of symptoms and treatment. However, there is little empirical evidence to support this suggestion. The timing of diagnosis and treatment in patients who present with symptoms likely does not have a major impact on prognosis. For this reason, improvements in survival are more likely to be obtained by identifying and treating presymptomatic patients through public screening programs. The timing of surgery in asymptomatic patients provides more survival benefits in patients with biologically aggressive tumors, and in patients at risk for developing an obstruction.

Studies show that patients with CRC suffer from significant functional and psychological impairment pre-operatively, and to a lesser extent physical pain. Evidence concerning the effects of surgery and ancillary treatments on functioning is moderately supportive, whereas the effect of surgery on pain appears to be equivocal at best. Quality of life measurements are shown to

improve with treatment, and the significant emotional distress, anxiety, depression and sleep disturbances experienced by many patients with CRC appear to benefit from timely treatment.

The stage of the tumor in CRC is the most consistently reported independent prognostic factor. Variables within the tumor staging system have also been shown to be independent prognostic indicators; these include the depth of the bowel wall invasion, lymph node involvement, histologic type and grade, and obstruction. Although less studied than the previous indicators, an elevated CEA level, specific symptoms and age, performance status, gender and the location of the primary tumor have all been shown to be possible predictors of survival.

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Colorectal Cancer Literature Review Appendix A: Search Terms

Relevant literature was obtained through electronic database searches of Medline, Best Evidence, Cochrane Library, LegalTrac, HealthSTAR, and the Science Reference Index. The following search terms and limitations were used to retrieve references.

Medline:

The Medline search was limited to articles published between 1989 and 2000 (unless otherwise noted). Articles were included if they were written in English, or had an English abstract. The following subject headings were combined with <u>colorectal neoplasms</u>*, or <u>colonic neoplasms</u>*, or <u>rectal neoplasm</u>* using an "and" connector.

The majority of terms were "exploded" to include all narrower terms. When exploded searches yielded a more than a hundred articles, the strategy was modified to "focus" the search to limit the search to those articles in which the subject heading is considered the major point of the article. In the list of search terms an asterisk refers to a focused search whereas "exp." Refers to an exploded strategy. For example "age factors* or (exp. 1999-2000) refers to the focused search for age factors for the years 1989-2000, combined with (or) an exploded search of age factors for the years 1999-2000.

- Activities of daily living
- Age factors* or (exp.1999-2000)
- Age of onset
- Aging
- APACHE
- Causality
- Consensus development conferences
- Cost allocation
- "Cost-benefit analysis"
- Cost control
- Cost savings
- Costs and cost analysis
- Decision making
- Decision support techniques
- "Delay$" (exp.1980-2000)
- Delivery of health care*
- Disability evaluation
- Disease management
- Disease progression
- "Duration of symptoms"
- Economic value of life
- Evaluation studies*
- Geriatric assessment
- Health care costs
- Health care rationing
- Health planning
- Health priorities
- "Health services needs and demand"
- Health status
- Health status indicators
- Jurisprudence
- Karnofsky performance status
- Lead time bias
- Liability
- Life expectancy
- Malpractice
- Medical futility
- Models, theoretical*
- Mortality* or (exp.1999-2000)
- Multivariate analysis* or (exp.1999-2000)
- Neoplasm staging* (1980-2000) or (exp. 1999-2000)
- Nutritional status
- "Outcome and process assessment (health care)"* or (exp. 1999-2000)
- "Outcome assessment (health care)"*
- Pain*
- Pain measurement
- Patient acceptance of healthcare*
- Patient satisfaction*

- Patient selection
- Population surveillance*
- Practice guidelines*
- Precipitating factors
- Predictive value of tests* or (exp.1998-2000)
- Preoperative care*
- Quality-adjusted life years
- Quality of life*
- Questionnaires
- Reference standards
- "Referral and consultation"
- Reoperation* or (exp.1999-2000)
- Risk factors* or (exp.1999-2000)
- Severity of illness index
- Sex factors* or (exp.1999-2000)
- Socioeconomic factors
- Surgical procedures, elective
- Surgical procedures, operative (economics, standards, statistics & numerical data, trends, utilization, mortality)*
- Survival analysis* or (exp.1999-2000)
- Survival rate* or (exp.1999-2000)
- Time factors* or (exp.1995-2000)
- Treatment failure
- Treatment outcome*
- Waiting lists
- Work capacity evaluation

Best Evidence:
Records from 1991 to issue 4/1999 were searched using the following terms:
- Colorectal cancer
- Rectal cancer
- Colon cancer
- Colorectal neoplasms
- Colonic neoplasms
- Rectal neoplasms
- Waiting lists
- Rationing

CancerLit
Records from 1993 to March 2000 with abstracts only using the following terms:
- Colorectal cancer
- Neoplasm
- Rectal
- Colon

Cochrane Systematic Reviews:
Issue 4/1999 was searched using the following terms:
- Colorectal cancer
- Rectal cancer
- Colon cancer
- Colorectal neoplasms
- Colonic neoplasms
- Rectal neoplasms
- Waiting lists
- Rationing

LegalTrac
Publications from 1980 to March, 2000 were searched using the following terms:
- Colorectal cancer

HealthSTAR:
The records from 1975 to January, 2000 were searched using the following terms:
- Colorectal neoplasms
- Colorectal surgery

- Colonic neoplasms
- "Delay$"
- Health care rationing
- Health priorities
- "Outcome assessment (health care)"
- "Prioritisation"
- "Prioritization"
- Rectal neoplasms
- Surgery
- Time factors
- Waiting List

Science Reference Index

References from 1994 to 2000 that cited any of the following articles:

- McDermott, F., et al., Symptom duration and survival prospects in carcinoma of the rectum. Surg Gynecol Obstet, 1981. **153**(3): p. 321-6.
- Mulcahy, H.E. and D.P. O'Donoghue, Duration of colorectal cancer symptoms and survival: the effect of confounding clinical and pathological variables. European Journal of Cancer, 1997. **33**(9): p. 1461-7.
- Pescatori, M., et al., Site, emergency, and duration of symptoms in the prognosis of colorectal cancer. Dis Colon Rectum, 1982. **25**(1): p. 33-40.

Web sites

Organizations with web sites were reviewed as follows:

- American Cancer Society, www.cancer.org
- American College of Radiology, www.acr.org
- American Society of Clinical Oncologists, www.asco.org
- American Society of Colon and Rectal Surgeons, www.fascrs.org
- Canadian Cancer Society, www.cancer.ca
- Canadian Cancer Statistics 2000, www.cancer.ca/stats2000/maine.htm
- CancerNet PDQ, www.cancernet.nci.nih.gov
- National Cancer Institute, www.nci.nih.gov
- National Cancer Institute of Canada, www.ncic.cancer.ca/
- National Comprehensive Cancer Network, www.nccn.org/cancer.htm
- National Institutes of Health, www.nih.gov/health
- Scottish Intercollegiate Guideline Network , www.show.scot.nhs.uk
- Society of Surgical Oncology, www.surgonc.org/
- Statistics Canada, www.statcan.ca/

Colorectal Cancer Literature Review Appendix B: Stage and Pathology Staging Systems

The following are three widely used tumor classification systems*: the TNM/UICC, the Dukes, and the modified Astler-Coller. TNM = tumor/node/metastasis.

TNM/UICC

Primary Tumor

TX	Primary tumor cannot be assessed
TO	No evidence of tumor in resected specimen (prior polypectomy or fulguration)
Tis	Carcinoma in situ (above muscularis mucosa)
T1	Invades submucosa
T2	Invades muscularis propria
T3 - 4	Depends on whether serosa is present Serosa present: T3 Invades through muscularis propria into Subserosa, Serosa (but not through), Pericolic fat within the leaves of the mesentery T4 Invades through serosa into free peritoneal cavity or through serosa into a contiguous organ No serosa (distal two thirds rectum, posterior left or right colon): T3 Invades through muscularis propria T4 Invades other organs (vagina, prostate, ureter, kidney)

Regional Lymph Nodes

NX	Nodes cannot be assessed (e.g., local excision only)
NO	No regional node metastases
N1	1-3 positive nodes
N2	4 or more positive nodes
N3	Central nodes positive

Distant Metastases

MX	Presence of distant metastases cannot be assessed
MO	No distant metastases
M1	Distant metastases present

Dukes' Staging System Correlated with TNM

Dukes' A	T1, NO, MO
	T2, NO, MO
Dukes' B	T3, NO, MO
	T4, NO, MO
Dukes' C	Any T, N1, MO
	Any T, N2, MO
Dukes' C2	Any T, N3, MO
Dukes' D	Any T, any N, M

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* In all pathologic staging systems, particularly those applied to rectal cancer, the abbreviations m and g may be used: m denotes microscopic transmural penetration; g or m + g denotes transmural penetration visible on gross inspection and confirmed microscopically. (Modified from American Joint Committee on Cancer. Manual for staging of cancer, ed. 3. Philadelphia: JB Lippincott, 1988; and Union Internationale Centre le Cancer. TNM classification of malignant tumors, ed. 4. Geneva: UICC, 1987).

Modified Astler-Coller (MAC) System Correlated With TNM

MAC A	T1, NO, MO
MAC B1	T2, NO, MO
MAC B2	T3, NO, MO
	T4, NO, MO
MAC B3	T4, NO, MO
MAC C1	T2, N1, MO
	T2, N2, MO
MAC C2	T3, N1, MO
	T3, N2, MO
	T4, N1, MO
	T4, N2, MO
MAC C3	T4, N1, MO
	T4, N2, MO

American Joint Committee on Cancer (AJCC)

The American Joint Committee on Cancer: Classification of Colon/Rectal Cancer used the TNM classification to 5 categories, stage 0 through stage IV, as follows:

Stage 0	Carcinoma in situ; the cancer does not extend beyond the smooth muscle that separates the mucosa from the submucosa (Tis, NO, MO)
Stage I	Cancer confined to the mucosa, submucosa, or external muscle; the cancer does not extend through the bowel wall (T1or T2, NO, MO)
Stage II	Cancer that penetrates all layers of the bowel wall, with or without invasion of adjacent tissues (T3, NO, MO)
Stage III	Cancer involving regional lymph nodes or extending into nearby tissues or organs without spread to lymph nodes (any T, N1-N3, MO; or T4, NO, MO)
Stage IV	Cancer that has spread to distant sites, usually the liver or lungs (any T, any N, Ml)

Comparison of AJCC, Dukes, and Astler-Coller Stages

This table was used to find the matching AJCC/TNM stage:

AJCC/TNM	Dukes	Astler-Coller
O		
I	A	A, B1
II	B	B2, B3
III	C	C1, C2, C3
IV	D	

Pathology

Based on the World Health Organization Classification of Malignant Primary Tumors of the Large Intestine:

- Epithelial: adenocarcinoma, mucinous adenocarcinoma, signet-ring cell adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, unclassified carcinoma
- Carcinoid: argentaffin, nonargentaffin, composite
- Nonepithelial: leiomyosarcoma, others
- Hematopoietic and lymphoid neoplasms
- Unclassified

Colorectal Cancer Literature Review Appendix C: Treatment Recommendations

Stage 0 Colorectal Cancer
Polypectomy (via colonoscopy) or local excision are sufficient for curative treatment; larger lesions may require resection with anastomosis.[7] Adjuvant therapy is not recommended.[31]

Stage I Rectal Cancer and Stage I/II Colon Cancer
Surgery is the treatment choice (either local excision or abdominoperineal resection (APR).[7] Stage I rectal tumors and stage I and II colon tumors are low risk for recurrence and should not receive adjuvant treatment unless part of a clinical trial.[31]

Although not without controversy, some stage II colon tumors, for example Dukes B2 tumors in the younger patient, may benefit from adjuvant chemotherapy, experiencing a reduction in the recurrence rate, although survival is not likely to be affected.[61]

Stage II Rectal Cancer
Treatment recommendations include resection with anastomosis and adjuvant chemoradiation therapy.[7, 31] For disease in upper two thirds rectosigmoid, sphincter saving surgery is recommended[108], with preoperative radiation therapy with or without adjuvant chemotherapy, preferably through participation in a clinical trial.[59] Disease in the lower two thirds should be candidate for total mesorectal excision (TME) followed by chemoradiation, preferably through participation in a clinical trial.[59]

The role of local excision is looking promising, provided strict patient selection criteria are adhered to. Improved recurrence rates with local excision of stage II rectal cancer have been demonstrated in tumors that are mobile, $\leq$ 4 cm diameter, $\leq$ 1/3 rectal circumference, $\leq$ 8cm from anal verge, are well to moderately differentiated, have no vascular, lymphatic or perineurium invasion, and are T1N0 or T2N0 on endosonography.[57, 62] Otherwise, radical resection should be performed.

The role of adjuvant radiotherapy in stage II rectal tumors, on the other hand, is currently being challenged by recent results of several randomized clinical trials. In 1996, the Medical Research Council Rectal Cancer study showed preoperative radiation improved recurrence rate but did not improve overall survival, when comparing surgery alone with surgery plus preoperative radiation.[109] The Swedish Rectal Cancer Trial published evidence in 1997 that showed preoperative radiation improves both survival and recurrence (compared surgery alone with surgery plus preoperative radiation.[33, 110] Final results of a phase III study of the European Organization for Research and Treatment of Cancer compared surgery alone with postoperative radiation and found no survival benefits and no reduction in recurrence rates.[32] And most recently, the National Surgical Adjuvant Breast and Bowel Project Protocol R-02 showed that the addition of postoperative radiation therapy to chemotherapy in Dukes' B and C (stage II/III) rectal cancer did not alter the subsequent incidence of distant disease, although there was a reduction in local or regional relapse when compared with chemotherapy alone.[30]

Stage III Colorectal Cancer

Radical surgical procedures may be necessary to clear all the margins, in addition to some kind of combined-modality adjuvant therapy. Surgery includes APR and anastomosis, such as sharp mesorectal excision (SME) and total mesorectal excision (TME) with j-pouch anastomosis or colostomy. In their 1990 consensus conference statement, the National Institute of Health recommended chemoradiation for stage III rectal cancer, and systemic chemotherapy or immunotherapy for stage III colon cancer.[31] Treatment with 5-FU based chemotherapy increases overall survival and disease-free survival in stage III colon cancer. One year 5-FU and levamisole, or 6 months 5-FU and leucovorin, should result in a reduction of cancer-related mortality by approximately 25-35%.[60].

Stage IV Colorectal cancer

Palliative surgery may improve and/or prolong quality of life, in addition to palliative adjuvant therapy. Hepatic resection can improve survival rates, particularly when staged interoperatively with ultrasound.[7, 63, 64] Chemotherapy has been shown to prolong survival and improve quality of life in several randomized studies of Stage IV colorectal cancer.[111-113] Chemoradiation may provide local palliation for stage IV rectal cancer. Multiple studies (both controlled and uncontrolled) have evaluated portal vein chemotherapy and hepatic artery infusion (HAI) and show varying degrees of successful survival outcomes.[114] However, after critical analysis of these studies, there is clearly a lack of consensus on the value of chemotherapy in advanced colorectal cancer.[115]

Laparoscopic Colectomy

Laparoscopically performed colectomy looks promising as an alternative to radical resections, as they have been shown to reduce hospital stay, speed recover, and reduce postoperative pain.[116-118] However, further research on this treatment modality is necessary to determine the impact on survival and recurrence rates.[119] The American Society of Colon and Rectal Surgeons do not recommend laparoscopically performed "curative" colorectal cancer resections except in a prospective, controlled clinical trial.

Follow-up Surveillance

It is generally accepted that follow-up surveillance improves survival rates and has some degree of cost-effectiveness. The literature review did not, however, reveal guidelines on surveillance routines. Two randomized controlled trials compared intensified follow-up programs with standard or conventional surveillance, and concluded that standard programs (every 5 years LFT, CEA, Colonoscopy, Hx and PE) were as good as intensified follow-up programs (yearly colonoscopy, CT scan, CXR).[120]

Colorectal Cancer Literature Review Appendix D: Delay Articles

Reference	Title	Methods summary	n =	Comments
Aithal, [54]	Adjuvant treatment for colorectal cancer. Reducing avoidable delays in establishing the diagnosis is also important	Retrospective study of diagnostic delays in all new cases of CRC in 1993	93	Reports on a review of patients that showed median delays of 60 days between onset of symptoms and reporting to doctor, plus 30 days between doctor visit and treatment. Encourages prompt treatment of symptomatic patients, in particular, performing rectal examinations routinely.
Arbman, [39]	A short diagnostic delay is more important for rectal cancer than for colonic cancer	Prospective, multicenter study examining the association between a short diagnostic delay and tumor stage in patients with colonic and rectal cancer, Sweden.	544	No correlations found in colon disease. A short delay (< 1 mo.) in the diagnosis of rectal cancer was associated with significantly larger proportion of stage I disease compared to patients with a longer delay (p < 0.004). Thought to be caused by the insidious and vague nature of colon cancer. Colon had slighter shorter symptom duration, 7.3 month vs. 7.8 mo. rectal). Blood in stool was the most common symptom associated with rectal cancer. Study defines "delay" at the period between onset of symptoms to registration of surgery. Rectal cancer patients waited about two weeks more before reporting to a doctor (mean 4.5 month rectal vs. 3 mo. colon); doctors took about one week more to diagnose colon cancer (mean 4 mo. Vs. 3.4 mo. Rectal). Showed that 30% of right colon cancer patients were being treated for anemia for a period of 8.3 months before the CRC diagnosed. Women had longer doctor delays, thought to be caused by gynecological side tracks. Multiple regression analysis showed that age and sex had no influence between total delay and stage.
Dent, [71]	Relationship of survival to stage of the tumor and duration of symptoms in colorectal cancer.	Review article on duration of symptom and tumor stage/survival.	NA	Suggests that there is a methodological flaw in study of relationship between duration of symptoms and survival. Tumor stage cannot be measured until the end of symptomatic period, therefore cannot draw conclusions about early diagnosis of symptomatic CRC and effects on survival. Tumor stage at which point symptoms have become so compelling that the patient has been forced to see a doctor for diagnosis and surgery . Suggests it would be more useful to know stage at onset of symptoms.

Reference	Title	Methods summary	n=	Comments
Edwards, [121]	Anal cancer: the case for earlier diagnosis	Case series review of patients with anal carcinoma over ten year period	22	High recurrence rate (76%) and poor overall survival (28%) "probably due to late presentation." Hypothesis that higher proportion of patients with locally advanced disease is due to delay in diagnosis of anal carcinoma by the general practitioner who mostly diagnose common benign anal conditions like piles. No method of analysis or survival data provided.
Fegiz, [42]	Right colon cancer: long-term results after curative surgery and prognostic significance of duration of symptoms	Review of right colon disease, compare patients with abdominal symptoms with patients without abdominal symptoms, stratified by duration of symptoms.	195	The five-year survival rate for patients treated within three months (22.2%) was considered not significantly different than patients who had symptoms for over one year (15.4%). Article did not mention statistical method or p values. 88% had symptoms less than six months before treatment. No correlation between symptom duration and stage, differentiation, operability and survival. However, patients admitted in asymptomatic phase (without abdominal symptoms like pain, bowel habit changes, mass) and treated promptly had better survival (88%) compared to those who waited 2 months longer (50%). Author suggests that right colon cancer is slower to be reported by patients due to its vague symptoms.
Goodman, [16]	Delay in the diagnosis and prognosis of carcinoma of the right colon	Study incidence of delay in treatment of patients with right colon cancer. Compares patients treated < 12 weeks with patients treated > 12 weeks.	152	40% of the study population "suffered delays in treatment of more than 12 weeks" from the onset of symptoms to definitive treatment, with a mean delay of 48 (38.9-57.3) weeks. Patients with delays in diagnosis had survival rates not significantly different from those who presented early (9.4 weeks, range 8.1-10.7). Investigation of patients presenting with iron-deficiency anemia is important. Just over half of the patients with longer duration of symptoms presented with Stage I and II CRC, and 41% presented with Stage III tumors. 12 weeks accepted as the "gold standard" following a review of reported delay in treatment. All patients were treated within 2 weeks of diagnosis.

Reference	Title	Methods summary	n=	Comments
Graffner, [40]	Patient's and doctor's delay in carcinoma of the colon and rectum	Prospective study on 50 rectal and 50 colon cancer patients, interview and abstraction by doctors	100	Defines patient delay as more than 3 months between onset of symptoms and first visit to physician. Doctor delay when more than 3 mo. Passed between first visit and surgery. 33% rectal patients delayed > 3 mo. Before reporting symptoms to a doctor, where as 17% colon patients waited. Doctor delay due to misinterpretation of symptoms leading to wrong diagnosis in 24% of rectal cancer (hemorrhoids). Other reasons for doctor delay include false negative x-ray, false-negative endoscopy, wrong diagnostic tool (no rectal exam or signmoidoscopy). No correlation between stage and delay. 50% rectal patients suffered total delays > 6 mo., whereas only 20% colon experience delay > 6 mo.
Holliday, [24]	Delay in diagnosis and treatment of symptomatic colorectal cancer	Retrospective review of patients to investigate delay and possible causes.	200	Mean delay between onset and treatment 38 weeks rectal, 30.5 weeks colon. Shows that patients with short duration of symptoms are generally associated with poorly differentiated rectal cancer, and survival was worse than those with longer duration of symptoms. Found no correlation between duration of symptoms and the tumor stage. This may explains why early diagnosis of symptomatic disease does not guarantee better prognosis. Better prognosis can be achieved by means of a pre-symptomatic diagnosis, since it leads to detection of tumor in early stage. Once symptoms appear, survival is not dependent on delay. Equal delays noted between patient and doctor. Patient delay related to not knowing importance of bowel habit changes. Doctor delay commonly due to not examining patient with possible rectal and not recognizing signs of colon cancer. Hospital delay due to waiting for investigation, poor quality barium enema, and inadequate sigmoidoscopy.

Reference	Title	Methods summary	n=	Comments
Irvin, [48]	Duration of symptoms and prognosis of carcinoma of the colon and rectum	Compare symptomatic history with long term survival, stratified by duration of symptoms	335	Irvin et al. Concluded that duration of symptoms had little bearing on the prognosis or survival of patients with CRC. No correlation between duration and the rate of obstruction and perforation. The study concluded that patients presenting with symptoms of short duration had more virulent and biologically active tumors than did patients presenting with a longer history of symptoms, and onset of symptoms. More frequency included complaints of abdominal pain and multiple symptoms. Appears that earlier diagnosis of symptomatic patients may result in small gains in survival.
Khubchandani, [49]	Relationship of symptom duration and survival in patients with carcinoma of the colon and rectum.	Review relationship of duration of preoperative symptoms, stage and survival of patients with adenocarcinoma of colon and rectum	194	Lack of relationship between duration of symptoms and stage. Suggests that colon tumors may not progress in stage during symptomatic period. Biologically aggressive tumors carry more dramatic symptoms and less delays. Places emphasis on early diagnosis during pre-symptomatic phase. Of 186 symptomatic patients, no differences noted in survival with different duration of symptoms.
MacLeod, [80]	Survivorship following treatment for cancer of colon and rectum	Retrospective examination of CRC patients and relationship between survival and prognostic variables.	370	Patients with symptoms for less than 4 months had slightly better five-year survival. Duration showed slight differences but author says "doubts statistically significant". Life table, did not control for stage, used relative survival ratio. No consistent relationship between duration of symptoms and stage.
McDermott, [17]	Prognosis in relation to symptom duration in colon cancer	28 year retrospective study of relationship between duration of preoperative symptoms, stage distribution, and survival rates.	711	Provides data that showed stage II/III with symptoms less than 3 months was significantly worse prognosis than patients with longer symptom duration. Concluded that early symptomatic diagnosis and treatment is not necessarily associated with improved overall survival. Stage distribution did not differ significantly with increasing duration. Cancer specific survival worse for < 3 month compared to 3-6 mo., or > 12 mo. Early treatment does not guarantee early stage or better survival. 45% had symptoms < 3 months

Reference	Title	Methods summary	n=	Comments
McDermott, [19]	Symptom duration and survival prospects in carcinoma of the rectum.	28 year retrospective study of relationship between duration of preoperative symptoms, stage distribution, and survival rates.	1081	Cancer specific survival rate better if symptoms present > 12 months compared to those of < 3 months. Worse prognosis if preoperative symptom duration < 6 months compared to > 6 month. Frequency of major symptoms did not differ with increasing symptom duration. Stage is largely set before onset of symptoms. Proportion of curative to palliative operative procedures unrelated to duration of symptoms. Early diagnosis during symptomatic phase cannot be expected to improve cancer specific survival rates. What is important is preclinical diagnosis.
Majumdar, [37]	How does colorectal cancer present? Symptoms, duration, and clues to location	Retrospective review of patients at one institution, where data was collected before diagnosis was known.	194	Duration defined as time between onset to tissue diagnosis. Encourages keeping CRC as a differential diagnosis of "chronic" gastrointestinal symptoms. Over half had three symptoms (rectal bleeding, abdominal pain, bowel habit changes), 57% anemia, 77% FOB. Median duration between onset and diagnosis 14 weeks. No association between stage and duration. Developed rule for predicting distal disease using multiple regression (rectal bleeding, high hemoglobin, and obstruction independent predictors), which may assist in deciding who really needs colonoscopy, or who might just have flex sign and barium enema. Also identified symptom clusters. Discusses current biological models of carcinogenesis, where most CRC is thought to be result of an orderly adenomacarcinoma sequence, requiring about 10 yr. From onset of a polyp to the presence of a symptomatic cancer.[10] Thus it seems unlikely that a delay of a few weeks or months could significantly affect stage and eventual overall survival. However, may decrease complications (obstruction/perforation) and increase quality of life (shortened symptoms duration or decreased anxiety).

Reference	Title	Methods summary	n=	Comments
Mulcahy, [51]	Duration of colorectal cancer symptoms and survival: the effect of confounding clinical and pathological variables	Prospective study of consecutive patients to determine the association between symptom duration and survival independent of other clinical and pathological variables	777	Found symptom duration shortened with advanced stage ($p < 0.0006$) and obstruction ($p < 0.0001$). Lost significance when controlled for stage.
Pescatori, [46]	Site, emergency, and duration of symptoms in the prognosis of colorectal cancer	Investigate correlation between prognostic factors and results of surgical treatment.	161	Length of clinical history did not correlate with staging, but duration of symptoms of shorter than six months showed statistically significant poorer prognosis. Significant correlation between patient and medical delay meaning that patients who delay in reporting symptoms are more likely to experience further doctor or hospital delays. Better prognosis can be achieved by means of pre-symptomatic diagnosis.
Polissar, [47]	Survival of colorectal cancer patients in relation to duration of symptoms and other prognostic factors	Review of cohort of CRC patients looking at relationship between duration of symptoms and other prognostic factors.	154	No association between survival and duration of symptoms. Symptom duration of up to one year before diagnosis had no effect on survival.
Potter, [55]	Audit: Diagnostic delay in colorectal cancer	Retrospective case note review over one year	59	Time to diagnosis from first hospital attendance to diagnosis. Mean delay 52 days. Arbitrarily defined a time to diagnosis of > 30 days as unreasonable. Incomplete exam or initial referral to a non-surgical specialty appeared to contribute to delay.
Ratcliffe, [122]	Early diagnosis in colorectal cancer still no benefit?	Study looks at delay to diagnosis from first symptom, all treated by the three general surgeons in Trafford Health Authority.	332	There was no significant difference in delay between Dukes stage B and C patients but there was a significant difference in survival at two years between these two stages. Concluded no correlation between duration of symptom with 2-year survival, and that prognosis was more based on stage. Delay in diagnosis of patients with colon tumor more common in right colon tumors.

Reference	Title	Methods summary	n=	Comments
Roncoroni, [11]	Delay in the diagnosis and outcome of colorectal cancer: a prospective study	Prospective examination of incidence of delay, causes of delay, and its effect on outcome.	100	Delays in diagnosis and treatment do not affect the outcome. Duration of symptoms was calculated from the date of onset of symptoms to the date of surgery. 69% suffered delays in treatment of more than 12 weeks from the onset of symptoms. In patients with symptoms of less than 12 weeks' duration there was a higher incidence of radical surgery and none of these patients presented, at the time of surgery, a neoplastic dissemination. The results of this study suggest that, independent of the diagnostic delay, the outcome of the colorectal cancer is only conditioned by tumor stage.
Schillaci,[73]	The importance of symptom duration in relation to prognosis of carcinoma of the large intestine.	Examine relationship between duration of symptoms and survival.	162	Found no correlation between duration of symptom and stage, no correlation with survival. Patients with CRC with short duration do not have either less advanced tumors or better survival prospects.
Smith,[22]	Colorectal cancer in patients younger than 40 years of age	Review experience of CRC treatment in patients aged < 40, and looking at prognostic factors.	50	Negative prognostic factors were stage III/IV ($p < 0.001$) and symptom duration of longer than three months ($p = 0.06$) Suggests the correlation with stage means a relationship with prognosis. Analysis did not control for stage.
Stebbing,[41]	Avoidable delay in the management of carcinoma of the right colon.	Retrospective study of delays in treatment of right colon disease.	89	A retrospective study over a five-year period is reported. 74% were anemic at the time of diagnosis and 27% of these had anemia or a low mean corpuscular volume (MCV) for a significant time (mean 177 days, range 76-496 days) before developing symptoms. Significant delay in the diagnosis of symptomatic disease occurs before referral to hospital (mean 61 days vs. 36 days, $p < 0.05$). Treatment delay is similar whether patients are referred to surgeons or physicians. The preoperative duration of symptoms for emergency admissions was significantly shorter than for elective admissions (mean 50 days vs. 119 days, $p < 0.05$). The 30-day mortality was significantly higher for emergency admissions (20.7% vs. 3.3%, $p < 0.05$). Earlier diagnosis of symptomatic disease may not reduce the proportion of emergency admissions (33%) or improve survival. Many tumors are at an advanced pathological stage (39% node positive) by the time symptoms develop.

Reference	Title	Methods summary	n=	Comments
Stubbs,[12]	Symptom duration and pathologic staging of colorectal cancer	Prospective study relationship between duration of symptoms and stage.	211	Defines duration from onset of symptoms until diagnosis. 60% patients were symptomatic for less than 3 months. Stage I had significantly longer duration of symptoms than those in stage IV ($p < 0.01$) and with all other stages ($p< 0.05$). . Mean duration of symptoms in stage I 11.2 mo., stage II 4.9 mo., stage III 5.3 - 3.9, stage IV 3.8 mo. Diagnosis more favorable only possible by pre-symptomatic tumor detection. There was no tendency for more advanced disease to have longer symptomatic period. No correlation between duration of symptoms and the pathologic stage of the disease. From current knowledge of solid tumor kinetics and doubling time, it is extremely doubtful that diagnosis even 6 months earlier could have made such a difference - this speculation was made with the knowledge that metastasis 1 cm across contains approximately 10 x 9 malignant cells and for this to arise from a single cell would require at least 30 cell doublings, and in all probability in excess of 2 years.
Turunen, [53]	Delay in the diagnosis of colorectal cancer	Prospective review of CRC as to causes of patient and doctor delay	100	Most common error of diagnosis were hemorrhoids and anemia. Tumors in right colon most difficult to diagnose, representing 53% of those with medical delay > 6 months. 30% had medical delays > 6 months, caused by false negative barium enema and lack of investigation of symptoms.

Colorectal Cancer Literature Review Appendix E: Measurement Tools

Measure (worst - best)	**Description**	**Reference**
Function		
Eastern Co-operative Oncology Group Performance Status Rating (ECOG-PSR) Function, generic (0 - 4)	Usually reported as a percentage of study population with the following function: 0=ambulatory, fully active, pre-disease status; 1=ambulatory with symptoms, capable of light work; 2= ≤ 50% bed rest, capable of self care, not able to work; 3= ≥ 50% bed ridden, limited self care; 4=completely bedridden, incapable of self care.	[91], [82]
Karnosfsky Performance Scale (KPS) (0 - 100) in 10 point increments Function, cancer-specific	Completed by clinician, used in cancer therapy trials. Rates physical functioning. Some use as indicator of QOL.	[92]
Nottingham Health Profile (NHP) General health (100 - 0)	Well validated indicator of departure from health. Each dimension yields a weighted score between 100 - 0 (worst to best). Dimensions include: Energy, Pain, emotional reactions, sleep, social isolation, physical mobility	[38]
Rotterdam Symptom Checklist (RSC) Symptoms, generic	Measures intensity and frequency of symptoms, modified for use in CRC, consisting of 30 questions. Responses include: Not at all, a little, quite a bit, very much	[38]
Functional Living Index - Cancer (FLIC) (22 - 154) Function, cancer specific	A psychometrically validated questionnaire which yields a global score. 7 sub-scores: role, sociability, emotional, current health, hardship, nausea, pain. Scores marked on linear graph, 1=not at all, 7 = great deal. 22 questions, each with score 1-7	[92]
American Society of Anesthesiologists Physical Status Scale (ASA) (4 - 1)	Class 1: a normally healthy person; Class 2: a patient with mild systemic disease; Class 3: a patient with severe systemic disease that is not incapacitating; Class 4: a patient with incapacitating systemic disease that is a constant threat to life; Class 5: a moribund patient who is not expected to survive 24 hours with or without operation	[76]

Measure (worst - best)	**Description**	**Referenc e**
Quality of Life		
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - C30 (EORTC-QLQ-C30 30 questions, (0-100 function), (100-0) symptoms Cancer specific tool to assess function, symptoms, and QOL	Patient self-rated. Includes six multi-item function scales: physical, role, social, emotional, cognitive, and global quality of life. Separate symptom scale:, pain, fatigue, emesis, economic consequences of tx, and five items to measure GI symptoms, dyspnea, appetite loss, and sleep.	[88], [123]
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - C38 (EORTC QLQ-C38) 38 questions, (0-100 function), (100-0 symptoms) Disease-specific tool to assess colorectal function, symptoms, and QOL	Patient self-rated. Includes multi-item function scales: body image, sexual function, sexual enjoyment, future perspectives. 4 symptom scales assess side effects of radiation and chemotherapy, stoma, GI symptoms, and sexual dysfunction. Not recommended as a stand-alone quality of life tool; should be combined with EORTC QLQ-C30.	[84]
UNISCALE (0 - 100)	Single item visual-analog scale that asks the respondent to place an "x" in a long rectangle to indicate how the patient would rate his or her QOL. Was compared with three other QOL Tools, including FLIC, and found strong correlation with overall measure of QOL.	[124]
Psychological		
Profile of Mood States (POMS) (108-0)	General measure of mood, negative mood score obtained by adding subscales: anxiety, depression, uncertainty, tiredness, confusion, anger.	[87]
Becks Depression Inventory (BDI) (63-0)	Severity of depression and psychological distress, 21 items. Mild to moderate depression if score > 15.	[87]

Colorectal Cancer Literature Review Appendix F: Prognostic Indicators

Legend:	
* Kaplan-Meier survival rate, using Cox regression multivariate analysis unless otherwise indicated # Univariate, Fishers' exact, Chi-square, or not stated DFS Disease free survival	Ψ Absolute, crude survival ** Three year survival ⌖ One year survival ^ Life table survival

Article's main subject	Prognostic indicator	5 year survival,* (significance) n =	Reference
1. Depth of wall invasion			
CRC	Depth of bowel wall invasion has independent prognostic value, associated with worse survival.	93% (T1) - 38% (T4) ($p = 0.001 - 0.05$) n = 3676	[15, 18]
CRC	Early mobile tumors (T0-T1) had better survival rates in multivariate analysis	($p<0.001$) n = 301$^{\Psi}$	[97]
CRC	Depth of bowel wall invasion correlates with poor survival in univariate analysis	#	[102]
Colon	Depth of bowel wall has independent prognostic value: T1 had better survival than T2 or T3/4. T2 had better survival than T3/4, which was worst of all. Multivariate analysis	78% vs. 42% vs. 4%^ ($p < 0.001$) n = 32 vs. 519 vs. 138	[78]
<30	Depth of bowel wall invasion correlates with poor survival	n = 16#	[75]
2. Lymph node involvement			
Colon	Significant difference noted on univariate analysis but lost significance in multivariate when controlled for stage	($p = 0.001$) n = 709	[78]
CRC	Lymph node metastasis has significant prognostic factor in both univariate and multivariate analysis. Patients without node involvement had better survival rates than patients with 1-3 lymph node (N1). Patients with > 4 nodes had worse survival rates than patients with 1-3 lymph nodes. Marked significance in both colon and rectal, but more prominent in rectal cancer patients. In multivariate analysis, nodal involvement exceeded stage in statistical significance and resulted in a loss of significance of stage.	78% vs. 51% vs. 29% ($p < 0.001$) n = 2230	[15]
Rectal	Lymph node metastasis has significant prognostic factor in both univariate and multivariate analysis. Patients without node involvement had better survival rates than patients with 1-3 lymph node (N1). Patients with > 4 nodes had worse survival rates than patients with 1-3 lymph nodes.	80 % vs. 59% vs. 43% ($p = 0.0001$) n = 1446	[18]

Article's main subject	**Prognostic indicator**	**5 year survival,* (significance) n =**	**Reference**
2. Lymph node involvement (cont.)			
<30	Presence of lymph node capsular invasion correlates with poor survival	n =16[#]	[75]
< 45	Regional lymph nodes (relative effect 2), extramural invasion (relative effect 3), tumor size (relative effect 1.8)	n = 92	[23]
CRC	Number of lymph nodes effects survival in univariate analysis	N0 79% vs. N1 31%[#] ($p < 0.003$) n = 156 vs. 86	[102]
3. Histopathologic grade			
CRC	Well or moderately differentiated, or absent mucous secretion associated with better survival rate than patients with poor cellular differentiation or mucinous type. Significance retained after Cox regression.	56% vs. 26% ($p < 0.001$) n = 392 vs. 97	[96]
CRC	Well differentiated tumors have better survival than patients with undifferentiated tumors.	52% vs. 20%[#ψ] n = 1084	[77]
Right colon	Well differentiated tumors have better survival than patients with undifferentiated tumors	48% vs. 26%[#] n = 195	[42]
CRC	High mucous secretion by tumor cells has significant and independent correlation to poor overall survival	39% vs. 44% ($p < 0.001$) n = 362 vs. 127	[96]
Rectal	Patients with poor cellular differentiation or mucinous type tumor have far lower survival rate than well differentiated or non-mucous producing tumor. No difference noted between well differentiated and moderately differentiated tumors. Study controlled for effects of stage and for nodal involvement.	73% vs. 44% ($p < 0.0002$) n = 1446	[18]
CRC	Significant difference in survival noted between well differentiated and poorly differentiated tumors. No difference between well differentiated and moderately differentiated.	57% vs. 17% ($p < 0.003$) n = 217 vs. 9	[102]
CRC	Differentiation associated with poorer survival. Difference more important prognostic factor in rectal cancer than for colon.	67% vs. 52% ($p < 0.0001$) n = 2230	[15]
<30	Patients with mucinous tumors have worse survival than well differentiated tumors	33% vs. 18%[#] n = 11 vs. 3[#]	[75]
4. Obstruction/perforation			
CRC	Obstruction or perforation associated with worse prognosis than patient without obstruction or perforation in univariate and multivariate analysis	($p < 0.04$) n = 250 vs. 50	[11]
CRC	Obstruction or perforation showed significant differences in survival in univariate and multivariate analysis	n = 191	[70]

Article's main subject	Prognostic indicator	5 year survival,* (significance) n =	Reference
4. Obstruction/perforation (cont.)			
CRC	Obstruction uniformly carried a poor prognosis when compared to absolute survival rates of the group as a whole	24% vs. 38%[ψ] n = 133 vs. 1084	[77]
Rectal	Obstruction associated with worse survival rates than patients with no obstruction in a univariate and multivariate analysis	72% vs. 63%[#] (p = 0.0032) n = 1446	[18]
Colon	Patients with obstruction had worse survival rates than patients without obstruction.	38% vs. 19%^ (p = 0.018) n = 606 vs. 103	[78]
5. Elevated CEA			
CRC	Patients with CEA level > 5 ng/ml have worse survival rates, as shown in a univariate and multivariate analysis. CEA holds independent prognostic value.	(p = 0.001 - 0.05) n = 3676	[15, 18]
CRC	Normal CEA preoperatively have better survival rates compared to patients with CEA > 5 ng/ml preoperatively, particularly one that fails to return to normal postoperatively following curative resection for colorectal carcinoma.	64 vs. 53%[ψ#] (p < 0.05) n = 428	[100]
CRC	Preoperative elevated CEA level associated with an increased risk of death due to recurrent tumor, in a prospective study using univariate and multiple stepwise regression analysis	n = 310	[79]
CRC	Normal CEA has better survival rates compared to patients with CEA > 5 ng/ml	57% vs. 39[#] (p < 0.001) n = 277	[99]
Node negative (N0)	In patients without node involvement, preoperative CEA > 5ng/ml associated with worse survival rate. Routine histologic factors did not predict outcome in node negative colon cancer (stage I, II).	85% vs. 74 (p = 0.02) n = 460 vs. 111	[101]
6. Symptoms			
Colon	Change in bowel habits and bleeding per rectum had no significant influence on survival in multivariate analysis	n = 219** (NS)	[14]
Colon	No association between survival and bowel habit changes or anemia in univariate and multivariate analysis	n = 709	[78]
Colon	Presence of rectal bleeding or absence of abdominal pain significantly associated with better survival but significance lost in multivariate analysis when controlled for stage	n = 709	[78]

Article's main subject	**Prognostic indicator**	**5 year survival,* (significance) n =**	**Reference**
6. Symptoms (cont.)			
CRC	Total number of symptoms significant predictor whereas presence or absence of specific symptoms not significant. Having more than 2 symptoms associated with worse survival rates.	72% vs. 50%** ($p = 0.02$) n = 72 vs. 82	[47]
CRC	Anemia (symptomatic or asymptomatic) or palpable mass not indicative of a poorer prognosis when compared to absolute survival rates of group as a whole	33-37% vs. 38%$^{\#\psi}$ n = 532 vs. 1084	[77]
CRC	Blood loss as a first presenting symptom had tendency for a better disease-free survival, in a prospective study using multiple stepwise regression analysis.	($p = 0.12$) n = 310	[79]
Colon	Abdominal distension had significant influence on survival in multivariate analysis	n = 219** ($p = 0.006$)	[14]
Right colon	In patients with right colon cancer, anemia and no abdominal symptoms had better survival rates than patients with abdominal symptoms.	48% vs. 17%^ ($p < 0.02$) n = 152	[16]
Right colon	In patients with right colon cancer, anemia, positive fecal occult, and no abdominal symptoms, or asymptomatic patients, had better survival rates than patients with abdominal symptoms present.	Analysis method not stated 87.5 vs. 50%$^{\#}$ n = 195	[42]
> 75	In patients older than 75, presence of anemia or bloody stools had better survival rates than patients with no anemia or no blood in stool.	54% vs. 29%^ ($p < 0.0017$) n = 46 vs. 173	[76]
> 75	Patients with an ASA score of 2 (mild systemic disease) had better survival rates than patients with ASA of 3 (severe systemic disease, not incapacitated). Data reflects exclusion of perioperative mortality	42% vs. 30%^ ($p < 0.001$) n = 56 vs. 86	[76]
> 75	Patients older than 75 who experience a weight loss < 5 kg (does not include patients without stable preoperative weight) associated with better survival; weight loss > 5 kg associated with worse survival.	56% vs. 25%^ ($p < 0.001$) n = 56 vs. 24	[76]
7. Age			
CRC	Age is not prognostic variable in univariate and multivariate analysis	($p = 0.05$) n = 3676	[15, 18]
CRC	Age not a significant factor in predicting survival, when looking at different age groupings.	($p = 0.22$) n = 154	[47]
CRC	Age not correlated with survival	n = 624$^{\psi}$	[72]
CRC	No prognostic value in a prospective study using univariate and multiple stepwise regression analysis	n = 310	[79]
< 40	When stratified by stage, patients younger than 40 had similar survival rates than patients older than 40	$^{\psi}$ stage I 100% vs. 96, stage II 70% vs. 68%, stage III 40% vs. 33% (not significant) n = 1037	[2]

Article's main subject	Prognostic indicator	5 year survival,* (significance) n =	Reference
7. Age (cont.)			
< 40	Age not a independent prognostic value, though patients < 40 had better survival rates than patients older than 40 when stratified by stage.	n = 36 vs. 382	[3]
< 45	Age not an independent prognostic variable in univariate and multivariate analysis	n = 92	[23]
< 65	Age not a prognostic variable	45 -33%^# (p = 0.05) n = 265 vs. 257	[103]
> 70	Age not a prognostic variable, however patients > 70 in good general fitness had better survival rates compared to patients > 70 in poor general fitness.	Not significant n = 882	[82]
> 75	Age not an independent prognostic variable (data excludes patients who died in perioperative period)	n = 132	[76]
CRC	Differences in survival noted between age groups, but not statistically significant	n = 191	[70]
Colon	Patients younger than 70 had better survival rates than patients older than 70.	38-47% vs. 20-30%^ (p < 0.001) n = 383 vs. 326	[78]
CRC	Patients age 50 - 69 had better survival rates than patients age < 50 or > 70.	46-50% vs. 31-42% (p < 0.001) n = 354 vs. 163	[96]
CRC	Patients age < 70 had better survival rates than patients older than 70.	42-50% vs. 31-38% (p < 0.001) n = 196 vs. 321	[96]
CRC	< 40 and > 70 had worse survival rates than patients age 41-69 in multivariate analysis, though significance lost when controlled for stage	n = 219	[14]
CRC	< 40 associated with poorer survival rate in univariate analysis	44% vs. 56%# (p < 0.05) n = 38 vs. 250	[102]
8. Performance status			
> 70	Elderly patients with good performance status tolerated adjuvant and palliative chemotherapy for CRC as well as did younger patients and had similar benefits from palliative chemotherapy at one year.	44% vs. 48% ⌖ (p = 0.04) n = 310	[105]
Stage IV	Improvement in Karnofsky performance status (KPS) was strongly correlated with survival	n = 181	[92]
Stage IV	Karnofsky performance status has significant relationships to survival in both univariate and multivariate analyses, confirming independent predictive value.	(p = 0.0001) n = 198	[106]

Article's main subject	Prognostic indicator	5 year survival,* (significance) n =	Reference
9. Gender			
CRC	Gender differences noted in survival but not significant, nor was it significant when Cox model applied.	60% male vs. 64% female ($p = 0.759$) n = 1300 vs. 930	[15]
CRC	Gender differences noted in survival but not significant, nor was it significant when Cox model applied.	39% male vs. 42% female ($p = 0.294$) n = 294 vs. 223	[96]
Rectal	Gender differences noted in survival in univariate analysis, women had better survival rates than men; but the significance was lost when Cox model applied.	64% vs. 73% ($p = 0.0105$) n = 613 vs. 415	[18]
CRC	Gender had no effect on survival	n = 1115$^{\psi\#}$	[107]
CRC	No prognostic value in a prospective study using univariate and multiple stepwise regression analysis	n = 310	[79]
CRC	Differences in survival noted between genders, but not statistically significant	n = 191	[70]
CRC	Gender has no significant prognostic effect on survival in univariate analysis	52% vs. 55% ($p = 0.54$) n = 110 vs. 178	[102]
CRC	Men have better survival rates than woman.	71% vs. 50%** ($p < 0.02$) n = 72 vs. 82	[47]
Colon	Woman have better survival rates than men	39% vs. 34%^ ($p = 0.029$) n = 203 vs. 506	[78]
10. Tumor location			
CRC	Location of tumor not a prognostic variable, however patients with right colon disease and localized stage and longer clinical history had better survival rates than patients with left colon disease who presented in emergency and had shorter clinical history.	44% vs. 28%$^{\psi\#}$ n = 161	[46]
CRC/ Rectal	Tumor location not significant prognostic factor in univariate and multivariate analysis	n = 3676	[15, 18]
CRC	Differences in survival noted between rectal and colon cancer, but not statistically significant	n = 191	[70]
CRC	Location not significant in univariate analysis	62% vs. 45 ($p = 0.072$) n = 140 vs. 148	[102]
CRC	Not related to survival in multivariate analysis	n = 301$^{\psi}$	[97]
CRC	Site has no effect on stage	n = 1115$^{\psi\#}$	[107]
CRC	No prognostic value in a prospective study using univariate and multiple stepwise regression analysis	n = 310	[79]

Article's main subject	Prognostic indicator	5 year survival,* (significance) n =	Reference
10. Tumor location (cont.)			
Colon	No significant difference in survival noted between colon and rectal tumors in univariate and multivariate analysis	n = 709	[78]
Colon	No significant influence on survival in multivariate analysis	n = 219	[14]
CRC	Colon cancer patients had significantly worse survival rates than patients with rectal cancer	49% vs. 77%** ($p = 0.02$) n = 93 vs. 61	[47]
11. Miscellaneous significant predictive indicators			
< 40	Tumor marker RER positive (DNA Replication Error) has worse survival rate	68% vs. 32% ($p < 0.05$) n = 17 vs. 19	[125]
CRC	Preoperative low protein level associated with an increased risk of death due to recurrent tumor, in a prospective study using univariate and multiple stepwise regression analysis	n = 310	[79]
Anal	Over expression of p53 protein associated with poor prognosis in study of anal cancer with chemoradiation therapy	n = 64	[126]
Rectal	The interaction between p53 status and the benefit of radiotherapy was statistically significant ($P = 0.018$). Expression of nuclear p53 protein in rectal carcinoma seems to be a significant predictive factor for local treatment failure after preoperative radiotherapy.	n = 168	[127]
CRC	Significant and independent correlation was found to exist between high p53 levels and prolonged disease-free survival ($P = 0.05$) at a median follow-up of 60 months. This survival advantage was most apparent among stage III cancer patients. The results from this study would suggest that expression of high p53 levels appear to be useful in selecting a group of colorectal cancer patients with a better prognosis.	n = 111	[128]
Rectal	p53 status was not found to be useful as a prognostic marker using both univariate and multivariate analysis for local recurrence rate, disease-free or overall survival.	n = 100	[129]
CRC	In a univariate analysis of 2230 patients' tumor size did not show any statistically significant correlation with prognosis.	n = 2230	[15]
> 75	Older patient aged > 75 living in institution before surgical treatment did worse than those who were living in their own home.		[76]

Article's main subject	Prognostic indicator	5 year survival,* (significance) n =	Reference
11. Miscellaneous significant predictive indicators (cont.)			
Stage IV	Significant and independent predictors of poor long term outcome: positive margin (p = 0.004), extrahepatic disease (p=0.003), node-positive primary (p = 0.02), disease-free interval from primary to metastases <12 mo. (p = 0.03), number of hepatic tumors >1 (p = 0.0004), largest hepatic tumor > 5 cm (p = 0.01) and CEA > 200 ng/ml (p = 0.01)	5 yr. 37%, 10 year 22% n = 1001	[29]
12. Duration of symptoms No correlation between duration of symptoms and survival or stage			
CRC	No statistically significant correlation between duration of symptoms and prognosis in univariate and multivariate analysis	n = 3676	[15, 18]
CRC	No prognostic value in either univariate and multivariate analysis. Significant correlation between patient and medical delay (those likely to delay reporting symptoms to a doctor are more likely to experience medical delay)	(p = 0.04) n = 100	[11]
CRC	No statistically significant correlation between duration of symptoms and prognosis in univariate and multivariate analysis	n = 191^[#]	[70]
CRC	No correlation between duration of symptoms and survival or stage. Review article, includes analysis of 8 older articles otherwise not included in this literature review.	Review article	[71]
CRC	Duration of symptoms not a prognostic indicator	72% vs. 50%** (p = 0.02) n = 72 vs. 82	[47]
CRC	Duration of symptoms not a prognostic indicator. Short symptomatic period did not have better prognosis than patients with longer history.	n = 335[#]	[48]
CRC	No correlation between stage and duration of symptoms. Early diagnosis during the symptomatic phase unlikely to contribute to improvements in survival	n = 146[ψ#]	[50]
CRC	No correlation between survival and duration of symptoms.	n = 624	[72]
CRC	Negative correlation between duration of symptoms and extent of spread suggests that the length of the symptomatic illness is not an important factor in prognosis	n = 230#	[74]
Colon	No significant influence on survival in multivariate analysis	n = 219	[14]

Article's main subject	Prognostic indicator	5 year survival,* (significance) n =	Reference
12. Duration of symptoms (cont.) No correlation between duration of symptoms and survival or stage			
Colon	Showed no differences between duration of symptoms and survival (whereas stage influenced survival)	49% - 71%**^ n = 162	[73]
Right colon	Duration of symptoms not a prognostic indicator in patient with right colon cancer	n = 152^	[16]
< 30	Duration of symptoms not a prognostic indicator for patients younger than 30	n = 16#	[75]
<40	No correlation between duration of symptoms and survival in review of article covering CRC in patients age < 40	Review article	[4]
> 75	Duration of symptoms not a prognostic indicator for patients older than 75	n = 202^	[76]
Correlation between duration of symptoms and survival or stage			
Colon	Duration of symptoms > 25 weeks had better 5 year survival than patients with duration of symptoms < 4 weeks, however it did not retain prognostic value after controlling for stage	45% vs. 24%^ (p < 004) n = 165 vs. 222	[78]
CRC	Duration of symptoms > 6 months had better survival rates than patients with symptoms < 6 months. Analysis did not control for effects of stage.	36% vs. 31%#ψ n = 487 vs. 493	[77]
CRC	Patients with longer duration of symptoms had better survival rates than patients with shorter duration. Analysis did not control for effects of stage	n = 200	[52]
CRC	Patients with duration of symptoms < 6 months had poor survival rates. Analysis did not control for effects of stage. Duration did not correlate with stage.	n = 161ψ#	[46]
CRC	< 6 months had worse survival rates compared to patients with preoperative symptoms > 6 months in univariate analysis	46% vs. 65%# (p = <0.05) n = 202 vs. 71	[102]
CRC	Duration of < 4 months has better survival rates. Analysis did not control for effects of stage	n = 370^#	[80]
CRC	< 1 week or > 6 months duration of symptoms associated with poorer survival in a multiple stepwise regression analysis. Intermediate duration correlated with longer survival, though not statistically significant in univariate analysis.	(p = 0.68)# n = 310#	[79]

Article's main subject	Prognostic indicator	5 year survival,* (significance) n =	Reference
12. Duration of symptoms (cont.) Correlation between duration of symptoms and survival or stage			
CRC	Duration shortened with advanced tumor stage and with bowel obstruction; however when controlled for stage and obstruction, no decrease in relative risk of death was seen as symptom duration increased. Measured < 1 mo - > 6 mo, 5 year survival consistently increases as duration increases	31 vs. 53% (p<0.0006) n=777	[51]
Colon	Duration of symptoms > 12 months had better survival rates than patients with duration of symptoms < 3 months. Analysis did not control for effects of stage.	(p = 0.01 - p = 0.04) n = 416	[17]
Rectum	Duration of symptoms > 12 months had better survival rates than patients with duration of symptoms < 3 months. Analysis did not control for effects of stage.	(p = 0.01 - p = 0.04) n =1081	[19]
< 40	In a study of patients age 40 or younger, duration of symptoms < 3 months had better survival rates than patients with symptoms > 3 months. 81% of study population had stage III or IV. Analysis did not control for effects of stage	DFS 22% vs. $0^{\#\psi}$ (p < 0.01) n = 22 vs. 17	[22]
40 - 50	Duration of symptoms of 9-12 months in patient group with CRC aged 40-50 had improved survival when stratified by stage in multivariate analysis. However patients treated < 2 weeks did not have better survival than those presented 9-12 months.	n = 301^{ψ}	[97]
Right colon	Duration of < 3 months had better survival rates than patients with symptoms > 1 year, though difference is not significant. Duration of symptoms not a prognostic indicator	22% vs. $15\%^{\#}$ n = 195	[42]