



# Smoking, Colorectal Disease and Colorectal Surgical Practice

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## Abstract

**Background:** Cigarette smoking adversely affects the natural history of a number of common colorectal conditions and their treatment. Colorectal cancer is now recognised as a smoking attributable cancer.

**Aim:** This is a narrative review of the effects of cigarette smoking on colorectal disease, colorectal surgery and colorectal surgical outcomes.

**Methods:** Literature search was carried out for relevant articles highlighting relationship between smoking and variety of colorectal conditions (cancer, diverticular disease, inflammatory bowel disease and perianal diseases). As we wanted to highlight the breadth of the problem to current colorectal practice, we have deliberately kept this as a narrative review.

**Results:** Smoking is associated with higher all-cause mortality and colorectal cancer-specific mortality in non-metastatic colorectal cancer and it worsens the outcomes of a number of inflammatory colorectal conditions including diverticular disease and Crohn's disease. Smoking impairs the inflammatory response, tissue repair and consequently impairs wound healing. Smoking during radiotherapy worsens acute toxicity and reduces disease free survival in anal cancer.

**Conclusion:** Approximately 10 million adults smoke cigarettes in Great Britain currently and therefore there is arguably no single greater reversible patient related parameter that affects outcomes in colorectal practice. Surgeons must advocate and facilitate smoking cessation in their patients putting particular emphasis on the likelihood of increased complication rates and poorer outcomes if an active smoker undergoes colorectal surgery or radiotherapy.

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**Keywords:** Smoking; Colorectal Disease; WHO

## Introduction

In 1887 Thomas Morton of Philadelphia arguably ushered in the age of modern colorectal surgery by performing the first appendectomy for appendicitis [1]. He was probably not aware that 400 miles away another significant, though malign, milestone in history had taken place six years earlier. In 1881 James Duke and James Bonsack of Raleigh, North Carolina created the world's first cigarette-rolling machine. Their machine rolled 120,000 cigarettes per day thus revolutionizing tobacco smoking as a habit.

According to the WHO report on the global tobacco epidemic (2013), tobacco kills approximately 6 million people worldwide and causes more than half a trillion dollars of economic damage each year. It is the leading global cause of preventable death and is predicted to kill 1 billion people this century. About 10 million adults smoke cigarettes in Great Britain, approximately 22% of adult men and 19% of adult women are smokers ([www.ash.org.uk](http://www.ash.org.uk) April 2014). Smoking caused 60,000 cases of cancer in 2010 and 43,000 cancer deaths in 2009 [2]. Approximately 1.6 million hospital admissions in 2012/13 among adults aged >35 were primarily smoking related [3]. According to the report by Surgeon General report in 2013, the annual cost for direct medical care of adults attributable to smoking between the years 2009 and 2012 was \$132.5 to 175.9 billion. More than 2.3 billion people are now covered by at least one of the WHO Framework Convention on Tobacco Control (WHO FCTC) but this covers mostly high income countries. Although substantial progress has been made

**Table 1:** Studies listed in the smoking and diverticular disease section.

Smoking and Diverticular Disease				
Author	Number of Patients	Study type	Conclusions	Comments
Turunen [7]	261	Retrospective	Among patients undergoing elective sigmoid colectomy for diverticular disease, smokers were found to have higher incidence of perforation (25.4% Vs. 10.6%, p=0.04), resection at younger age (p=0.001) and recurrent diverticulitis episode (10.5% Vs. 3.0%, p=0.019)	
Papagrigrariades [8]	80	Retrospective	Analyzed the difference in patient characteristics between Group 1 (45 patients with complicated diverticular disease requiring surgical intervention) and Group 2 (35 patients with incidental asymptomatic diverticular disease). Percentage of smokers were higher in group 1 (24/45 Vs. 10/35, OR 2.9, 95% CI 1.1 – 7.3, p 0.028)	
Hjern [9]	561 (from a cohort of 35809)	Retrospective	Current smokers, as compared to non smokers, had increased risk of symptomatic diverticular disease (RR 1.23, 95% CI 0.99 – 1.52). Smokers also had a higher risk of developing complicated diverticular disease (RR 1.89, 95% CI 1.15 – 3.10)	Women recruited to the Swedish Mammography cohort study formed the cohort for this study too.
Aldoori WH [14]	47678	Retrospective cohort	Heavy smokers (>40 cigarettes /day) had a 21% greater risk of symptomatic diverticular disease compared to non smokers.	Male only cohort from US health professionals study.

**Table 2:** Studies listed in the smoking, colorectal cancer and colorectal treatment outcomes section.

Smoking, Colorectal Cancer and Colorectal Treatment Outcomes				
Author	Number of Patients	Study type	Conclusions	Comments
Chao [29]	781351	Prospective cohort	Long term cigarette smoking is associated with increased risk of colorectal cancer mortality in both men and women. Clear reduction in risk is observed with early smoking cessation.	Part of Cancer Prevention Study II set up by American Cancer Society.
Phipps [30]	2826	Population based cohort	Disease-specific and all-cause mortality were significantly higher for smokers (HR, 1.30; 95%CI, 1.09-1.74) compared with never-smokers (HR, 1.51; 95%CI, .24-1.83), among patients found to have incident CRC.	
McCleary [31]	1045	Retrospective	Heavy tobacco usage (>12 pack years) early in life (<30 years of age) may be an important, independent prognostic factor of cancer recurrences and mortality in patients with stage III colon cancer.	Included only Stage III CRC referred for CALGB phase III trial
Yang [32]	2548	Prospective cohort	Among the 2,548 colorectal cancer survivors, 1,074 died during follow-up, including 453 as a result of colorectal cancer. In multivariable-adjusted Cox proportional hazards regression models, prediagnosis current smoking was associated with higher all-cause mortality (relative risk [RR], 2.12; 95% CI, 1.65 to 2.74) and colorectal cancer-specific mortality (RR, 2.14; 95% CI, 1.50 to 3.07), whereas former smoking was associated with higher all-cause mortality (RR, 1.18; 95% CI, 1.02 to 1.36) but not with colorectal cancer-specific mortality (RR, 0.89; 95% CI, 0.72 to 1.10).	Part of Cancer Prevention Study II Nutrition Cohort set up by American Cancer Society.
Vincenzi [33]	200	Retrospective	Current smoking was associated with poor response rate to Cetuximab (13.6% Vs. 27.1%), quicker time to progression (2.8 Vs. 5.5 months) and decreased overall survival rate (7.8 Vs. 11.4 months) compared to non smokers.	Included patients with metastatic colorectal adenocarcinoma which have been refractory to both oxaliplatin and irinotecan based chemotherapy
Munro [34]	284	Prospective	Active smoking significantly reduced cause specific survival at 5 years by around 20%	Included only a cohort of patients referred for oncological treatment following colorectal cancer surgery
Chen [35]	101	Retrospective	Active smokers had significantly inferior 5-year overall survival (23% Vs. 55%), locoregional control (58% Vs. 69%), and disease-free survival (42% Vs. 65%) compared with the former smokers who had quit before radiation therapy (p< 0.05 for all). These differences remained statistically significant when patients treated by postoperative or definitive radiation therapy were analyzed separately. The incidence of Grade 3 or greater late complications was also significantly increased among active smokers compared with former smokers (49% Vs. 31%, p = 0.01).	
Steinberger [36]	2358	Prospective	Current smoking significantly increased the risks of both prostate-specific antigen relapse [hazard ratio (HR) 1.4, P = 0.02] and distant metastases (HR 2.37, P< 0.001), as well as prostate cancer-specific death (HR 2.25, P< 0.001). Multivariate analysis showed that smoking was also associated with increased risk of EBRT-related genitourinary toxicities (current smoker, HR 1.8, P = 0.02; former smoker, HR 1.45, P = 0.01).	

in the global tobacco use since the adoption of WHO FCTC 10 years ago, more work is needed in the low and middle income countries [4].

The medical profession appreciate these devastating statistics and the general ill effects of smoking, in particular lung cancer and cardiovascular disease, but there is paucity of data on the effects of smoking in patients with colorectal disease. The aim of this narrative is to present a general review of smoking and its effect on colorectal disease with special reference to contemporary colorectal surgery.

### Smoking and Appendicitis

Appendicectomy is currently the commonest general surgical emergency operation. In 1999 Montgomery et al. [5] showed that maternal smoking and or patient smoking was positively associated with appendicectomy by the age of 26 years. The unadjusted odds ratio for appendicectomy associated with cigarette smoking was 2.34 (95% CI 1.52–3.59) [5]. A more recent study found associations between tobacco use and risks of perforation of an inflamed appendix [6]. Smoking therefore increases the incidence of appendicitis and also the likelihood of complications.

### Smoking and Diverticular Disease

Smoking is a risk factor for the development of complicated diverticular disease at a young age (Table 1). Turunen et al. [7] reported on 261 patients undergoing sigmoid colectomy for complicated diverticulitis. Smokers were younger, had more evidence of strictures, histological perforations and more episodes of diverticulitis following surgery. A smaller study comparing complicated diverticular disease and asymptomatic diverticular disease showed a greater proportion of smokers in the former group. Regression modelling demonstrated smoking to be an independent risk factor predisposing to postoperative complications [8].

Hjern et al. [9] concluded that in women, smoking appears to increase the risk of symptomatic diverticular disease even after controlling for confounding factors such as age, diabetes and obesity. Of particular note smokers had almost double the risk of perforation or abscess formation. Why smoking should be associated with increased complicated disease in women is uncertain, but it is known that smoking increases VIP (vasointestinal polypeptide) levels in the colonic mucosa [10], thus increasing colonic motility and intraluminal pressure [11], while impairing blood supply [12,13]. A contradictory study including only male health professionals concluded that smoking was not a substantial risk for symptomatic diverticular disease although less than 10% of the study population smoked (RR 1.25, 95%CI 0.75-2.09) [14].

### Smoking, Colorectal Cancer and Colorectal Cancer Treatments

The International Association for Research on Cancer added Colorectal cancer to the list of smoking attributable cancers in 2009 [15,16]. The US Surgeon General did the same in 2014 [17]. According to several recent meta-analyses, the relationship between smoking and colorectal cancer incidence is likely dose dependent [18-21]. The association seems strongest for three correlated molecular phenotypes of the disease: microsatellite instability (MSI) [22-25], CpG island methylator phenotype (CIMP) [26-28] and BRAF mutation positive [25-27].

The association between colorectal polyps, cancer and smoking habits has been extensively studied (Table 2). The Cancer Prevention

Study II was a large prospective cohort established by the American Cancer Society in 1982. Smokers of 20 or more years experienced higher colorectal cancer death rates, even when adjusted for multiple potential confounders. Consistent with a causal relationship with smoking, risk was higher in current than in former smokers and increased with smoking duration, number of cigarettes smoked per day, and pack-years. Among former smokers, risk decreased with the number of years since smoking cessation [29]. The association between smoking and increased all causes mortality and disease specific mortality is especially pronounced in colorectal cancer with micro satellite instability (MSI). Across sex, tumour site, stage, and MSI status, and for both all-cause and CRC-specific mortality, an increased mortality was found in patients who were smokers than in former smokers and highest in patients with a >40 pack-year history [30].

Using the cohort of patients who participated in the Cancer and Leukaemia group B phase 3 trials, a spin off study evaluated the impact of smoking on colon cancer recurrence and survival. Surgically treatable stage III colon cancer patients with no evidence of distant spread were included. Smoking status or time since smoking cessation did not impact on the disease-free survival, overall survival or recurrence-free survival, but a dose-response association was noted for smoking intensity, particularly for the risk of death or recurrence in higher quartiles of pack-years smoked before age 30 years when compared with non-smokers [31].

Yang et al. [32] have recently shown that in colorectal cancer survivors smoking is associated with a nearly two-fold higher risk of death compared with never smoking. These studies indicate that cigarette smoking is associated with higher all-cause and colorectal cancer-specific mortality in non-metastatic colorectal cancer.

In treatment of metastatic colorectal cancer with Cetuximab, current smoking was found to be associated with poorer response, quicker time to progression and decreased overall survival. There was no dose relationship among current smokers [33]. In another study observing survival among patients with a potentially curative colorectal resection and referred for consideration for adjuvant chemotherapy/radiotherapy, smoking was found to significantly lower cause-specific survival by around 20% at 5 years [34].

There is little data on the effect of smoking on outcomes after radiotherapy for rectal cancer in smokers versus non-smokers, but there is compelling evidence from other diseases. In head and neck cancer patients having radiotherapy active smokers had significantly more complications and significantly poorer 5 years overall survival, locoregional control and disease free survival [35]. Prostate cancer patients who were current smokers had a 40% relative increase of cancer relapse and were twice as susceptible to disease spread and death due to prostate cancer compared to non-smokers [36].

### Smoking and Anal Cancer

Risk factors for anal cancer include HPV infection, multiple sexual partners and ano-receptive intercourse. Smoking, as a risk factor is less well known (Table 3). In a retrospective review of about 300 patients with anal cancer, current smokers were at higher risk for anal cancer, independent of age and other risk factors [37]. Two studies using standard chemoradiotherapy found that smoking adversely affected local disease control, however this did not affect disease specific survival and colostomy free survival [38,39]. The European Society of Medical Oncology Clinical practice guidelines

**Table 3:** Studies listed in the smoking and anal cancer section.

Smoking and Anal Cancer				
Author	Number of Patients	Study type	Conclusions	Comments
Daling [37]	306	Prospective	Current smokers among men and women were at particularly high risk for anal cancer, independent of age and other risk factors (OR, 3.9 [95% CI, 1.9-8.0] and OR, 3.8 [95% CI, 2.4-6.2], respectively).	The high proportion of tumors with detectable HPV suggests that infection with HPV is a necessary cause of anal cancer, similar to that of cervical cancer. Increases in the prevalence of exposures, such as cigarette smoking, anal intercourse, HPV infection, and the number of lifetime sexual partners, may account for the increasing incidence of anal cancer in men and women.
Mai [38]	68	Retrospective study	Local disease control for anal cancer patients, receiving standard chemoradiotherapy was poorer among smokers compared to non smokers (74% Vs. 94%, p 0.03)	
Ramamoorthy [39]	64	Retrospective study	In patients undergoing chemo radiotherapy for anal SCC, recurrence (32% Vs. 20%) and mortality rate (45% Vs. 20%) were higher among smokers compared to non smokers.	

**Table 4:** Studies listed in the smoking and inflammatory bowel disease.

Smoking and Inflammatory Bowel Disease				
Author	Number of Patients	Study type	Conclusions	Comments
Reese [42]	2962	Metaanalysis	Smokers had significantly higher clinical post-operative recurrence than non-smokers (OR 2.15; 95%CI 1.42–3.27; p<0.001). Smokers were also more likely to experience surgical recurrence by 5 (OR 1.06; 95%CI 0.32–3.53, p=0.04) and 10 years of follow-up (OR 2.56; 95%CI 1.79–3.67; p<0.001) compared to non-smokers. When matched for operation and disease site, smokers had significantly higher re-operation rates to nonsmokers (OR 2.3; 95%CI 1.29–4.08; p=0.005). There was no significant difference between ex-smokers and non-smokers in post-operative acute relapses (OR 1.54; 95%CI 0.78–3.02; p=0.21).	
Papay [44]	326	Retrospective	Surgical recurrence following initial surgery for Crohn's disease is more common among smokers (HR 1.6, 95%CI 1.14–2.4, p=0.008)	The main aim of this study was to assess the lack of immunosuppressive therapy as a risk factor for surgical recurrence in CD.
Unkart [45]	176	Retrospective	Smoking at the time of initial ileocolic resection (HR 2.08, 95%CI 1.11–3.91, p=0.023) for CD was associated with an increased risk of second ileocolic resection.	
Cottone [46]	182	Retrospective	Smoking was a risk factor for clinical (HR 1.46, 95%CI 1.1–1.8), surgical (HR 2.0, 95%CI 1.2–2.3 and endoscopic (HR 2.2, 95%CI 1.2–3.8) recurrence in CD.	
Martin [47]	286	Retrospective	Risk factors for recurrence included: smoking, blood transfusion, contamination, localisation of the disease, length of resection, microscopic margins and the duration of follow-up. The length of resection and the positive margins can statistically predict recurrence (p=0.046 and p=0.016), both having a predictive value of 72%. A resection with clear margins decreases the recurrence rate significantly (15%) (p=0.0025).	
Timmer [48]	152	Prospective	Univariate analysis showed unfavorable outcomes for women (p=0.05), current smokers (p=0.005), and use of oral contraceptives (p=0.001). The Cox model retained current smoking Vs. never smoking (HR, 2.1; 95%CI, 1.1-4.2) as predictors of relapse. Ex-smokers did not have an increased risk. Finally, sex, age, time in remission, disease location, and disease duration were not significant predictors.	
Medina [49]	264	Prospective	Smoking habit was similar between operated and non-operated patients for both UC (73% and 80% non-smokers) and CD (67% and 63% smokers) The number and type of complications after surgery were not related with smoking habit. In CD patients, although the recurrences did not depend on the smoking habit, they did occur earlier in smokers than in non-smokers (83.6 +/- 21 Vs. 155 +/- 50 weeks, p=ns).	
O'Riordan [50]	81	Retrospective	In patients who underwent colectomy and ileorectal anastomosis for Crohn's colitis, smoking was associated with both re-operative surgery (HR 2.12, 95%CI 0.96–4.72) and proctectomy (HR 3.93, 95%CI 1.46– 10.55)	

Liu Z [51]	434	Retrospective	Smoking was associated with development of de novo CD in the Ileal Pouch Anal Anastomosis site (HR 1.58, 95%CI 1.03 – 2.43).
Shen B [52]	622	Retrospective	Among patients who underwent IPAA for IBD, smoking was found to be associated with pouch related hospitalization (HR 1.78, 95%CI 1.09 – 2.89, p=0.020) and pouch failure (HR 2.30, 95%CI 1.09 – 4.84, p=0.029).
Nunes [53]	3224	Retrospective	Smokers had more strictures (22.6% Vs. 19.3%, p<0.05) and less colonic involvement (7.2% Vs. 10.9%, p<0.05), and were more frequently under treatment with steroids (91.6% Vs. 85.8%, p<0.05), immunosuppressant's (73.5% Vs. 63.6% p<0.05) or anti-TNF drugs (31.4% Vs. 25.1%, p<0.05) than nonsmokers. In the time-dependent multivariate analysis, smokers were found to have a significantly decreased survival free of stricturing disease (HR: 1.5, 95%CI 1.18-1.90) or perianal complications (HR: 1.50, 95%CI 1.01-1.46), and had a higher risk for requiring thiopurine therapy (HR: 1.20, 95%CI 1.05-1.30).
Joyce [54]	319	Retrospective	Smoking does not appear to predispose to complications for CD patients undergoing surgery. Current smokers and ex-smokers have a persistently reduced quality of life in comparison to non-smokers post-surgery.
Lunney [55]	1203	Retrospective	CD patients were more likely to smoke than UC patients (19.2% Vs. 10.2%, p<0.001). A history of smoking in CD was associated with an increased proportional surgery rate (45.8% Vs. 37.8%, p = 0.045), requirement for IBD-related hospitalization (P = 0.009) and incidence of peripheral arthritis (29.8% Vs. 22.0%, P = 0.027). Current smokers with UC demonstrated reduced corticosteroid utilization (24.1% Vs. 37.5%, P = 0.045), yet no statistically significant reduction in the rates of colectomy (3.4% Vs. 6.6%, P = 0.34) or hospital admission (P = 0.25) relative to nonsmokers. Ex-smokers with UC required proportionately greater immunosuppressive (36.2% Vs. 26.3%, P = 0.041) and corticosteroid (43.7% Vs. 34.5%, P = 0.078) therapies compared with current and never smokers [55].

state that smoking may worsen acute toxicity during treatment and lead to a poorer disease free and colostomy free survival. Every effort should be made to ensure patients stop smoking before therapy [40].

## Smoking and Inflammatory Bowel Disease

There is a dichotomy in the relationship between smoking, ulcerative colitis and Crohn's disease (Table 4). The British Cohort Study in the 1980's concluded that smoking protects against Ulcerative Colitis (UC). The risk of developing UC is decreased in current smokers compared with lifetime non-smokers (OR 0.41 95%CI 0.34–0.48). In contrast smoking increased the risk of developing Crohn's Disease (CD) (OR 2.0 95%CI 1.65–2.47) [41].

In a meta-analysis of 16 studies that included 2962 patients, there was almost twice the rate of clinical relapse of CD, following surgery among smokers. The risk of re-operation was also twice as high at 10-year follow up. There was no significant difference in re-operation rate or postoperative acute relapses between ex-smokers and non-smokers, indicating that smoking cessation reduces clinical and surgical recurrence rates [42]. A more recent review article also suggests an increased risk of clinical recurrence rates among smokers with CD [43]. In smaller studies, where risk factors for re-do surgery for CD were analysed, smoking was found to increase the risk of re-do [44] and secondary ileocolic resection [45].

Smoking has also been shown to increase the risk of endoscopic recurrence, with macroscopic lesions found in the neo-terminal ileum of 70% of smokers 1 year after surgery compared with 35% of non smokers and 27% of ex-smokers [46]. Endoscopic recurrence rates appear similar for ex-smokers and non smokers [47-49]. After ileo-rectal anastomoses for CD smoking was an independent risk factor which predicted further intervention and proctectomy [50]. In recent studies involving Ileal Pouch Anal Anastomosis (IPAA) patients, active smoking was a risk factor associated with development of CD

in patients who underwent this procedure for indeterminate colitis [51]. Smoking was also found to be associated with pouch related hospitalization and pouch failure [52].

In a large retrospective cohort study of 3000 patients, evaluating the effect of smoking on current medical treatment (immunosuppressant's and anti-TNF drugs) for CD, smokers were found to have a significantly decreased survival free of structuring disease, perianal complications and had a higher risk for requiring thiopurine therapy. Moreover, smokers were more frequently treated with steroids, immunosuppressants and anti-TNF drugs [53]. These results suggest that, despite the widespread use of immunosuppressant's and anti-TNF drugs, smokers with Crohn's disease still have a more severe disease course with increased therapeutic requirements. In a smaller study of about 300 patients with CD, there was no statistically significant difference between smokers (current and ex) and non-smokers in relation to disease characteristics or post-operative complications. The smokers, however had a lower Cleveland Quality of Life score [54]. In a more recent study from Sydney IBD Database Cohort comprising about 1200 patients, smoking in CD was associated with increased proportional surgery rate (45.8% vs. 37.8%, P = 0.045), requirement for IBD-related hospitalisation (P = 0.009) and incidence of peripheral arthritis (29.8% vs. 22.0%, P = 0.027). Current smokers with UC demonstrated reduced corticosteroid utilisation (24.1% vs. 37.5%, P = 0.045), yet no statistically significant reduction in the rates of colectomy (3.4% vs. 6.6%, P = 0.34) or hospital admission (P = 0.25) relative to non-smokers. Ex-smokers with UC required proportionately greater immunosuppressive (36.2% vs. 26.3%, P = 0.041) and corticosteroid (43.7% vs. 34.5%, P = 0.078) therapies compared with current and never smokers [55].

## Smoking and Perianal Disease

In an epidemiological study of US veterans (74 with anal abscess

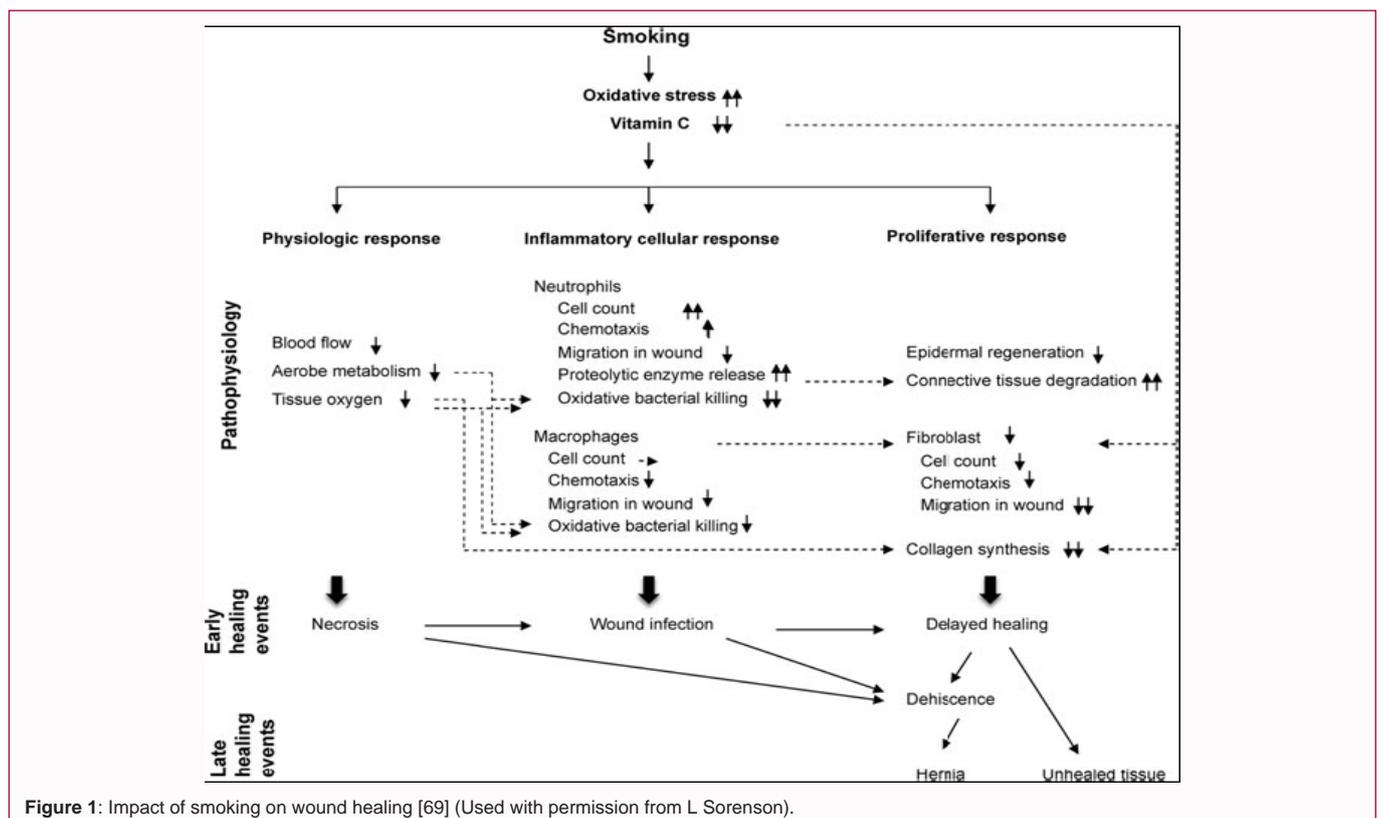
**Table 5:** Studies listed in the smoking and perianal disease.

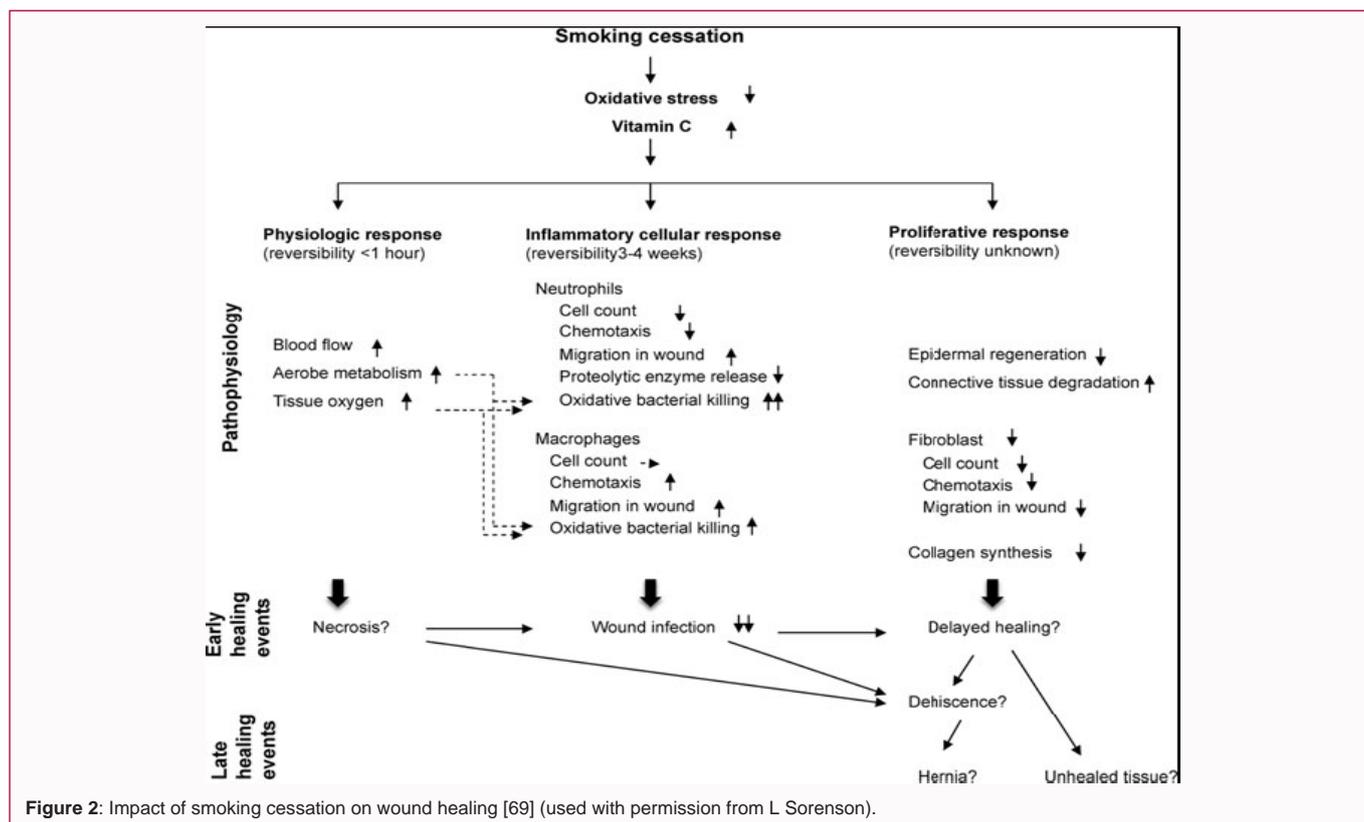
Smoking and Perianal Disease				
Author	Number of Patients	Study type	Conclusions	Comments
Devaraj [56]	931 (74 cases and 816 controls)	Case control	Current smokers or those who quit less than a year have an Odds ratio of 2.15 (95% CI 1.34 – 3.48) of developing anal abscess or fistula compared to non-smokers or those who quit more than a year ago.	Excluded patients with IBD and/or HIV. Similar effect was seen in patients who quit smoking < 5 years ago and the effect was not seen if quit > 10 years.
Vazquez [58]	268	Retrospective	Age-adjusted incidence of HS was significantly higher in women compared with men (8.2 (95%CI), 7.0-9.3) Vs. 3.8 (95%CI, 3.0-4.7). The highest incidence was among young women aged 20-29 years. 54.9% were obese; 70.2% were current or former smokers; 42.9% Smoking and gender were significantly associated with more severe disease.	
Konig [59]	84	Matched pair case-control	The rate of active cigarette smokers was 88.9% whereas 6.4% had never smoked. The rate of smokers in the matched-pair control group was 46%. The significantly higher proportion of active smokers among patients with hidradenitis suppurativa OR 9.4, 95%CI 3.7-23.7 (p< 0.001). 73% of our patients had no family history of hidradenitis suppurativa whereas 27% reported at least one affected first-degree relative.	Randomized matched-pair control study with an equal number of patients admitted for various other skin diseases such as atopic dermatitis, varicose veins, skin tattoos, alopecia areata or melanoma was matched for sex and age and evaluated for smoking habits.

or fistula and 816 without) recent smoking was found to be a risk factor for anal abscess/fistula development [56] (Table 5). Current smokers developed more perianal disease than smokers who quit less than a year ago. Increased OR 1.72 (95% CI 1.03–2.86, p=0.0375) was also observed when comparing current smokers and smokers who quit within the past 5 years compared with non-smokers. An

accompanying editorial questioned our understanding of the origin of perianal sepsis and explores a plausible case for a causal relationship between smoking and perianal sepsis [57].

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory disorder of hair follicles in apocrine gland-bearing sites.

**Figure 1:** Impact of smoking on wound healing [69] (Used with permission from L Sorenson).



In a population based study of 200 patients, smokers (current and past) were found to have more severe HS compared to non-smokers (OR 2.0, 95% C.I 1.1–3.5) [58]. In a pair matched case-control study between patients presenting with HS and other dermatological conditions (atopic dermatitis, melanoma, varicose veins etc), the rate of active smokers was higher in the HS group (90% vs. 46%) [59]. The percentage of smokers among patients with HS was found to be higher in the above German and Polish study (73%) [60] compared to the national average (27% and 23% respectively).

## Smoking and Wound Healing

Smoking causes changes in all three phases of wound healing. Smoking enhances the initial haemostatic phase through elevated levels of circulating fibronectin; it reduces blood flow, aerobic metabolism and tissue oxygenation. It impairs the inflammatory phase with reduced neutrophil phagocytosis and abnormal monocyte-macrophage responses whilst the proliferative phase is deranged with reductions in fibroblast function, epithelial regeneration and collagen metabolism. These events are manifested clinically as delayed healing, wound infection and necrosis [61-67] with subsequent anastomotic breakdown or herniation [68].

In a systematic review of 177 articles, smoking cessation was seen to reverse certain adverse factors on wound healing. Cessation restores tissue oxygen levels rapidly and reduces oxidative stress. The number of circulating neutrophils and the negative impact on neutrophil and monocyte-macrophage function are normalized. In the healing wound, inflammatory cell infiltration increases and wound contraction is partially reversed. In contrast, smoking cessation does not appear to reverse epidermal regeneration, fibroblast proliferation, and collagen synthesis and deposition, indicating that in the wound the detrimental effect of smoking on proliferation and remodeling is

prolonged [69]. The pathophysiological effects of both smoking and smoking cessation are summarized in Figure 1 and 2.

In a post hoc analysis of data from PROXI trial, including 1386 patients (emergency and elective laparotomy for surgical and gynaecological causes), smoking was found to be significantly associated with higher frequency of surgical site infections (SSI) (25% versus 17%, p value < 0.001) and burst abdomen (3.8% vs. 2.4%, p value 0.04) [70].

## Cigarette Smoking and Outcomes after Colorectal Surgery

Smokers are more likely to suffer surgical, as well as, cardiovascular and respiratory complications [71,72]. Smokers are more likely to be admitted to an intensive care unit [73], have longer lengths of stay and higher mortality.

Two large retrospective studies from the Veterans Associations Surgical Quality Improvement Programme (VA SQIP) showed that smoking was associated with more post-operative complications following both general and cancer related surgical procedures [74,75]. In a further large study of patients undergoing curative resection for colorectal cancer, smoking (as a preoperative risk factor) was associated with more post-operative complications poorer overall survival and systemic recurrence [76] (Table 6).

In a more recent retrospective database (VA SQIP) study of almost 48,000 patients undergoing colorectal surgery for cancer, diverticular disease or IBD; current smokers were at a significantly increased risk of post-operative morbidity and mortality [77]. In a small study involving 38 patients, non-healing perineal wounds after abdominoperineal resection were observed in 26%. On principal component analysis of seven other factors, smoking was found to contribute 13.8% of delayed wound healing [78].

**Table 6:** Studies listed in the smoking and outcomes after colorectal surgery.

Smoking and Outcomes After Colorectal Surgery				
Author	Number of Patients	Study type	Conclusions	Comments
Hawn [74]	393794	Retrospective cohort	34.5% were current, 18.1% prior, and 47.4% never smokers. A total of 6225 pneumonias, 11,431 deep and superficial surgical-site infections, 2040 thromboembolic events, 1338 myocardial infarctions, and 4792 deaths occurred within 30 days of surgery. Compared with both never and prior smokers individually and controlled for patient and procedure risk factors, current smokers had significantly more postoperative pneumonia, surgical-site infection, and deaths ( $P < 0.001$ for all). There was a dose-dependent increase in pulmonary complications based on pack-year exposure with greater than 20 pack years leading to a significant increase in smoking-related surgical complications.	Patients recruited from the Veterans Affairs Surgical Quality Improvement Program for all surgical specialties
Gajdos [75]	502647	Retrospective cohort	Compared to never smokers, prior smokers and current smokers with GI malignancies were significantly more likely to have surgical site infection (SSI) (OR 1.25, 95%CI 1.09–1.44) (OR 1.20, 95%CI 1.05–1.38), combined pulmonary complications (CPO: pneumonia, failure to wean from ventilator, reintubation) (OR 1.60, 95%CI 1.38–1.87) (OR 1.96, 95%CI 1.68–2.29) and return to the operating room (OR 1.20, 95%CI 1.03–1.39) (OR 1.31 95%CI 1.13–1.53), respectively. Both prior and current smokers had a significantly higher mortality at 30 days (OR 1.50, 95%CI 1.19–1.89) (OR 1.41, 95%CI 1.08–1.82) and one year (OR 1.22, 95%CI 1.08–1.38) (OR 1.62, 95%CI 1.43–1.85). Thoracic surgery patients who were current smokers were more likely to develop CPO (OR 1.62, 95%CI 1.25–2.11), and mortality within one year (OR 1.50, 95%CI 1.17–1.92) compared to non-smokers, but SSI rates were not affected by smoking status. Current smokers had a significant increase in postsurgical length of stay (overall 4.3% [ $p < 0.001$ ], GI 4.7% [ $p = 0.003$ ], thoracic 9.0% [ $p < 0.001$ ]) compared to prior smokers.	Patients recruited from the Veterans Affairs Surgical Quality Improvement Program for all surgical specialties
Richards [100]	423	Retrospective	The postoperative mortality rate was 4% and the morbidity rate 34%. The most important predictors of complications were smoking (OR 1.32), ASA grade (OR 1.90) and POSSUM operative score (OR 1.32).	
Sharma [77]	47574	Retrospective cohort	After adjustment, current smokers were at a significantly increased risk of postoperative morbidity [OR 1.3; 95%CI 1.21–1.40] and mortality (OR 1.5; 95%CI 1.11–1.94) after colorectal surgery. This finding persisted across malignant and benign diagnoses and also demonstrated a significant dose-dependent effect when stratifying by pack-years of smoking.	Patients recruited from the Veterans Affairs Surgical Quality Improvement Program for all surgical specialties between 2005–2010.
Artioukh [78]	38	Prospective	Impaired healing of the perineal wound was observed in 26% patients. In 11% the wound remained nonhealed in 1 year after surgery. Preoperative radiotherapy, delayed primary closure of the wound and alcohol consumption in excess of 28 units/week was statistically significantly associated with impaired wound healing. Principal component analysis identified the following seven factors that cumulatively contributed to 96% of impaired healing: (i) distant metastases, (ii) preoperative radiotherapy, (iii) T-stage of the tumour, (iv) smoking, (v) perioperative blood transfusion, (vi) preoperative chemotherapy and (vii) development of side effects of preoperative chemoradiation.	
Sorensen [79]	78	Randomised Controlled Trial	In smokers the wound infection rate was 12% (11 of 93 wounds) compared with 2% (1 of 48 wounds) in never-smokers ( $P < 0.05$ ). Wound infections were significantly fewer in abstinent smokers compared with continuous smokers after 4, 8, and 12 weeks after randomization. No difference between transdermal nicotine patch and placebo was found.	
Abbas [80]	156	Retrospective case-matched	A history of heavy tobacco use ( $>$ or $=$ 20 pack-years) was more prevalent in those who had acute facial wound dehiscence (46%) compared with the control group (16%; $p = 0.0002$ ; OR 3.7). Wound infection occurred in 5%. Best-fit logistic regression models demonstrated that steroid use, smoking, prolonged operative time, and use of absorbable mesh, acting as a surrogate marker for a more complex procedure, were significant independent predictors of wound infection.	
Finan [81]	1505	Retrospective	Regression analysis determined that prolonged operative time (odds ratio [OR], 2.7; $P < .001$ ) and American Society of Anesthesiologists $>2$ (OR, 1.8; $P = .009$ ) were positively associated, whereas advanced age (OR, 0.5; $P = .005$ ) was negatively associated with the occurrence of major operative complications.	Subjects undergoing ventral hernia repair from 13 regional Veterans Health Administration sites
Fischer [82]	1706	Retrospective	The healing rate of Perianal fistula following a transanal mucosal advancement flap repair, varied from 60 % among smokers to 79 % among non smokers ( $p = 0.037$ ).	Subjects recruited from the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) patient database.
Zimmerman [90]	105	Prospective		Included patients with cryptoglandular origin fistulas only

Zimmermann [13, 90]	23	Prospective	Median blood flow before transanal advancement flap repair was 35 (range, 8-70) volts in patients who did not smoke. In patients who smoked the median blood flow before transanal advancement flap repair was 18 (range, 7-35) volts. Blood flow was significantly lower in patients who smoked ( $p=0.018$ ; Mann-Whitney). In conclusion, it seems likely that impaired wound healing caused by a diminished rectal mucosal perfusion is a contributing factor in the breakdown of advancement flaps in patients who smoke cigarettes.	Included patients with cryptoglandular origin fistulas only
Ellis [91]	95	Retrospective	In both, univariate (51% Vs. 19%, $p < 0.05$ ) and multivariate regression analysis, recurrence rate of Perianal fistula following mucosal advancement flap repair, was more common among smokers.	Included transphincteric and rectovaginal fistulas.
Van der Hagen [92]	30	Randomised Controlled Trial	100% of the tobacco smokers developed a recurrent fistula in the FS group, and 17% of the tobacco smokers developed a recurrent fistula in the TAFR group ( $P < 0.001$ ).	All patients with high complex cryptoglandular fistulas were randomized to closure of the internal opening by a mucosal advancement flap (MF) or injection with fibrin sealant (FS) after treatment with setons

**Table 7:** Studies listed in the smoking and anastomotic leaks.

Smoking and Anastomotic Leaks				
Author	Number of Patients	Study type	Conclusions	Comments
Fawcett A [106]	147	Retrospective	Increased incidence of anastomotic dehiscence among smokers (75 % Vs. 29.6%, $p < 0.005$ )	Combined clinical and histopathological study, includes left sided colonic resections
Kim MJ [98]	215	Retrospective	Smoking and history of heavy smoking were identified as risk factors for anastomotic stricture and leak, both in univariate and multivariate analysis	Includes low anterior resection performed by a single surgeon.
Sorensen LT [99]	333	Retrospective	Multiple regression analysis, smokers compared to non-smokers had increased risk of anastomotic leak. (RR 3.18, 95%CI 1.44 – 7.00)	Included colonic and rectal resections/ anastomosis.
Richards CH [100]	233	Prospective	Current smokers, on multivariate analysis were at an increased risk of anastomotic leak (OR 3.68, 95% CI 1.38 – 9.82. $p=0.009$ )	Includes low anterior resection for benign and malignant disease.
Baucom RB [102]	246	Retrospective	The overall clinical leak rate was 6.5% (16) and smokers were significantly more likely than non-smokers to develop a leak (17% Vs. 5%, $p = 0.01$ ). In multi variable analysis smokers had 4 times the odds of developing a clinical anastomotic leak than non smokers (O.R 4.2, 95% C.I 1.3 – 13.5, $p = 0.02$ )	Elective left sided colonic resections without stomas or a diagnosis of IBD were included.
Jannasch O [103]	17867	Retrospective	Anastomotic leak occurred in 2134 (11.9%) cases. Univariate analysis revealed gender, ASA status, smoking, alcohol, intraoperative blood loss, no protective ileostomy, cancer stage and height of tumour as significant risk factors. Multivariate analysis confirmed all of the above to be independent risk factors too.	The study only included surgery for rectal cancer and looked at risk factors for anastomotic leak and their consequences

In another small, but well conducted randomised clinical trial, where an experimental wound was made and followed up, between non-smokers and smokers, wound infection was commoner among smokers (12% vs. 2%,  $p < 0.05$ ). After four weeks of abstinence the wound infection levels were similar to never smokers [79]. In a retrospective case matched study of patients who developed acute fascial wound dehiscence requiring return to theatre following an earlier laparotomy, incidence of smoking was more common (46%) compared to those who did not develop the complication (16%,  $p=0.0002$ ) [80].

In two large retrospective studies of over 3000 cases undergoing ventral hernia repair [81] and abdominal wall reconstruction [82], smoking was the only modifiable risk factor associated with wound infection and major operative complication. Current smoking was approximately 1.5 times more prevalent in subjects with postoperative wound infections. In 2010, the Ventral Hernia Working Group actively recommended smoking cessation as part of patient optimisation prior to elective surgery [83].

Transanal advancement flap repair (TAFR) has been advocated as a possible treatment of choice for trans-sphincteric fistula in ano. Initially promising reports [84-87] have been followed by less favourable results [88,89]. To examine this further 105 patients with crypto glandular perianal fistulae underwent TAFR and were assessed for healing outcomes. TAFR was successful in 69% at a median of 14 months. The healing rate varied between 60% in smokers and 79% in non smokers with a significant correlation between number of

cigarettes smoked per day and reduced healing [90]. The same group went on to show significantly decreased blood flow in the rectal mucosa among smokers prior to TAFR [13], mainly demonstrated at the apex of the flap. In another study smoking was again found to be a factor adversely affecting healing of advancement flaps and increased recurrence rates [91]. In a study evaluating “staged fibrin sealant (FS)” technique and TAFR for treatment of complex perianal fistulae, 100% of smokers in the FS group developed recurrent fistulae [92].

## Smoking and Anastomotic Leaks

Anastomotic leakage is a very serious complication after colorectal surgery [93,94], leak rates vary between 1.5% and 16% being highest in low rectal anastomoses [95]. Anastomotic complications cause increased morbidity and mortality [96], poor long term outcomes and impaired functional results [97] (Table 7).

A combined clinical and histopathological study, correlating smoking, hypertension and anastomotic dehiscence, among 147 patients, found a positive correlation between microvascular disease and anastomotic dehiscence, with an increased incidence among smokers [12]. In a retrospective analysis of 215 patients who underwent low anterior resections for rectal cancer multivariate analysis revealed the presence of a protective stoma and history of heavy smoking to be significantly and independently associated with anastomotic complications [98]. Similar studies of patients undergoing colonic or rectal resections used regression analyses to identify smoking, metastatic disease and alcohol abuse to be significantly associated with higher anastomotic leak rates [99,100]. A recent systematic

review showed smoking to be an important adjustable risk factor for anastomotic leak [101]. It is also reasonable to hypothesise that there might be a cumulative effect of smoking and radiotherapy in particular on anastomotic healing [101]. A more recent clinical study of 246 patients undergoing left sided colonic resections, the percentage of anastomotic leak requiring an intervention, was significantly higher among smokers (17%) compared to non-smokers (5%) [102]. A much larger multicentre study from Germany including almost 18,000 patients over a 10 year period, also found smoking (reliant on patient history) to be an independent factor in both univariate (leak rate of 17% vs. 11%, p value >0.001) and multivariate analysis (O.R 1.332, 95% C.I 1.106 – 1.604) [103].

## Conclusion

Cigarette smoking adversely affects the natural history of common colorectal conditions, their treatment and surgical outcomes. As well as the deleterious cardiorespiratory effects on blood supply, pulmonary function and tissue oxygenation there is also a smoking related impairment of the inflammatory response and tissue repair. The latter, directly associated with impaired wound healing, an increased incidence of anastomotic leakage, hernia formation and flap failure. Smoking is associated with poorer cancer outcomes and increased complications after colorectal surgery. Smoking is also associated with poorer outcomes after radiotherapy.

Smoking history should be an integral part of the colorectal patient's assessment. There is an obligation to explain the effects of smoking on the natural history of the disease and its treatment. Surgeons must advocate and facilitate smoking cessation in order to empower patients to alter the course of their disease for their benefit. Whilst aware of the health risks of smoking in general terms many patients don't appreciate the specific risk to their colorectal disease or their proposed surgery or radiotherapy. Smoking cessation should become an integral part of enhanced recovery protocols which is not the case at present in the UK. The optimal duration of smoking cessation and success of smoking cessation programmes has been a subject of few studies. A systematic review and Meta analysis concludes that at least four weeks of abstinence from smoking reduces respiratory complications and abstinence of at least three to four weeks reduces wound healing complications [104]. Another systematic review and meta analysis of smoking cessation interventions among oncology patients (counselling, nicotine replacement therapy, bupropion and varenicline) concludes that interventions in the perioperative period had a pooled odds ratio of 2.31 (95% C.I 1.32 – 4.07), making this an important teachable moment [105].

If smoking cessation advice is unsuccessful then the appropriateness of proceeding with elective surgery in the face of active smoking should be reconsidered [106]. If proceeding with surgery, then alteration in surgical strategy with reconsideration of anastomoses or flaps needs to be undertaken, particularly if other risk factors are present.

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