TOPIC HIGHLIGHT

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Squamous cell cancer of the rectum

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Abstract

Squamous cell carcinoma of the rectum is a rare malignancy. It appears to be associated with chronic inflammatory conditions and infections. The clear association seen between Human Papilloma Virus and various squamous cancers has not been firmly established for the squamous cell cancer of the rectum. The presentation is nonspecific and patients tend to present with advanced stage disease. Diagnosis relies on endoscopic examination with biopsy of the lesion. Distinction from squamous cell cancer of the anus can be difficult, but can be facilitated by immunohistochemical staining for cytokeratins. Staging of the cancer with endoscopic ultrasound and computed tomography provides essential information on prognosis and can guide therapy. At present, surgery remains the main therapeutic option; however recent advances have made chemoradiation a valuable therapeutic addition. Squamous cell carcinoma of the rectum is a distinct entity and it is of crucial importance for the practicing Gastroenterologist to be thoroughly familiar with this disease. Compared to adenocarcinoma of the rectum and squamous cell cancer of the anal canal, squamous cell carcinoma of the rectum has different epidemiology, etiology, pathogenesis, and prognosis but, most importantly, requires a different therapeutic approach. This review will examine and summarize the available information regarding this disease from the perspective of the practicing gastroenterologist.

INTRODUCTION

Squamous cell carcinoma of the gastrointestinal (GI) tract is a rare malignancy. When encountered, it usually involves the esophagus or the anal canal. Occasionally it can be associated with a GI tract fistula, lined by squamous mucosa. Squamous cell carcinoma of the rectum is extremely unusual and unlike squamous cell carcinoma of the esophagus and anal canal, little is known about the etiology, prognosis, and optimal treatment. This review will examine and summarize the available information regarding this disease from the perspective of the practicing gastroenterologist.

EPIDEMIOLOGY

Squamous cell carcinoma of the rectum is a rare entity and only case reports and relatively small case series have been published^[1-24] (Table 1). Schmidtman^[25] in 1919 described the first case of squamous cell carcinoma of the large intestine localized to the cecum. It was not until 1933 that the first case involving the rectum was subsequently described by Raiford^[1]. Since that time, 73 cases have been reported in the English language literature. Based on a review of this literature, the incidence of the disease is approximately 0.10 to 0.25 per 1000 colorectal cancers^[22,26-29]. Of all cases of squamous cell carcinoma of the large intestine, the rectum is the most frequent location for the disease, followed by the right colon^[29]. This is likely an underestimation due to reporting bias and histologic variability.

Given the rarity of the disease, strong epidemiological data regarding patient demographics, risk factors, natural history and optimal treatment is lacking. However, there have been several retrospective reviews that have tried to

Table 1 Reported cases of squamous cell carcinoma of the rectum

Study	Age	M/F	Surgery	Adjuvant	Outcome
Raiford ^[1] (1933)	43	F	Surgery		Dead at 17 mo
Catell <i>et al</i> ^[2] (1943)	63	M	LAR		Alive at 3.5 yr
Wiener <i>et al</i> ^[3] (1962)	52	F	APR		Dead at 1 yr
Cabrera <i>et al</i> ^[4] (1967)	62	F	APR		NR
	50	F			NR
Minkowitz ^[5] (1967)	49	F	Proctocolectomy		Dead at 5 mo
Williams <i>et al</i> ^[6] (1979)	45	M	APR		Dead at 9 mo
Vezeridis <i>et al</i> ^[7] (1983)	56	M	APR		IO death
	44	M	APR		Dead at 9 d
	61	F		EC	Dead at 4 mo
	66	F		5-FU & XRT	Dead at 15 mo
	62	F	APR	Bleo, Vin, Mtx-post	Dead at 13 mo
Lafreniere <i>et al</i> ^[8] (1985)	60	M	TAE	5FU/MC XRT-post	Alive at 2 yr
Pigott <i>et al</i> ^[9] (1987)	60	F	APR	XRT-post	Alive at 13 mo
Woods ^[10] (1987)	57	F	APR		Dead at 3 mo
Prener <i>et al</i> ^[11] (1988)	43	F	APR		Dead at 1 yr
	77	F	Polypectomy		Dead at 3 yr
	55	F	APR		Alive at 3 yr
	55	M	APR	XRT-post	Dead at 3 mo
	53	M	APR		Dead at 1 yr
Schneider <i>et al</i> ^[12] (1992)	44	M		5FU/MC & XRT	NR
	69	F	TAE	5FU/MC&XRT-post	Alive at 6 mo
Martinez-Gonzalez <i>et al</i> ^[13] (1996)	40	M	LAR	5FU & XRT-pre	Alive at 18 mo
Copur <i>et al</i> ^[14] (2001)	54	M	APR	Chemo& XRT-post	NR
Frizelle <i>et al</i> ^[15] (2001)			9 cases		
Sotlar <i>et al</i> ^[16] (2001)	87	M	LAR	5FU/MC & XRT	Dead at 20 mo
Gelas <i>et al</i> ^[17] (2002)	47	F	APR	XRT-pre	Alive at 16 yr
	63	M	APR	5FU/Cis & XRT-IO	Dead at 14 mo
	70	F	APR	XRT	Dead at 18 mo
	93	M	none	XRT	Dead at 4 mo
	45	F	LAR	5FU/Cis-pre & XRT/5FU/FA-post	Alive at 6 mo
	43	F	LAR	5FU/Cis & XRT	Alive at 2 yr
Anagnostopoulos <i>et al</i> ^[18] (2005)	75	M	APR	5FU/Cis-post	Alive at 14 mo
Lam <i>et al</i> ^[19] (2006)	44	F	LAR	XRT-pre	NR
Theodosopoulos <i>et al</i> ^[20] (2006)	39	F	APR	5FU/MC-pre/post & XRT	Alive at 18 mo
Pikarsky <i>et al</i> ^[21] (2006)	57	F		5FU/MC & XRT	Alive at 7 yr
Nahas <i>et al</i> ^[22] (2007)	58	F10/M2		Chemo/XRT-pre	Alive at 2.6 yr
				Chemo/XRT-pre	
			TAE	Chemo/XRT-pre	
			TAE	Chemo/XRT-pre	
			APR	Chemo/XRT-pre	
			LAR	Chemo/XRT-pre	
			APR	Chemo/XRT-pre	
			LAR	Chemo/XRT-pre	
			LAR	Chemo/XRT-pre	
			APR	Chem/XRT-post	
			TAE	Chem/XRT-post	
				Chemo-pre	
Kong <i>et al</i> ^[23] (2007)	48	F	TAE	5FU/MC & XRT-post	Alive at 3 yr
	53	F		Oxal, xelo, avastin, carbo, gemzar	
Clark <i>et al</i> ^[24] (2008)	75	M		5FU/Cis & XRT	Alive at 20 mo
	71	F		5FU/MC & XRT	Alive at 31 mo
	42	F		5FU/MC/Cis & XRT	Alive at 13 mo
	70	M		5FU/MC & XRT	Alive at 14 mo
	55	F	LAR	5FU/Cis & XRT	Alive at 19 mo
	45	F		Capecitabine/Cis & XRT	Alive at 23 mo
	71	F		5FU/Cis & XRT	Alive at 5 mo
Rasheed <i>et al</i> ^[53] (2009)	55	F		5FU/MC & XRT	Alive at 11 yr
	50	M		5FU/MC & XRT	Alive at 7 yr
	69	F		5FU/Cis & XRT	Alive at 4 yr
	61	M	APR	5FU/Cis & XRT	Alive at 4 yr
	58	M	APR	5FU/Cis & XRT	Alive at 2 yr
	41	F		5FU/Cis & XRT	Alive at 2 yr

NR: Not reported; F: Female; M: Male; LAR: Low anterior resection; APR: Abdominoperineal resection; TAE: Transanal excision; Chemo: Chemotherapy; XRT: Radiation therapy; IO: Intraoperative; 5FU: 5-fluorouracil; MC: Mitomycin C; Bleo: Bleomycin; Vin: Vincristine; Cis: Cisplatin; EC: Ethyl [bis (2,2-Dimethyl-L-aziridinyl) Phosphiny] carbamate; MTX: Methotrexate; Oxal: Oxaliplatin; Xelo: Xeloda; Carbo: Carboplatin; FA: Folic acid.

provide a framework for understanding this disease.

Squamous cell carcinoma of the rectum appears to affect individuals between the ages of 39 to 93 years old, with a mean age of 57 years. The disease tends to occur more frequently in women than in men. A review of available reports shows that 66% of cases occurred in women and 34% in men. Patients often present with advanced disease, Dukes C or Stage III^[8]. This might be due to a reporting bias based on the fact that most of these case reports come from tertiary care centers. There is no geographic or ethnic predilection that has been established for this disease, but it is interesting to note that Mel'nikov *et al*^[30] reported 107 cases of squamous cell cancer of the rectum in Russia in one center alone. The details of the study are unavailable, and it is unclear why this population would have such a seemingly high incidence of this malignancy. One plausible explanation is that some cases of anal squamous cell carcinoma might have been misclassified as originating in the rectum.

While no clear set of risk factors can be established, several associations have been observed. Some case reports have found squamous cell carcinoma in association with inflammatory processes involving the colon and rectum. Several cases have been reported in patients with ulcerative colitis^[27,31-33], while others have been found in association with infections including Schistosomiasis^[3], *Entamoeba histolytica*^[6] and human papilloma virus (HPV)^[16,23]. Adenocarcinoma has also been associated with squamous cell cancer of both the colon and rectum. Multiple studies have described either synchronous^[5,15,34] or metachronous lesions^[7,15,35,36] of adenocarcinoma occurring in the large intestine of patients with squamous cell cancer of the rectum. Additional coexisting diseases have been described including colonic duplication^[37,38], ovarian cancer^[39], prostate cancer^[7], endometrial cancer^[40], and breast cancer^[15].

PATHOGENESIS

With so few cases described, the exact mechanism behind the development of squamous cell cancer of the rectum remains elusive. Over the years, four hypotheses have developed regarding the pathophysiology of the disease. (1) Some suggest that inflammation or irritation, secondary to inflammatory bowel disease^[32,41,42], infection^[3,6,43] or radiation^[39,44], results in squamous metaplasia from which carcinoma develops^[10]; (2) Hicks and others^[45-47] have described the possibility of pluripotent stem cells capable of squamous differentiation. This theory is supported by the fact that squamous carcinoma is often found in the midst of poorly differentiated cells; (3) Michelassi *et al*^[48] have suggested that epithelial damage causes proliferation of uncommitted basal cells into squamous cells, which then undergo malignant transformation; (4) Histological reviews of adenocarcinomas have demonstrated areas of squamous differentiation, suggesting the possibility that these carcinomas may arise out of preexisting adenomas or adenocarcinomas^[6,46].

A clear association between HPV and squamous cell cancer of the anus has been established. Furthermore,

HPV has been associated with many squamous cell cancers including: skin, oral, vaginal, penile, esophageal and anal. The subclasses most commonly associated with virulent disease include HPV-16, 18, 31 and 33^[49]. The studies relating to HPV and squamous cell cancer of the rectum however, are few and varied in the methods of detection and the results obtained. Frizelle *et al*^[15] and Nahas *et al*^[22] evaluated a total of 11 squamous cell carcinoma patients for HPV using in situ hybridization and detected no HPV deoxyribonucleic acid (DNA) in any of the specimens. Audeau *et al*^[43] used immunohistochemistry to evaluate 20 patients with squamous cell cancer, adenosquamous cancer, and squamous metaplasia of the rectum, none of whom had detectable HPV. Polymerase chain reaction (PCR) has been considered the gold standard for detection of HPV. In two studies^[16,23], a total of four patients, have been evaluated *via* this methodology. All of those evaluated *via* PCR were HPV-16 positive. There have been concerns that the use of PCR for detection of HPV may lead to false positive results secondary to cross contamination. Indeed, two out of the above four patients with squamous cell cancer of the rectum evaluated *via* PCR were noted to have a history of cervical dysplasia, a condition known to be associated with HPV^[23]. At present we do not have firm evidence for a cause/effect relationship between infection with HPV and squamous cell cancer of the rectum.

DIAGNOSIS

Patients with squamous cell carcinoma of the rectum present with symptoms similar to those with adenocarcinoma of the rectum. The symptoms most frequently encountered are rectal bleeding, abdominal pain, change in bowel habits and weight loss^[8,43]. Patients usually experience symptoms for several weeks to months^[4,7].

Proctoscopy or colonoscopy with forceps biopsies of any visible abnormalities are the primary modalities for definitive diagnosis of rectal squamous cell carcinoma. The endoscopic appearance can range from a polyp to an ulcerated obstructing mass. Recent advances in endoscopy have been utilized to detect more subtle lesions. An example of this is narrow band imaging (NBI), a new endoscopic technique that highlights mucosa and underlying capillary networks. Fu *et al*^[42] describe the use of this technique in detection of squamous metaplasia in a patient with ulcerative colitis. If the metaplasia-dysplasia-carcinoma pathway is established as for other cancers, then NBI might play an important role in detecting premalignant lesions.

Occasionally, there can be difficulty either in distinguishing squamous cell cancer of the rectum from that of the anus or other small cell, poorly differentiated tumors on biopsy specimens. Immunohistochemistry has proved useful in characterizing these lesions. The most useful cytokeratins are CAM 5.2, AE1/AE3, and 34B12. CAM 5.2 helps to differentiate rectal from anal lesions. It characteristically stains rectal squamous

cell and adenocarcinoma but not anal squamous cell lesions^[22]. The cytokeratins AE1/AE3 stain positively for cells of squamous origin, helping to delineate less well-characterized lesions^[18,50].

In 1979, Williams *et al*^[6] established diagnostic criteria for squamous cell cancer involving the rectum which included: (1) absence of evidence of squamous cell carcinoma of any other part of the body, indicating possible metastasis; (2) careful proctoscopy to exclude proximal extension of anal squamous cell carcinoma; and (3) lack of a fistulous tract lined by squamous cells. The above criteria are required in conjunction with histology consistent with a squamous carcinoma^[51] without glandular differentiation^[52].

Squamous cell carcinoma antigen (SCC Ag) is a tumor marker that has been found to be associated with squamous carcinoma of the anus. Rasheed *et al*^[53], found SCC Ag to be elevated in three out of six patients with squamous cell carcinoma of the rectum. It was noted that after treatment with chemo- and/or radiation therapy, the SCC Ag normalized. In 2001, Comer *et al*^[27] found an elevated SCC Ag along with metastatic disease in a patient previously treated for rectal squamous cell cancer. Retreatment with chemotherapy and radiation resulted in an improvement in SCC Ag levels. Based on these observations, it appears that SCC Ag level is not suitable for initial diagnosis of squamous cell carcinoma of the rectum, but might be helpful to monitor disease response and progression.

Once the diagnosis of squamous cell carcinoma of the rectum has been established, the work-up should focus on staging of the tumor and evaluation for regional and distant metastasis. Trans-rectal endoscopic ultrasound (R-EUS) has become an integral part of the staging process of rectal cancer of all types. Accurate staging helps to determine appropriate surgical treatment (local excision *vs* radical resection) and the need for adjuvant therapy. The stage of the disease as determined by R-EUS is also predictive of patient survival. In squamous cell cancer of the anus, an increase in stage is associated with a decrease in five-year survival^[54]. While there are no large studies to support this for squamous cell cancer of the rectum, a review of available case reports supports a similar trend. R-EUS helps to determine the depth of tumor invasion. Superficial T1 lesions involve one or more of the first three echo layers (superficial mucosa, deep mucosa, and submucosa) of the rectal wall. Extension into the muscularis propria, the 4th echo layer, denotes a T2 lesion. Transmural invasion through the muscularis propria into the perirectal fat characterizes a T3 lesion, and T4 lesions involve invasion of surrounding organs^[55]. In addition to depth of tumor invasion, local nodal involvement can also be assessed. Size, echogenicity, shape and demarcation are felt to be helpful in distinguishing benign from malignant lymph nodes^[56], although this concept has yet to be validated in rectal cancer. Park *et al*^[57] evaluated the accuracy of R-EUS with fine needle aspiration (FNA) in the detection of rectal cancer. They found nodal involvement *via* only R-EUS in 33% of histologically confirmed nodes. When FNA was added

to the endosonographic examination, the accuracy of the test increased to 87%.

R-EUS should be performed in conjunction with computed tomography (CT) for complete staging. Several studies have compared the two modalities with regards to the staging of rectal cancer. The accuracy of R-EUS was superior to CT for evaluation of wall invasion (T staging), with a sensitivity of 67% to 93% *vs* 53% to 83%, respectively. R-EUS also outperformed CT for nodal staging, sensitivity 80% to 87% *vs* 57% to 72%^[55,58,59]. The current consensus is that R-EUS and CT are complimentary. R-EUS provides better tumor and local lymph node evaluation and CT has the advantage of detecting distant metastasis. Endorectal magnetic resonance imaging (MRI) has also been used for evaluation of local disease, allowing a larger area of view than R-EUS. In the limited studies available, endorectal MRI has yet to be shown to be superior to R-EUS^[60].

TREATMENT

The treatment paradigm for squamous cell carcinoma of the rectum primarily involves surgery. Secondary to the perceived aggressiveness and often late stage of presentation, surgery has always been thought to offer the best chance of a cure. Surgical techniques have been adopted from rectal adenocarcinoma treatment, despite the lack of randomized studies indicating the most appropriate therapy.

Surgery

Surgical options often depend upon tumor characteristics, such as size, location, depth of invasion, and local and distant metastasis. Additional considerations dictating surgical technique include the patient's body habitus and comorbidities^[61].

Local excision is appropriate in selected cases of stage T1 (invasion to the mucosa or submucosa) cancers or possibly stage T2 (invasion to the muscularis propria) lesions. There is growing evidence however, that T2 lesions particularly require close follow-up, as recurrence after local excision can be as high as 20%^[61]. In adenocarcinoma, low-risk lesions have been characterized as those that are well differentiated on histology and demonstrate no endovascular or lymphatic involvement^[62,63]. Clearly, this is in conjunction with no evidence of local or metastatic disease on R-EUS, CT or MRI^[61]. In 1985, Lafreniere *et al*^[8] reported a case of a 60-year-old successfully treated with local excision followed by chemotherapy and radiation. The patient was noted to be alive and well two years after the diagnosis.

For more advanced disease, low anterior resection (LAR) or abdominoperineal resection (APR) can be used for treatment, depending upon tumor location. For lesions in the proximal two-thirds of the rectum, LAR can be performed to remove the tumor-containing rectum. Preserving the anus allows for anastomosis of the descending colon with the distal rectum or anus thus maintaining rectal continuity. APR is performed not only for distal rectal lesions, but also for locally advanced

lesions, where disease free margins cannot be assured. APR allows for excision of anus and rectum as well as abdominal exploration for metastatic disease prior to creation of an ostomy. Overall, APR is associated with increased postoperative complications and poor long-term patient satisfaction^[64]. Review of the available case reports shows APRs have been performed more frequently; 2:1 compared to LAR. This is likely due to more advanced disease at diagnosis, which is frequently the case in squamous cell cancer of the rectum. Only seven of the 41 patients with adequately described surgical interventions underwent local resection^[8,12,22,23].

Chemoradiation therapy

Several studies have evaluated the utilization of chemoradiation therapy (CRT) for the treatment of squamous cell carcinoma of the rectum, as the primary therapy or in conjunction with surgery. Secondary to the infrequency in which cases are encountered, a standard protocol has yet to be established.

Several case reports have used CRT as the primary therapeutic intervention, usually in patients who are high-risk surgical candidates. The early studies^[7,13,29] showed suboptimal results with no significant change in mortality or maintenance of bowel continuity. Recently, Rasheed *et al*^[53] and Clark *et al*^[24] in two separate populations, evaluated the success of CRT in the treatment of squamous cell carcinoma of the rectum. Unlike previous cases^[7,13], these treatment regimens used primarily 5-fluorouracil based treatment along with either mitomycin-C or cisplatin. These were the same drug regimens that revolutionized the therapy squamous cell carcinoma of the anus^[65-68]. Around the same time, the benefits of radiotherapy combined with chemotherapy were also established, making CRT the treatment modality of choice for squamous malignancy involving the anus^[69-73]. Surgery was relegated to the role of salvage therapy^[54]. It was following this paradigm that CRT was adopted for treatment of squamous cell cancer of the rectum. Of the 13 patients treated with CRT by Rasheed and Clark, only three ended up with surgical resections. After histological evaluation, only one of the three resected specimens demonstrated residual tumor. The issue of which chemotherapeutic regimen to use in conjunction with radiotherapy, has not been evaluated in patients with squamous cell cancer of the rectum. Extrapolations can be made from trials in patients with anal canal cancer. A recent large prospective randomized study compared mitomycin C with cisplatin in patients with anal cancer^[74]. There was no difference in five-year survival, locoregional recurrence and distant metastasis between the two groups, but the patients receiving cisplatin had a higher rate of conversion to colostomy.

Endoscopy

Up to this point, endoscopy has not been reported as a treatment option for squamous cell cancer of the rectum, probably due to its rarity. Lee *et al*^[75] in 2000 reported a case of squamous cell metaplasia in the rectum successfully treated with argon plasma coagulation

Table 2 TMN classification for squamous cell rectal cancer

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
II A	T3	N0	M0
II B	T4	N0	M0
III A	T1-T2	N1	M0
III B	T3-T4	N1	M0
III C	Any T	N2	M0
IV	Any T	Any N	M1

(APC). The metaplasia-dysplasia-carcinoma relationship has not been established for squamous cell cancer of the rectum. If it is found to be similar to that of colon adenocarcinoma, then APC might provide a safe and easy alternative for the treatment of these lesions. Endoscopic mucosal resection (EMR) involves removal of lesions *via* the endoscopic resection of mucosa and submucosa. It has been used in the removal of superficial adenocarcinoma lesions, particularly in poor surgical candidates^[55]. When used in the treatment of adenocarcinoma, EMR shows a low-risk of recurrence and decreased need for surgery in appropriate populations^[54]. This might prove to be transferable technology to the treatment of rectal squamous cell carcinoma.

PROGNOSIS

The process of evaluating tumor spread is based on the TNM classification system used for squamous cell cancer of the anus: T = tumor invasion into the wall, N = nodal involvement, M = metastasis, (Table 2). From this information, the stage of disease can be established which is the most important predictor of prognosis^[76]. Frizelle's^[15] evaluation of 52 patients with squamous cell carcinoma of the colon revealed a prognosis similar to Stage I / II, node negative adenocarcinoma of the colon. However when nodal involvement occurred, squamous cell cancer demonstrated a worse prognosis stage for stage. Its overall prognosis is poor, secondary the tendency of rectal cancer to have local lymph node involvement compared to malignancy in other parts of the colon. This is in addition to the fact that it frequently presents at a late stage. Mixed squamous cell carcinoma and poor differentiation on histology have been found to be poor prognosticators^[15].

The overall five-year survival rate is 32%, with significant variation by stage; Duke B 50%, Duke C 33% and Duke D 0%. With the addition of adjuvant therapy, it is likely these numbers will improve. Studies have shown better outcomes with preoperative CRT. Nahas^[22] showed there was an increase in sphincter preserving surgeries from 67% to 71% when radiation therapy was added preoperatively.

CONCLUSION

Squamous cell carcinoma of the rectum is a rare malignancy. The available information for review is

clouded by a lack of uniformity in diagnosing staging and treating the disease. It is likely we will never be able to fully establish a firm relationship between it and adenocarcinoma of the colon, as found in other diseases, such as ulcerative colitis. Given the significant number of adenomas and adenocarcinomas reported in these patients, close follow-up for the development of colorectal cancer is warranted. It is likely that advances in technology and treatment of other diseases will also aid our success in management of this disease. Advances in CRT will likely supplant surgery as the primary intervention.

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