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Anal Cancer: The KUMC Experience

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Abstract

Background. Anal cancer is a relatively rare GI malignancy with some controversy regarding several aspects of therapy including chemotherapy agents, radiation dose, and timing.

Methods. A retrospective review of all patients treated for anal cancer from 1986 to 2006 was conducted at the University of Kansas Medical Center (KUMC) Department of Radiation Oncology.

Results. This report details 33 patients treated with external beam radiation. Most patients (88%) had chemotherapy consisting of 5-FU and either mitomycin (42%) or cisplatin (45%), concurrently (88%) or sequentially (3%) with radiation. Surgery was performed prior to the radiation in 12 (36%) patients, 2 (6%) with an abdominoperineal resection, and 10 (30%) with local excision. Acute grade 3-4 morbidity was seen in 22 (67%) patients and late grade 3-4 morbidity was present in 2 (6%) patients. Two patients had progression of disease and 4 patients had disease recurrence, with local recurrence in 2 patients and distant recurrence in 2 patients; 29 patients (88%) had no evidence of disease at last follow-up. At a median follow-up of 4.6 years, overall survival was 74% and disease free survival was 79%.

Conclusion. Treatment factors including radiation dose, treatment time, and chemotherapy agents were not found to influence either overall survival or local control. *KJM 2007; 1(2):27-37*

Introduction

Although relatively rare, an estimated 4600 new cases of anal cancer will be diagnosed in 2006.[1] The treatment option for these patients at one time would have consisted of an abdominoperineal resection (APR) entailing total anal sphincter sacrifice and a permanent diverting colostomy. Today, treatment options include sphincter-sparing approaches using radiation and chemotherapy without compromising local control or survival.[2] While local control is good, there are still many issues in the treatment of this disease that are unsettled.

Chemotherapy has not shown a survival advantage when compared to radiation alone although it is associated with an improved local control rate and is considered standard of care. The chemotherapy used in the initial chemoradiation trials was mitomycin and 5-FU that are associated with significant treatment morbidity.[3-5] To reduce the side effect profile of combination therapy, some have investigated if cisplatin chemotherapy could prove to be equivocal or even superior to mitomycin. Good clinical outcomes with cisplatin chemotherapy have been shown in several retrospective reviews[6-8] and the preliminary reports of a phase III trial[9], but more information is needed before cisplatin can be considered standard of care.

Another unclear aspect of anal cancer treatment is the ideal radiation dosage and schedule. While some reviews[10] have found 30 gray (Gy) to be adequate for tumor

control, others[11,12] have not found this to be true. Higher radiation doses have been associated with a greater degree of treatment complications[13-14] and it is not established what dose best balances toxicity and tumor control.

A retrospective review of the anal cancer patients treated at the University of Kansas Medical Center (KUMC) was conducted to provide more information regarding treatment outcomes and the role of chemotherapy agents, radiation dose, and treatment morbidity.

Methods

Treatment information was obtained by retrospective review of the hospital and radiation oncology charts for all anal cancer patients treated at KUMC from 1986 to 2006. Prior to review, approval for the study was granted by the KUMC Human Subjects Committee. Thirty-four patients were available for analysis; one patient had metastatic disease at presentation and was not included in this analysis. Of the 33 patients included in the analysis, there were 15 males and 18 females, with a median age of 57 years at the time of radiation. Six (18%) patients were known to have HPV and 3 (9%) patients had HIV.

Patient characteristics are summarized in Table 1. Most of the patients were early stage, with one Tis (3%), six (18%) T1, 15 (45%) T2, five (15%) T3, and six (18%) T4 tumors. (See Table 2 for staging characteristics.) Twenty-one (64%) patients were lymph-node negative with 12 patients (36%) having positive lymph nodes.

Treatment involved external beam radiation for all 33 patients (see below for dose and timing of radiation), chemotherapy for 29 (88%) patients, and primary surgery followed by adjuvant radiation in 12 (36%) patients, with nine (27%) having adjuvant chemoradiotherapy.

Table 1. Patient characteristics.

Median age	57 years
Age range	34-80 years
Male	15 (45%)
Female	18 (55%)
HIV positive	3 (9%)
HPV positive	6 (18%)
Tumor location	
Anorectal junction	6 (18%)
Anal canal	20 (60%)
Cloacogenic zone	7 (21%)
Tumor histology	
SCC in situ	1 (3%)
Basaloid	2 (6%)
SCC keratinizing	30 (90%)

Table 2. Staging characteristics.

T1	6 (18%)
T2	15 (45%)
T3	5 (15%)
T4	6 (18%)
Tis	1 (3%)
N1	5 (15%)
N2	3 (9%)
N3	4 (12%)
N0	21 (64%)

All patients were treated exclusively with external beam radiation; no patients had brachytherapy as a component of their treatments. The initial treatment plan was a whole pelvis plan that consisted of two lateral and two anterior-posterior radiation beams (see Figure 1). The purpose of the whole pelvis field is to supply radiation to the cancer and the surrounding areas that are at risk for microscopic tumor involvement. The median radiation dose for the initial treatment was 45 Gy (range 30.6 Gy to 50.4 Gy).

Four radiation beams are used for the pelvic field to reduce the radiation dose to the normal tissues such as the bladder, rectum, and bowel. The initial pelvic field

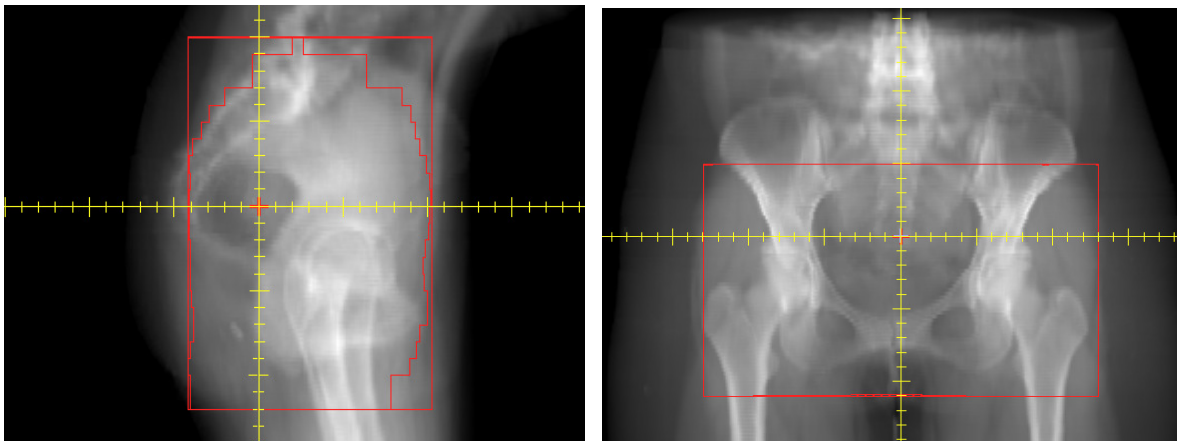

Figure 1. Lateral and anterior-posterior field images.

was followed by a reduced-volume boost treatment in 21 (64%) patients to deliver further radiation to the target while keeping the radiation dose to the normal structures as low as possible. The boost treatment targeted the areas of gross disease without targeting areas of possible microscopic involvement; the theory being that the lower dose used in the larger pelvic field is adequate for microscopic disease while the gross tumor requires more radiation.

The median boost dose was 16.2 Gy (range 4 Gy to 30.6 Gy). The median total dose, excluding one noncompliant patient, was 54.9 Gy with a range of 45 to 66.6 Gy. The median number of total fractions was 31 with a range of 25 to 49 fractions. Treatments were delivered daily (Monday through Friday). Radiation treatments were scheduled consecutively without break unless patient toxicity required a break for healing. Any break in the radiation will prolong the overall treatment time. The median treatment time was 56 days with a range of 32 days to 149 days. Table 3 exhibits treatment characteristics.

The type of surgical resection was an APR with diverting colostomy in two (6%) patients, and local excision in 10 (30%) patients. The two patients treated with an initial APR had subsequent treatment

Table 3. Treatment characteristics.

Primary treatment	
Radiation	33 (100%)
Surgery	12 (37%)
Chemotherapy	29 (88%)
Surgery + Radiation	3 (9%)
Surgery + Radiation + Chemotherapy	9 (27%)
Chemotherapy	
5-FU + Mitomycin	14
5-FU + Cisplat	15
Cycle (median)	2
Cycle (range)	0-3
Concurrent	28
Sequential	1
Radiation	
Dose (median)	54 Gy
Dose (range)	12.0-66.6 Gy
Fractions (median)	31
Fractions (range)	7-49
Patients receiving boost treatment	20
Boost dose (median)	16.2 Gy

secondary to advanced disease found at the time of surgery (T4N0 and T2N3). Chemotherapy consisted of 5-FU and mitomycin in 14 (42%) patients, 5-FU and cisplatin in 15 (45%) patients. Twenty-nine (88%) chemotherapy regiments were concurrent

with the radiation with one patient (3%) receiving sequential 5-FU and cisplatin prior to the radiation. One (3%) patient had one cycle of chemotherapy, 16 (48%) patients had two cycles, and seven (21%) patients had three cycles. Information on the number of chemotherapy cycles was not available for five (15%) patients.

One patient was noncompliant with radiation therapy and discontinued treatment after seven fractions (12.6 Gy) and two rounds of chemotherapy (5-FU, cisplatin). One patient had a reduced boost dose from an initially-prescribed 10.8 Gy in six fractions to a received 4 Gy in two fractions secondary to skin morbidity. The rest of the patients received the prescribed doses.

Follow-up data were obtained from the hospital and radiation therapy charts and the KUMC tumor registry that collects information on cancer patients annually. Patients were seen in follow-up typically every three months after the completion of treatment for two years, then every six months for five years and annually thereafter.

Statistical analysis was performed with SPSS for Windows (Release 12.0, SPSS Inc, Chicago, IL). Categorical variables were summarized by frequencies and percentages, and quantitative variables were summarized by medians and ranges. Quantitative variables were compared across groups using the Kruskal-Wallis test. The Wilcoxon rank sum test was used to perform pairwise comparisons on quantitative variables that were globally different among groups. The Fisher's exact test was used to compare categorical variables among groups.

The duration of follow-up was calculated from the time of diagnosis until the date of death or last known follow-up. Univariate analysis of time to death (overall or disease-specific) was analyzed by the Kaplan-Meier survival analysis. Categorical variables were compared by the log-rank test and continuous variables by Cox proportional hazards analysis. Probability values of $p<0.05$ were considered to be statistically significant. No corrections for multiple comparisons were made.

Results

At last follow-up, 21 (64%) of the 33 patients were alive. At a median follow-up of 4.6 years (range, 0.1 years to 17.6 years), 74% of patients were alive. Twenty-nine patients (88%) were free of disease at last follow-up with 2 (6%) patients alive but with evidence of disease. At the median follow-up time, 79% of patients were free of disease.

Two patients (6%) had persistent disease after treatment; these patients never achieved a disease-free state. Four patients had disease recurrence. The median time to recurrence was 1.9 years with a range of 0.6 years to 2.2 years. No recurrences were seen after 2.2 years. Two of the four recurrences were distant sites occurring in one patient with lung and another patient with both lung and liver metastases. Treatment for recurrences consisted of a colostomy in two patients and a pulmonary resection for one patient. Local control was established in 29 (88%) patients (see Tables 4 and 5).

Table 4. Summary data for patients with persistent disease or recurrence.

Persistent disease	2
Recurrences	4
Persistent disease or recurrence	6
Time to recurrence (median)	1.9 years
Time to recurrence (range)	0.55 to 2.2 years
Recurrence Site	
Local	4
Distant	2
Distant Sites	
Lung	2
Liver	1

Table 5. Patients with persistent disease or recurrence.

Patient	Recurrence type	Time to recurrence (years)	CTX	Dose (Gy)	Treatment time (days)	HIV status	Age	T stage	N stage	Gender	Primary Surgery	Salvage surgery
1	Persistent	*	5-FU, MMC	45	39	Negative	76	2	0	Female	No	No
2	Local	2.16	5-FU, Cisplatin	49	52	Negative	69	3	1	Female	No	Colostomy
3	Persistent	*	5-FU, Cisplatin	65	149	Negative	38	4	0	Female	Local excision	No
4	Local	0.55	None	66.6	71	Positive	35	2	2	Male	Local excision	Colostomy
5	Distant	1.63	5-FU, MMC	45	82	Positive	43	2	0	Male	No	No
6	Distant	2.16	5-FU, Cisplatin	53.8	62	Negative	57	1	0	Female	No	Pulmonary resection

*Patient was never disease free.

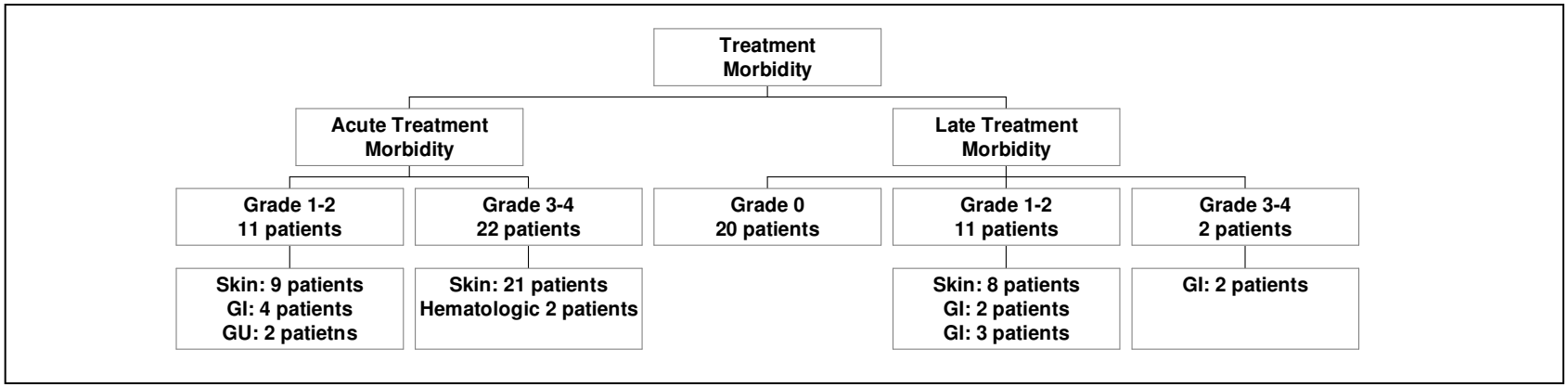

Figure 2. Treatment morbidity.

A colostomy was performed prior to radiation in two (6%) patients and after definitive treatment in three of the remaining 31 patients (9.6%). Two (6%) of these patients had a colostomy for disease recurrence and one (3%) for late radiation side effects. The time-to-colostomy for the two patients with colostomy for disease recurrence were 0.6 and 2.2 years and 5.4 years for the patient with colostomy for treatment morbidity. The median colostomy-free survival was 5.1 years for the 31 patients not having a colostomy prior to definitive treatment and 4.6 years overall.

Treatment morbidity was graded by the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria. Per the RTOG scale, treatment toxicities are divided into acute (occurring during treatment or within 6 months of the end of radiation therapy) or late (occurring after 6 months of the completion of radiation therapy). Toxicity is graded for both acute and late toxicities on a scale of 1 (most benign) to 5 (toxicity resulting in patient demise). All patients had some form of acute morbidity. Eleven (39%) patients had acute grade 1-2 morbidity and 22 (66%) patients had acute grade 3-4 morbidity. No patients died during treatment (no grade 5 toxicity). Twenty (60%) patients had no late treatment toxicity, 11 (33%) patients had grade 1-2 late morbidity, and two (6%) patients had grade 3-4 late morbidity.

For the 10 patients who had surgical excision prior to radiation, 30% had grade 1-2 morbidity and 10% had grade 3-4 morbidity. This was not statistically different from patients who did not have pre-radiation surgery. The acute toxicities for the two chemotherapy regimens were different (p=0.017, Fishers exact test), with the 5-FU and cisplatin regimen having over twice as many (13 versus 6) grade 3-4 acute side effects compared to 5-FU and mitomycin (see Figure 2 and Table 6).

Table 6. Comparison of chemotherapy agents.

Chemotherapy	Number	G3-4 Acute	G1-2 Late	G3-4 Late	Recurrences
5-FU + mitomycin	14	6	6	1	2
5-FU + cisplatin	15	13	6	0	3

Patients with HIV had worse disease-free survival than patients without HIV (p=0.0021, log-rank test). Of the 3 HIV positive patients, two (66%) had a local recurrence at 0.6 and 1.6 years. None of the six HPV patients had a disease recurrence with a median follow-up of 6.8 years. Side effects for the HPV patients were similar to that of the non-HPV population with two (33%) having grade 1-2 acute morbidity, four (66%) having grade 3-4 acute morbidity, and two (33%) having grade 1-2 late morbidity. None of the HPV positive patients had a grade 3-4 late morbidity.

The total dose received did not influence local control or overall survival. Two (13%) of 16 patients that received more than 55 Gy had a recurrence (both local) and four (24%) of 17 patients that received less than 55 Gy had a recurrence (two local and two distant) (p=0.48). Overall survival at the median follow-up time was approximately 70% for patients that received greater than or less than 55 Gy (p = 0.61). There was a relation between age and total dose, with a median age of 46 years for patients that received more than 55 Gy and a median age of 66 years for patients that received less than 55 Gy (p = 0.011).

Acute and late morbidity was not related to treatment dose. Twelve of 16 (75%) patients receiving doses greater than 55 Gy had acute grade 3 or 4 morbidity compared to 10 of 17 (59%) patients receiving below 55 Gy. Eight of the 14 patients with late morbidity occurred in the above 55 Gy treatments, with 6 occurring in the lower treatment dose (see Table 7).

No survival difference was seen in the patients who received 5-FU and mitomycin versus those receiving 5-FU and cisplatin. For the 12 patients who had a primary surgical treatment, there was one patient with persistent disease and one patient with a local recurrence. Patients who had surgery prior to radiation had a median overall survival of 3.3 years and a disease free survival (DFS) of 3.3 years compared to a median overall survival of 5.2 years and median DFS of 4.9 years for patients without primary surgery.

Elapsed treatment time did not influence local control or overall survival with four (20%) recurrences in 20 patients that required more than 55 days to complete their radiation therapy and two (15%) recurrences in 13 patients that finished treatment in less than 55 days. There were no differences in treatment morbidity between patients who finished treatment in more compared to less than 55 days.

Table 7. Treatment morbidity and total dose.

Dose	# of Patients	G1-2 Acute	G3-4 Acute	G1-2 Late	G3-4 Late
< 55 Gy	17	7	10	5	1
> 55 Gy	16	6	12	7	1

Discussion

Local control of 88% of the patients and the survival outcomes were consistent with some of the ranges reported in the literature. Local control rates reported in the literature ranged from 39% to 61% in the prospective randomized trials[3-5] and 60% to 89% for retrospective reviews[13-25]. In some recent reports, Das et al.[25] described 3-year local control rates of 81% and overall survival of 84%, the University of Florida[23] reported an overall local control rate of 85% with 53% of the reviewed patients receiving chemotherapy, and Ferrigno et al.[13] found a local control rate of 79% using chemo-radiotherapy with 5-FU and mitomycin. An interesting aspect of the current data was that there was no recurrence past 2.2 years. If this finding is demonstrated in other reviews, it may be possible that future anal cancer trials can report findings with confidence at the 3-year mark (see Figures 3 and 4).

The results of this retrospective review did not yield any guidelines for some of the unanswered questions regarding the treatment for anal cancer. No difference was found between patients treated with the 5-FU and mitomycin regimen compared to 5-FU and cisplatin. The side effect profile for the two chemotherapy regimens was not different for late toxicities, but there was a greater number of acute grade 3-4 complications (13 versus 6) with the 5-FU and cisplatin than with 5-FU and mitomycin. Several authors[6-8] have reported the success of 5-FU and cisplatin, although the preliminary report[9] of the randomized trial comparing the two chemotherapy regiments did not show a significant difference in overall survival.

There may be select patients not requiring any chemotherapy. A report from the University of Florida does not recommend chemotherapy for T1 or early

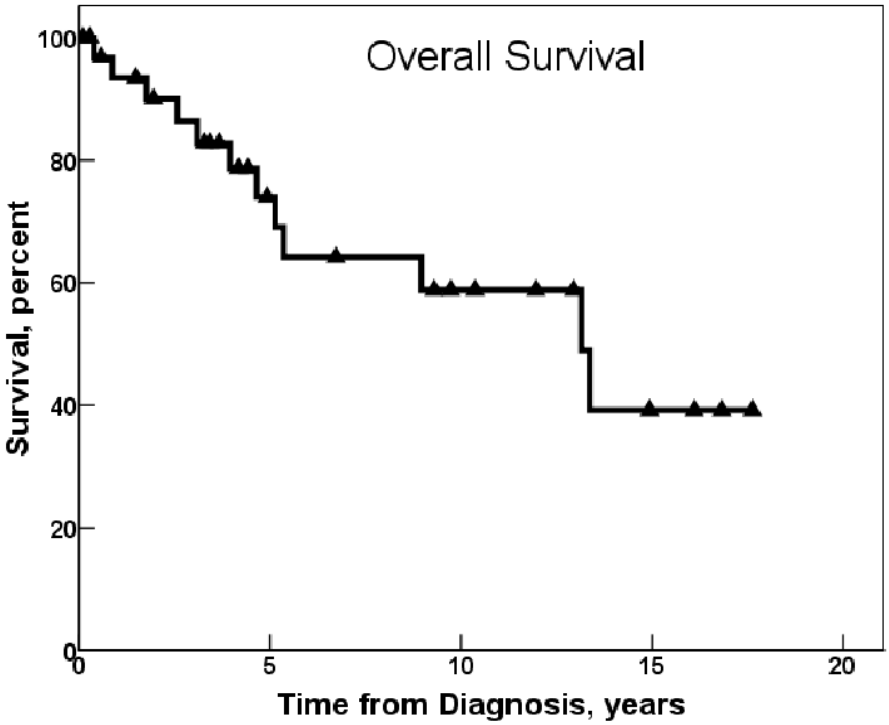

Figure 3. Kaplan-Meier overall survival curve. The marks indicate censored patients.

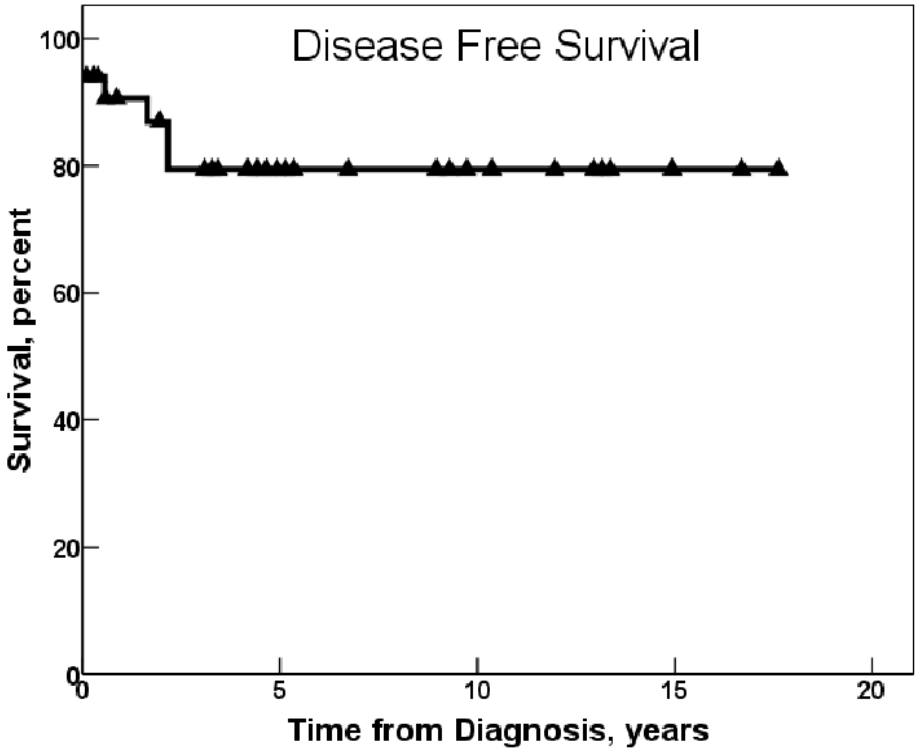

Figure 4. Kaplan-Meier disease free survival curve. The marks indicate censored patients.

T2 malignancies.[23] Four patients in this report did not receive any chemotherapy. These patients had similar local control and overall survival to the patients who did receive chemotherapy. Again, the small number of treated patients makes it hard to detect differences and most patients not receiving chemotherapy had early-stage cancers. Three of the four patients not receiving chemotherapy had T1N0 cancers and the fourth patient had a T2N2 cancer. This last patient was an HIV positive male with multiple co-morbidities contra-indicating chemotherapy. The patient had an early recurrence requiring colostomy after 0.6 years.

Another controversy in the treatment of anal cancer is radiation dose. Hu et al.[12] concluded that a certain subset of patients (excisional biopsy in combination with chemotherapy) may only require 30 Gy for local control. Several other authors[13-14] found a lower dose to be an adverse prognostic factor. Constantinou et al.[10] found doses below 54 Gy to have inferior local control (61%) versus higher doses (77%). Ferrigno et al.[13] also reported that higher doses had improved local control, with local control rates of 87% and 34% for patients above and below 50 Gy.

The present study found no statistically significant difference in patients treated to higher doses. However, there was a statistically significant difference in the age of patients treated to higher doses. Elderly patients were more likely to be prescribed lower radiation doses, and it was possible that this masked the benefits for higher doses of radiation.

Side effects were seen in the majority of patients. Only one patient required a colostomy for late radiation complications and there were no statistically significant relations between side effect profile and treatment dose, treatment duration, or chemotherapy regiment. The overall late grade 3-4 morbidity was 6% and grade 1-2 late toxicity was 33%. This was slightly lower than the late toxicity range of 8-19% found by others.[18]

Allal et al.[11] reported an association between late toxicity and initial (pre-boost) radiation dose with large-volume treatments above 39.6 Gy having a 23% incidence of late complications versus 7% for whole pelvis treatments less than 39.6 Gy. Age and previous excision were risk factors for treatment complications.

In the present study, no association between late toxicity and previous excision, radiation dose, or age was found. A statistically significant difference, however, was found in the median dose between patients older and younger than 55. The selection bias for treating older patients to less radiation could account for the lack of relationship between late toxicity and age or radiation dose.

A small subset of the treated patients had HIV or HPV. While HPV did not appear to have a worse prognosis, there was a disproportionate number of failures in the HIV positive population. The HIV patients did not receive lower doses of radiation (two of the three patients received higher than the median dose) and two of the three had concurrent chemotherapy. The one HIV patient that did not have a recurrence had an aggressive treatment course consisting of local surgical excision followed by 5-FU, mitomycin, and 59.4 Gy of radiation. Edelman et al.[26] retrospectively reviewed 17 HIV positive patients treated with radiation and chemotherapy (5-FU and mitomycin or cisplatin) and found an actuarial 18-month survival of 67%. Others have found similar survival rates.[27-28] Thus, HIV positive patients have worse outcomes than the general population which is influenced largely by HIV-related infections.

There are several limitations to the information in this report. First, the

information is retrospective. Although there is a long-term follow-up, it is possible that some recurrences were missed. Second, all patients were from a single institution and regional differences in practice and patient characteristics may bias the generalizability of these data. Third, the small number of patients may be under-powered to detect treatment differences in terms of radiation dose, treatment duration, and the difference chemotherapy regiments. Overall, despite these possible limitations, the information is valuable in adding to the literature base about the treatment outcomes for anal cancer, especially in showing that smaller institutions can achieve results comparable to larger volume centers.

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Keywords: anus neoplasms, anal cancer, radiotherapy, chemotherapy, Kansas

Delayed Splenic Rupture: A Myth or A Reality

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Introduction

The spleen is the most commonly injured organ in blunt abdominal trauma.[1] Most splenic injuries manifest immediately after trauma, however, delayed splenic rupture (DSR) may occur days to weeks following a blunt abdominal trauma. It has been debated whether delayed splenic rupture is simply a delayed diagnosis of a missed contained splenic rupture or rather an initially latent splenic lesion that may have been undetected by conventional imagery and evolved later to rupture.[2,3]

The majority of case reports describing DSR have relied mainly on clinical evaluation without obtaining an initial computed tomography (CT) scan of the abdomen to confirm what is genuinely delayed. Very few articles have reported a truly delayed splenic rupture with a normal CT scan upon admission.[4]

Case Report

A 42-year-old female presented with abdominal pain that started 2 weeks prior following a non-collision, deceleration motor vehicle accident in which she was wearing her seatbelt. Her history included gastric bypass four years prior and systemic lupus erythematosus (SLE).

On initial examination, the patient was stable and in no acute distress. The abdominal examination revealed a mild left upper quadrant tenderness and a palpable spleen, but no evidence of trauma. Further findings included a butterfly rash.

The patient's hemoglobin was 6.9 g/dl and hemoccult testing was positive. A CT scan of the abdomen with intravenous contrast obtained on admission (see Figure 1A) was unremarkable, except for the splenic size, which was in the upper limits of normal. After four units of packed red blood cells were transfused, her hemoglobin increased to 11.0 g/dl. She was scheduled for esophagogastroduodenoscopy and colonoscopy. She subsequently developed worsening nausea and emesis with retching followed by increasing left upper quadrant (LUQ) pain without evidence of hemodynamic compromise. A repeat hemoglobin revealed a drop to 7.0 g/dl.

The patient denied hematemesis, hematochezia, or melena. A LUQ ultrasound revealed free abdominal fluid, and a stat repeat abdominal CT scan with intravenous and oral contrast (see Figure 1B) demonstrated intraperitoneal free fluid and capsular changes consistent with splenic rupture.

Surgery was consulted. The decision was made to proceed with splenic artery embolization. Embolization was successful, with five coils deployed in the distal splenic artery. The follow-up hemoglobin remained stable. The workup of splenomegaly, including viral serology and clotting studies, was normal. The rest of her hospital course was uneventful, and she was discharged a few days later.

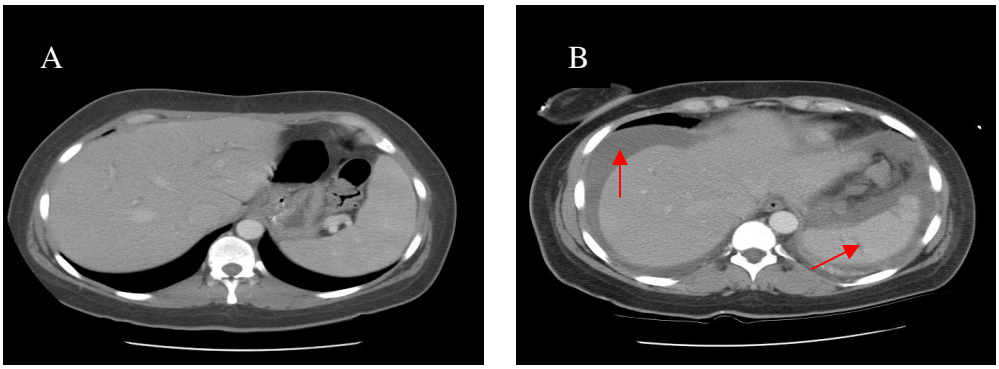

Figure 1. (A) CT scan of the abdomen upon admission without evidence of splenic rupture. (B) Repeat abdominal CT scan two days later revealed free intraperitoneal fluid, hypodensity in the spleen, and capsular changes consistent with splenic rupture (see arrows).

Discussion

Delayed splenic rupture can be explained by either a subtle splenic lesion which is not visualized and/or a false negative CT scan. Subtle splenic lesions that can progress to splenic rupture include subcapsular hematoma, pseudocyst, and pseudoaneurysm.[1] Sources of false negatives include: 1) artifact or interference from the surrounding tissues which make the injury difficult to detect, 2) an early CT scan taken before a subcapsular hematoma has bled enough to be detected on CT, 3) technical performance of the machine, 4) diluted oral contrast, and 5) variability in the intravenous contrast protocol used.[4]

This case exemplified splenic rupture as a true clinical entity. Contributing factors most likely included the recent decelerating motor vehicle accident and vomiting/ retching with abdominal adhesions from previous gastric bypass surgery which may have affected positioning and exerted traction on the spleen. Additionally, underlying SLE also may have contributed to DSR through pathologic changes within the spleen.

Of note, many cases of DSR occur along with underlying diseases such as end stage renal disease, amyloidosis[5], rheumatoid arthritis[6], chronic lymphocytic leukemia[7], and sarcoidosis[8]. Although not all of these studies reported a normal initial CT scan, these cases supported the hypothesis that certain co-morbid conditions can favor the occurrence of DSR by making the spleen more fragile[7] and the small splenic lesions more prone to progress later to frank splenic rupture.

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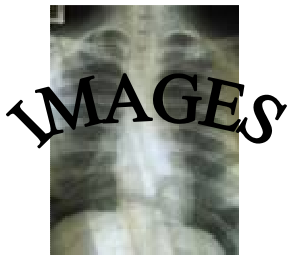
Keywords: splenic rupture, spleen, case report



Unusual Cause of Gastric Compression: Pancreatic Pseudocyst

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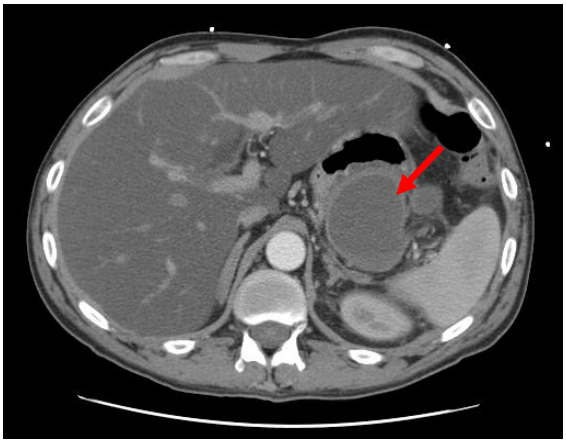

A 47-year-old male patient was admitted for a one-week history of nausea, vomiting, and abdominal discomfort. He had a partial gastrectomy secondary to peptic ulcer disease ten years earlier and was diagnosed with alcoholic pancreatitis one month prior to this hospitalization. The physical examination showed mild distention of the abdomen with tenderness on deep palpation of the epigastric region. Laboratory examinations revealed a hemoglobin of 11.6 g/dl, a potassium level of 2.6 meq/L, and a lipase level of 331 U/L. A contrast-enhanced CT of the abdomen showed multiple pseudocysts in the pancreatic bed and tail with significant mass effect on the stomach (see arrow). The patient was treated conservatively with resolution of symptoms after 72 hours. He was discharged on total parenteral nutrition and analgesics. Repeated CT of the abdomen six weeks later revealed complete resolution of the pancreatic pseudocyst.

Pancreatic pseudocyst is a well-recognized complication of pancreatitis occurring in 10% of the cases.[1] Occasionally, the pseudocyst extends to distant areas within the abdominal cavity or may invade a nearby anatomic structure. Direct extension into the stomach infrequently is noted both radiographically and clinically.[2] The thickening of the stomach wall offers resistance for direct compression or infiltration. In this patient, the partial gastrectomy and secondary weakening of the gastric muscle wall could be the major contributory factor for these unusual findings.

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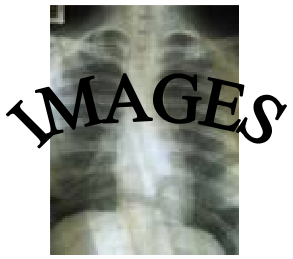
Keywords: pancreatic pseudocyst, pancreatitis, gastrectomy, case report



Leukostasis

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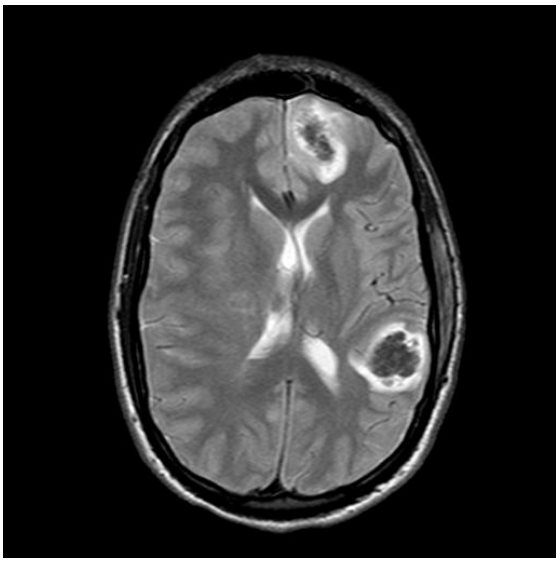

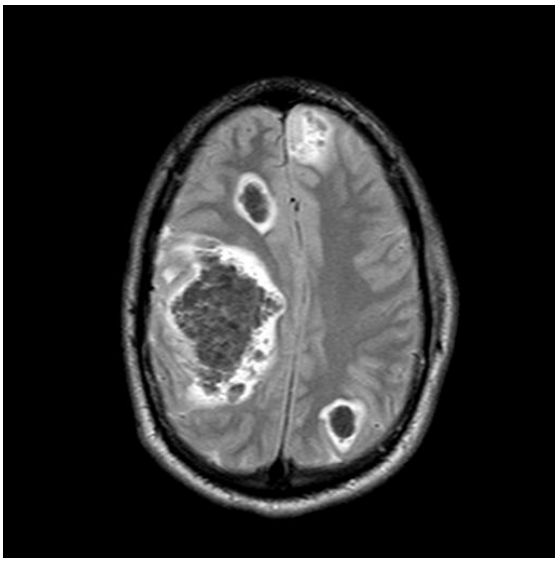

A 20-year-old male with a one-month history of headache presented for acute onset of left-sided hemiparesis. Physical examination showed a confused, agitated, and combative patient with petechiae in the lower extremities. Laboratory evaluation revealed a white blood cell count of 204,000 with 92% blast cells, hematocrit of 28.2, and platelet count of 20,000. Magnetic resonance imaging of the brain (T2-weighted) showed multiple hypo-intense lesions compatible with multi-focal hemorrhagic foci within the cortical and subcortical white matter. Flow cytometry on peripheral blood was consistent with acute myeloid leukemia (AML). Despite aggressive treatment, a repeated computed tomography scan of the head demonstrated expansion of the intracranial bleed. The patient deteriorated into brain death after 36 hours from admission.

Intracerebral hemorrhage (ICH) associated with leukocytosis is seen most commonly in AML. Severe leukostasis with both dense leukocytes and lack of mobility of the myeloblast lead to direct infiltration and rupture of small brain vessels. Unfortunately, leukapheresis and cranial irradiation do not improve survival or decrease the incidence of ICH in adults with hyperleukocytic AML.[1]

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Keywords: leukostasis, pancreatitis, acute myeloid leukemia, intracerebral hemorrhage, case report

Cardiovascular Risk and the Endocannabinoid System

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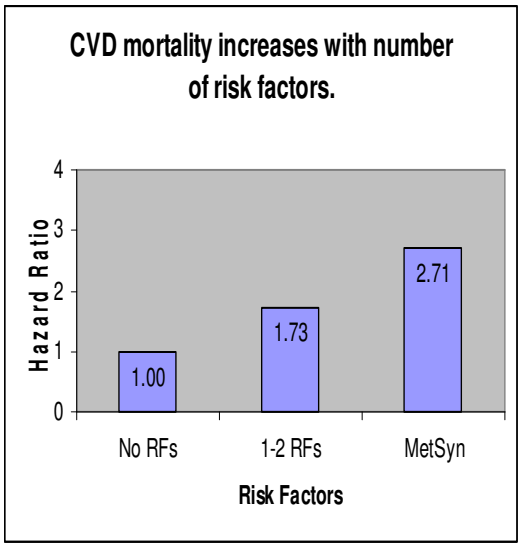
A number of studies and analyses have illustrated the increased rate of cardiovascular disease conferred by multiple risk factors.[1,2] Up to now, however, the primary focus for addressing cardiovascular risk has been the treatment of each risk factor separately (e.g., LDL cholesterol, hypertension, and diabetes). Major gaps in our overall understanding of the ways in which these individual risk factors act together in creating an increased cardiovascular risk exist. Still, an emerging focus on the additive nature of multiple risks has led to an effort to reduce the overall number of risk factors and evaluate the relative strength of the effect of each on the others. The development of the metabolic syndrome (defined as the presence of three or more of five individual risk factors including elevated triglycerides, low levels of HDL-C, elevated blood pressure, expanded waist circumference, and borderline elevated glucose or diabetes) represents a notable example of a more global risk factor assessment (Figure 1).[3]

The Role of Visceral Adiposity

In searching for a place to start, obesity, perhaps more than any other single risk, plays the central role in overall cardiometabolic risk. In fact, obesity appears to be a major driver of insulin resistance, which in turn, can result in dyslipidemia, hypertension, inflammation, and even glucose intolerance and diabetes.[4] A case can be made that obesity is the risk factor that drives the entire metabolic syndrome.

Figure 1. Cardiovascular mortality increases with number of risk factors.

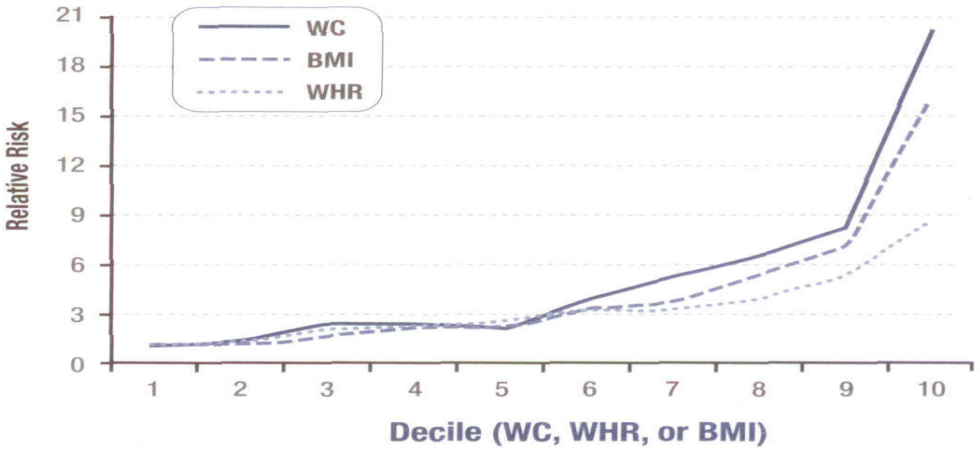


It is important to recognize that not all fat is created equal. The International Diabetes Foundation (IDF) identified *visceral* obesity as the most critical cardiovascular risk.[5] Abdominal obesity appears to be a greater predictor of non-insulin-dependent diabetes mellitus (NIDDM) than overall obesity (Figure 2).[6] Indeed, visceral adiposity (not overall obesity) appears to be the primary predictor of both NIDDM and the metabolic syndrome in general.[7-9]

The Endocannabinoid System

In the midst of research on cardiovascular risks and visceral adiposity, a previously little known physiologic system has been identified that appears to play a major role in the co-regulation of interactions between fat and other physiologic systems. First suggested during the recognition of the

Figure 2. Age-adjusted relative risk of Type 2 diabetes by baseline waist circumference (WC), waist-to-hip ratio (WHR), and BMI deciles.



appetite-inducing properties of the cannabinoid, Cannabis Sativa,[10] the endocannabinoid system (ECS) was not well understood until the discovery of endogenous cannabinoids (ECs) and their receptors. Despite this late start, the last twenty years has seen a remarkable increase in researchers' understanding of the structure and vital function of the ECS.

The initial discovery of where cannabinoids bind to sites in the brain of rats was followed by the discovery of two endogenously-produced cannabinoids, anandamide and 2-arachinodonyl glycerol. The binding sites for these cannabinoids include the CB1 receptor, which is involved in the regulation of energy homeostasis, and the CB2 receptor, which is found primarily in the immune system and is not thought to play a significant role in feeding or energy balancing.[11]

Once these basic elements of the ECS were described, research turned to how the system functions. The CB1 receptors are activated by endocannabinoids, which are arachidonic-acid derivatives that are synthesized as needed, then bind to the CB1 receptors. Upon binding, they activate the system, then rapidly degrade. Endocannabinoid production and binding with CB1 receptors modulates energy balance and metabolism in the brain and also is active in adipose tissue, the liver, skeletal muscle, and the gut.[12]

Centrally, CB1 activation stimulates food intake directly by increasing the motivation to eat and the sensory appeal of food.[13] In addition, CB1 receptors in the hypothalamus appear to participate in hunger and satiety signaling.[13] The direct evidence of this central activation of the system came with the injection of the endocannabinoid anandamide directly into the brain of pre-fed and satiated rats. When the ventromedial hypothalamus was stimulated in this fashion, the rats significantly overate.[14] Having demonstrated that central nervous system (CNS) stimulation can bolster food intake, genetically engineered CB1 receptor-deficient mice were underfed, and unlike their normal wild-type littermates, the receptor-deficient mice ate far less when exposed to food.[15] When rimonabant, a CB1 antagonist, was added to the daily regimen of obese, overfed mice, body

weight was reduced. This confirmed that the endocannabinoid system, when stimulated, plays a critical role in the development of obesity.[15]

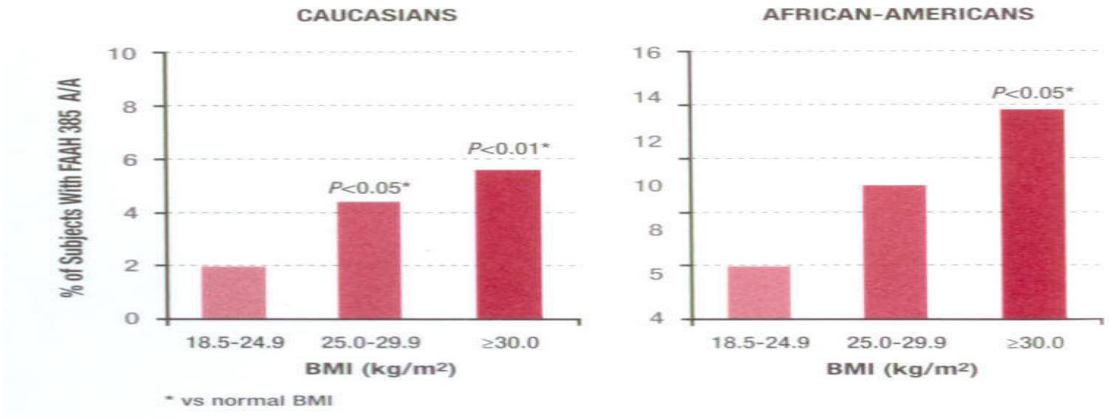
In addition to the effects on the CNS, the actions of the endocannabinoid system have been found in peripheral tissues, where ECS stimulation is believed to modulate a number of other mechanisms. In the liver, CB1 stimulation appears to facilitate the formation and storage of triglycerides and to promote lipogenesis and the formation of fatty liver.[16] In the GI tract, cannabinoid and ghrelin levels increase together in response to fasting. When the endocannabinoid antagonist rimonabant is intraperitoneally injected, it has the effect of decreasing endocannabinoid and ghrelin levels, thereby reducing hunger signals.[16] In addition to these effects, blockade of CB1 receptors appears to upregulate the critically important plasma protein adiponectin positively, which in turn decreases hyperinsulinemia and weight.[17]

ECS in Humans

Not surprisingly, considering these animal studies, human data indicate that higher levels of endocannabinoids are found in obese humans when compared to their lean counterparts. In fact, compared to lean subjects, both anandamide and 2-AG have been found in significantly higher quantities in obese women.[18] Further studies need to be conducted to ensure these findings apply to men. It is interesting, and perhaps not unexpected given the difficulty of maintaining weight loss, that endocannabinoid levels have not been found to decrease during weight loss.

Further evidence of the action of the ECS in promoting human obesity comes from the discovery of a genetic deficiency caused by a missense mutation in fatty acid amide hydrolase (FAAH; an enzyme that helps degrade endocannabinoids). With a deficiency in FAAH, higher circulating levels of the endocannabinoids and a significant increase in the likelihood of obesity are noted (Figure 3).[19] In addition, a study comparing levels of endocannabinoids in human subcutaneous and visceral fatty tissues revealed the presence of higher levels of endocannabinoids in visceral fatty tissue, reinforcing the importance of the ECS in preferentially modulating the most important human depot of fatty tissue: visceral fat.[20]

Figure 3. Percentage of subjects with increasing percentage presence of FAAH missense by Body Mass Index.



The ECS in the Development of Cardiometabolic Risk

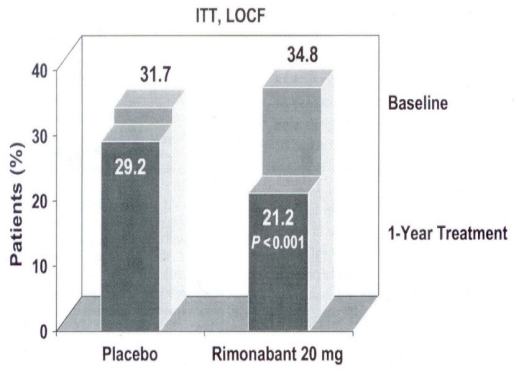
Emerging evidence suggests that stimulation of the ECS centrally and peripherally leads to increased food intake, increased waist circumference (indicative of increased visceral adiposity), elevated triglycerides, decreased HDL-cholesterol, and insulin resistance. Recent phase 3 trials on the ECS antagonist rimonabant have demonstrated its ability to block the central and peripheral effects of the ECS. In four phase 3 clinical trials, rimonabant was not only associated with significant weight loss, but also with a decreased waist circumference and improved glucose tolerance.[21-24] Interestingly, the improvement in HbA_{1c} in the Rimonabant-in-Obesity (RIO) Diabetes trial was much greater than would have been predicted by the degree of weight loss achieved.[21]

With additional benefits noted in triglyceride levels, HDL-C and blood pressure[21-24], rimonabant achieved a significant decline in a number of individual risk factors and in the prevalence of the overall metabolic syndrome (Figure 4).[23] However, a major obstacle to approval of rimbonant in the United States is the Food and Drug Administration Advisory Committee's recommendation that approval be delayed, pending resolution of safety issues concerning increased levels of depression and suicide ideation.[25]

Summary

In the search for better ways to prevent and treat cardiovascular disease, notation of multiple risk factors and the central role that visceral adiposity plays in modulating overall risk are important. The challenge of reducing this risk has led to a search for ways to reduce adiposity consistently and efficiently while positively impacting other classic cardiovascular risks. The discovery of the ECS and the ability to block the effects of its over-stimulation gives a new approach to reduce multiple cardiometabolic risk factors significantly. With continued efforts to improve the lifestyles of our patients, combined with exciting new pathways for pharmacologic intervention, we can achieve the reduction in cardiovascular risks needed to tame the epidemic of obesity-mediated cardiovascular disease.

Figure 4. Change from baseline in metabolic syndrome status at one year.



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Keywords: cardiovascular disease, endocannabinoid, risk factors, obesity