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

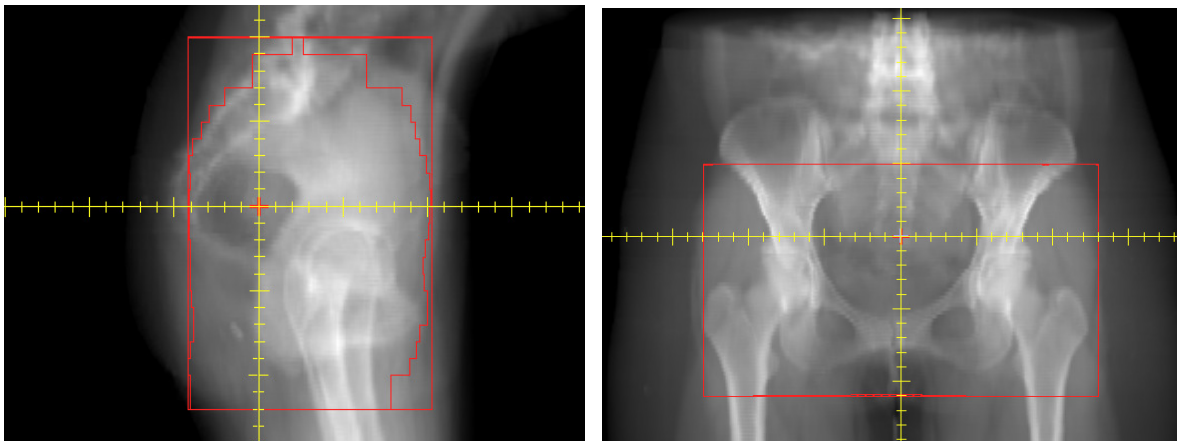

Figure 1. Lateral and anterior-posterior field images.

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.

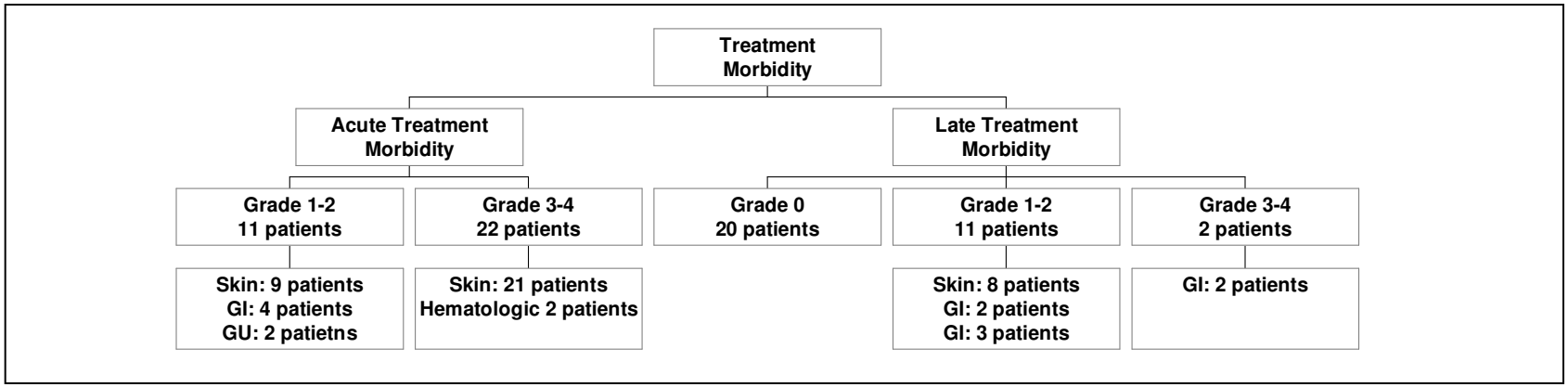

Figure 2. Treatment morbidity.

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

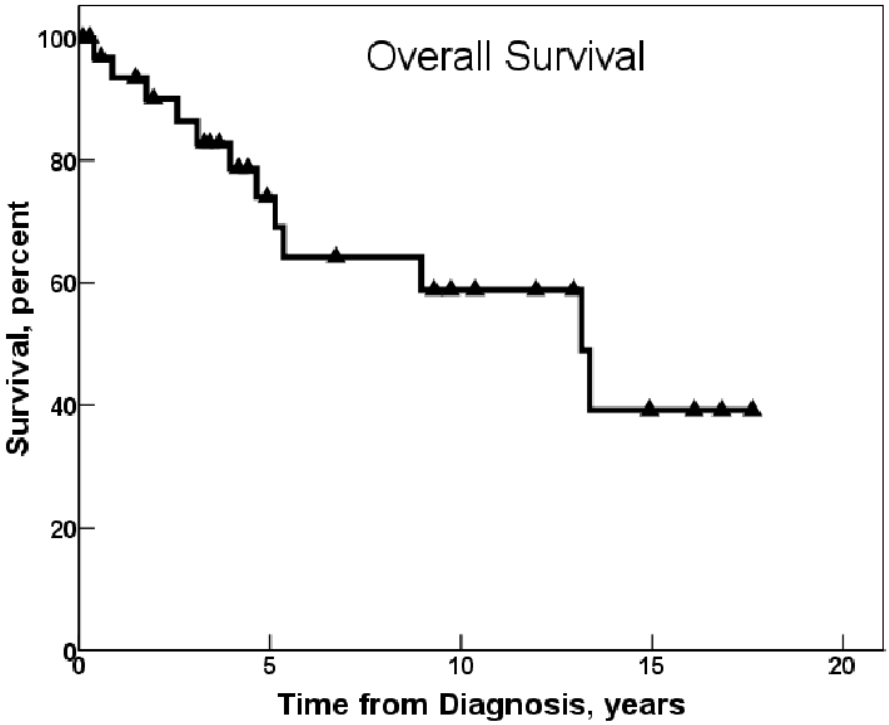

Figure 3. Kaplan-Meier overall survival curve. The marks indicate censored patients.

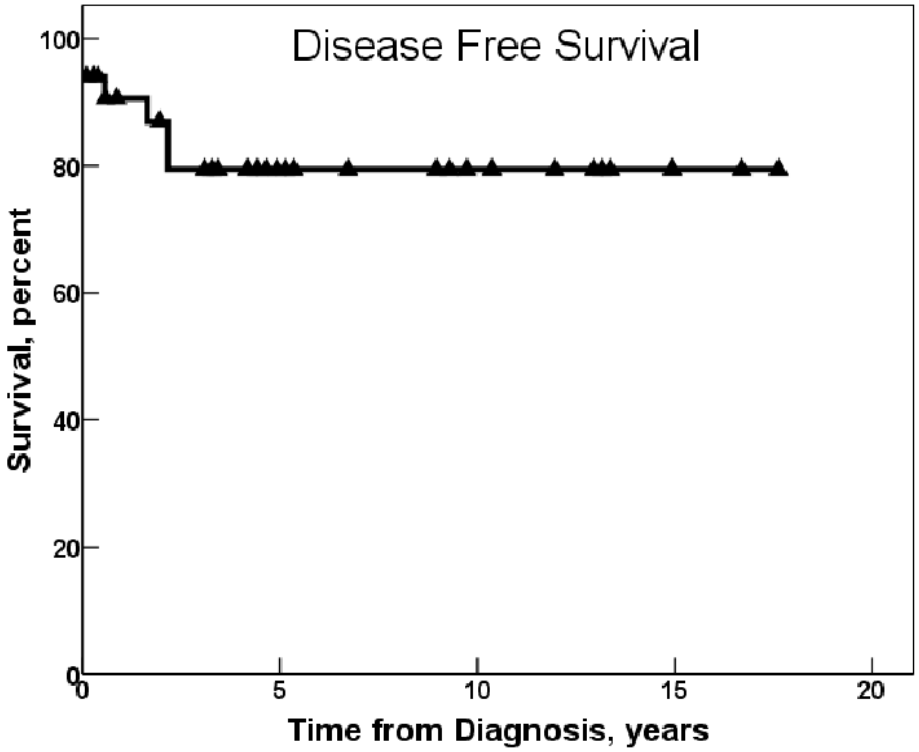

Figure 4. Kaplan-Meier disease free survival curve. The marks indicate censored patients.

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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