original article

Anal canal carcinoma treatment results: the experience of a single institution

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BACKGROUND AND OBJECTIVES: Prior to the mid-1980s, the treatment of choice for anal cancer was abdominoperineal resection. Currently, combined chemoradiation is the standard of care. Or objective was to analyze results of treatment for anal canal carcinoma treated with combined chemoradiation.

DESIGN AND SETTING: Retrospective review of data in local cancer registry at King Faisal Specialist Hospital and Research Centre (KFSHRC) from a 12-year period (1993 to 2005).

METHODS: We identified patients with confirmed diagnosis of anal canal squamous cell carcinoma.

RESULTS: Of 40 patients identified, 33 were considered eligible for our analysis. All patients were treated by concurrent chemoradiation with mandatory treatment break (MTB) There were 10 (30%) local recurrences. Five-year progression-free survival (PFS) was 50.9%; overall survival (OS) at 5 years was 73.4%. Patients with stage II disease had a median PFS period of 10 years, with no relapses until their last follow-up. There was no statistically significant difference in PFS between patients with stage IIIA disease and those with stage IIIB disease—44.7% and 45%, respectively (P=.8). Five-year PFS according to 'T' stages was as follows: T1, 66%; T2, 71%; T3, 59%; T4, 30% (P>.05). The 5-year colostomy-free survival (CFS) for all patients was 74%. Distant metastases were observed in 4 patients.

CONCLUSION: Combined chemoradiation in treatment of anal cancer is effective in terms of local control and sphincter preservation. Five-year estimates of PFS, OS, as well as CFS, in patients treated with a MTB were surprisingly comparable to those determined in most non-MTB series. However, we reported a higher local failure rate, for which we are reevaluating our treatment protocol.

Anal carcinoma is a relatively rare malignancy, accounting for only 1.6% of cases of gastrointestinal tract cancer in the U.S.[1] Squamous cell carcinoma is the most common histology among tumors arising in the anal canal.[2] Variants of squamous cell carcinoma, such as transitional cell carcinoma, basaloid carcinoma, large cell carcinoma, mucoepidermoid carcinoma and cloacogenic carcinoma, exhibit a natural history, patterns of spread and prognosis similar to those of squamous cell carcinoma.[2] Prior to the mid-1980s, the treatment of choice for anal cancer was abdominoperineal resection (APR), a procedure involving removal of the anus and rectum as well as their draining lymph nodes, resulting in a permanent colostomy. The 5-year survival rate after APR for anal carcinoma is in the range of 40% to 70%, with worse outcomes for those with larger tumors and nodal metastases.[3] APR is now reserved as salvage therapy for those individuals with persistent disease after combined chemoradiation. The use of chemotherapy in combination with radiotherapy was first evaluated in the early 1970s by a group at Wayne State University. Working on the observation that the use of fluoropyrimidine-based chemotherapy potentiates radiation, Nigro and colleagues used preoperative 5-fluorouracil (5-FU) (1000 mg/m^2 continuously on days 1-4 and 29-32) and mitomycin (10-15 mg/m^2 on day 1) in combination with moderate-dose (30 Gy) external beam radiation therapy (EBRT).[4] The first three patients treated with this regimen had no evidence of residual disease at the time of surgery, raising the question of whether combined chemoradiation therapy obviated the need for APR. This approach was further evaluated in three phase III randomized controlled trials.[5-7] All three trials compared radiotherapy

with combined chemoradiation, but to date there has been no randomized trial to compare APR with chemoradiation. However, chemoradiation is now considered the standard of care, as the patient is saved from having a permanent stoma. Mitomycin-based chemotherapy is still the standard of care, especially after the results of the RTOG 98-11, which showed that cisplatin-based chemotherapy is not superior to mitomycin and has even worse colostomy-free survival.[8] The aim of this retrospective review was to evaluate and analyze our experience between 1990 and 2006 in the treatment of anal canal squamous cell carcinoma with concurrent chemoradiation.

METHODS

This was a retrospective analysis of patients with the diagnosis of squamous cell carcinoma of the anal canal treated from January 1993 to December 2005 (12 years) at King Faisal Specialist Hospital and Research Centre (KFSHRC). Patients were identified in our local cancer registry. This study was approved by the Research Accreditation and Ethical Committee at KFSHRC.

All pathological specimens referred from other hospitals were reviewed at our institution. Information taken from each patient chart included the following: gender, date of birth, nationality, tumor location, tumor size, nodal status, total radiation dose, dose per fraction, tumor control status, date of recurrence if any, date of last follow-up and records for radiation complications. Late radiation-complications were scored according to the Radiotherapy Oncology Group (RTOG) and European Organization of Research and Treatment of Cancer (EORTC) common toxicity criteria. 9 All patients had a biopsy for diagnosis on the grounds that it was done initially upon referral. Abdominoperineal resection was used as salvage treatment only.

Radiotherapy consisted of two courses with a gap of 2 weeks, in 2 phases. Phase I treatment comprised whole pelvic radiation with the upper limit at the level of L5-S1, by means of two parallel opposing fields to a total dose of 24 Gy in 12 fractions over 17 days, followed by a period of rest of 2 weeks. Phase II, which included the initial gross disease with a 3-centimeter uniform margin, comprised the use of 3-field technique (1 posterior field and 2 lateral fields) ± a boost to the inguinal region using a direct electron field E6 to E12 depending on the measured depth from the CT scan. The overall median tumor dose was 50 Gy. Most of the patients were planned to be treated using two-dimensional techniques, implementing data from diagnostic CT and/ or MRI, as the majority of patients presented early, viz., in the period during which three-dimensional treatment planning was not yet routine practice in our department. All treatments were carried out on linear accelerators with energy ranging between 6 and 18 MV depending on tumor site. The standard chemotherapy schedule consisted of two cycles with mitomycin C at 12 mg/m^2 given as bolus on day 1 of radiotherapy, and 5-fluorouracil at 750 mg/m^2 /d given as continuous infusion from day 1 to day 5. The second cycle was started on the first day of the second radiotherapy course following the mandatory break.

All patients were seen in our combined colorectal/ radiation therapy clinic 2 months after the end of treatment, and then every 3 months for the first 2 years, every 6 months in the third year and yearly thereafter. In each visit, all patients were examined thoroughly for local recurrence, using per rectal (PR) exam and/or sigmoidoscopy. Magnetic resonance imaging or CT scan was requested whenever recurrence or disease progression was clinically suspected. Recurrence was determined radiologically and/or clinically followed by biopsy. Local tumor control was reported from the date of documentation of no evidence of disease by examination and/or imaging.

All statistical analyses were performed with SPSS software (SPSS Inc, Chicago, IL, USA). Descriptive statistics are presented as number and percentage (frequency distribution). Analyses of local failure rate and survival were performed by the Kaplan-Meier method, and the log rank test was used to compare survival distribution; a P value of $<.05$ was used for determining significance.

Progression-free survival (PFS) was determined as the period from the date of initial diagnosis to the date of progression, death from any cause or to the date of last contact for nonprogressing surviving patients. Colostomy-free survival was determined as the period from date of diagnosis to the date of recurrence salvaged by colostomy. Overall survival (OS) was defined as the period from date of diagnosis to date of last follow-up or death from any cause. Potential prognostic factors for local control were assessed for statistical significance by the log-rank method for binary variables and the Cox proportional hazards model for continuous variables.

RESULTS

We identified 40 patients with a confirmed diagnosis of squamous cell carcinoma of anal canal. Seven patients were excluded from the study—three patients treated by primary surgery and four patients who refused any treatment. Patient characteristics are described in **Table 1**. Median follow-up period for all patients was 2 years (range, 2 months to 11 years). Of 40 patients, 33 were

Table 1. Characteristics of patients.

Characteristic	Number of patients (%)
Gender	
Male	20 (60.6)
Female	13 (39.4)
Mean age, range (years)	59, 28-80
T stage	
T1	4 (12.12)
T2	10 (30.3)
T3	5 (15.15)
T4	12 (36.4)
Tx	2 (6)
Nodal stage	
N0	20 (60.6)
N1	1 (3)
N2	6 (18.2)
N3	4 (12.1)
Nx	2 (6.1)
Stage	
I	0 (0)
II	5 (15)
IIIA	16 (48.6)
IIIB	12 (36.4)
Nationality	
Saudi	28 (84.8)
Non-Saudi	5 (15.2)
Symptoms	
Anal pain	3 (9.1)
Bleeding per rectum	6 (18.2)
Anal pain and bleeding	9 (27.3)
Mass	8 (24.2)
Mass and pain	7 (21.2)

considered eligible for analysis; there were 13 (39.4%) females and 20 (60.6%) males. The most common presenting symptoms were anal pain and bleeding. Mean age was 59 years (range, 28-80 years). Twelve patients had T4 disease, but most were diagnosed with N0 disease (60.6%). Thirty-one (93.3%) patients were treated with radiation therapy; all patients were treated by chemotherapy concurrently with radiotherapy. The median dose of radiation was 50 Gy. Thirty-one (94%) patients received a radical dose of radiotherapy. On account of poor performance status, 2 patients received a palliative dose of 30 Gy in 10 fractions. Sixteen patients presented with stage IIIA disease; 12 with stage IIIB; and only 5 patients with stage II disease. No stage I patients were included in this cohort. As a consequence of mandatory treatment-break protocol, more than 90% of the patients completed their radiation treatment without interruptions.

There were 10 (30%) local recurrences, all of which were within the original primary site. Five-year PFS was 50.86%; OS at 5 years was 73.4% (**Figures 1 and 2**). Patients with stage II disease (only 5 patients) had a median PFS period of 10 years, with no relapses until their last follow-up. There was no statistically significant difference in PFS between patients with stage IIIA disease and those with stage IIIB disease—44.7% and 45%, respectively (P=.8). Five-year PFS according to T stages was as follows: T1, 66%; T2, 71%; T3, 59%; T4, 30% (P>.05). The 5-year colostomy-free survival for all patients was 74%. Distant metastases were observed in 4 patients. Of these, 2 developed liver metastases; 1 peritoneal metastases; and 1 pulmonary spread. Concerning acute toxicity, based on RTOG-EORTC toxicity criteria, 19 (51.5%) were grade I, 16 (48%) were grade II, and 3 (9%) were grade III. Diarrhea was observed in 4 (12%) patients, vomiting in 7 (21%), and oral mucositis in 2 (6%). Late complications were minimal, with 1 patient developing anal canal stenosis (**Tables 2 and 3**).

DISCUSSION

Treatment for anal canal squamous cell carcinoma has changed dramatically during the past 20 years and is often considered as a model for organ-preservation treatment. Before 1980, APR was considered the standard treatment. The publishing of the results of the study by Nigro et al in 1981 elicited more interest in the combined-treatment approach, with concurrent chemoradiation.[9] They reported on three patients with squamous cell carcinoma of the anal canal who after preoperative radiation with concurrent chemotherapy achieved complete remission of the primary tumor at the time of surgery. The radiation dose was 30 Gy, and the chemotherapy was based on 5-FU and mitomycin.[10] Since then, this combined modality has been performed all over the world, and a number of phase II trials have shown local control and survival similar to those reported with radical surgery, keeping APR for salvage.[11-14] This strategy is considered standard for treatment of anal canal cancer, yet without phase III prospective and randomized trials,

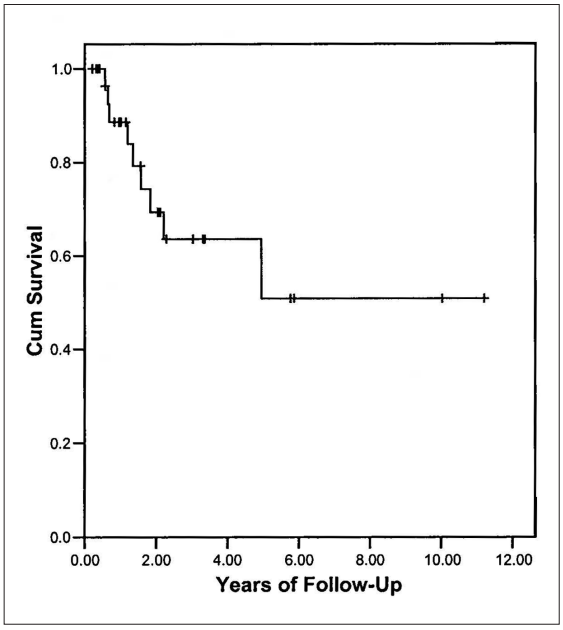

Figure 1. Five-year progression-free survival.

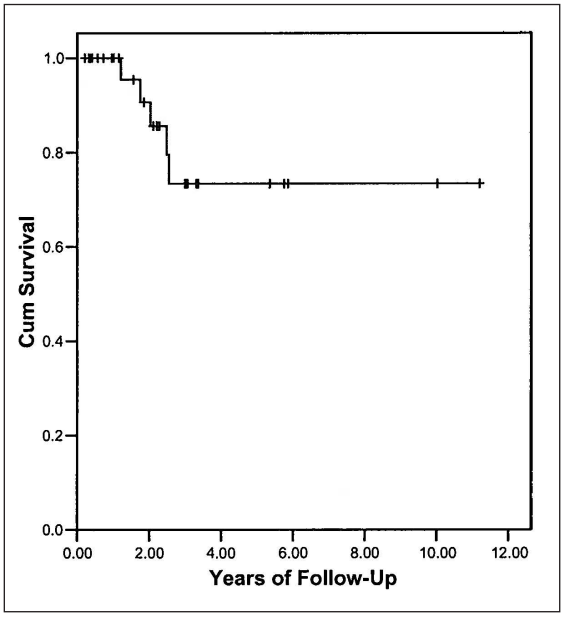

Figure 2. Overall survival at 5 years.

questions still remain, including the optimal dose volume of radiation therapy for adequate local control.[15]

The UKCCCR (UK Coordinating Committee on Cancer Research) trial reported a 3-year local failure rate of 39% in patients treated with chemoradiation.[6] The European Organization for Research and Treatment of Cancer reported an overall 5-year survival of 56% for all patients, with patients treated with combined modality therapy having a 5-year survival of slightly more than 60%.[5] The RTOG 92-08 began as a single-arm phase II trial for patients with anal cancer; the treatment protocol incorporated radiotherapy in a dose of 59.4 Gy with a chemotherapy regimen comprising 5-FU + mitomycin C with a mandatory 2-week break, which was amended after completion to evaluate the same treatment regimen without a treatment break.[16] Five-year estimates of progression-free survival and colostomy-free survival were 53% and 58%, respectively.[16] Survival in nonmandatory treatment-break cohort of RTOG 92-08 was higher compared to that in the mandatory treatment-break cohort, and was comparable to that in other series with uninterrupted treatment protocols mentioned above. However, it is important to keep in mind that the sample size in both cohorts of the RTOG 92-08 was very small. While establishing the need for mitomycin C with a radiochemotherapy protocol, the RTOG 87-044 also showed a sizable rate of 19% (radiotherapy + 5-FU + mitomycin C arm) to 30% (radiotherapy + 5-FU arm) of local regional failure. These results are comparable to our data as well as that of the RTOG 92-08. The relatively higher failure rate seen in patients with a mandatory treatment break in the RTOG 92-08 and our series could have been secondary to repair of sublethal damage or tumor repopulation.[16]

In our analysis, the local failure rate was approximately 30%. Five-year PFS was 50.86%; OS at 5 years was 73.4%. Long-term data from the RTOG experience and data reported by other authors have suggested a local failure rate of 20% to 30%, particularly for

Table 2. Acute toxicity grading.

Acute toxicity	Number of patients (%)
Grade I	19 (51.5)
Grade II	16 (48)
Grade III	3 (9)

Table 3. Treatment toxicity.

Acute toxicity	Number of patients (%)
Diarrhea	4 (12)
Vomiting	7 (21)
Mucositis	2 (6)
Late toxicity	
Anal stenosis	1 (3)

advanced T stage disease. Our results are comparable to those reported in the literature using the same chemotherapy scheme, but with different radiation therapy schedules, suggesting that our treatment strategy with chemotherapy and spilt-course radiation was still effective for local tumor control and sphincter preservation, keeping in mind, however, our small sample size. Out of 10 patients with locally recurrent disease in our cohort, 8 were salvaged with APR, whereas 2 received systemic chemotherapy following palliative colostomy.

The median dose in our analysis was 50 Gy. Dose escalation has been considered to improve the local failure rate. M. D. Anderson Cancer Center experience showed local control rates of 31%, 71% and 80% for doses of 45-49 Gy, 50-55 Gy and 55-60 Gy, respectively.[17]. Data from Massachusetts General Hospital, for patients treated with EBRT, 5-FU, and mitomycin C, with doses lower than 54 Gy, confirmed a significantly lower rate of local control when compared to a dose of 54 Gy.[18]

A combined modality of treatment for patients with anal cancer can cause morbidity due to its potential for treatment interruptions owing to gastrointestinal and dermatologic toxicities. In our cohort of patients, only 1 patient developed grade I cutaneous toxicity and there were no reported incidences of ≥ grade 3 late toxicity, which is in accordance with reports found in the literature.[16] Cummings et al reported that an interrupted course of chemoradiation produced less severe normal-tissue damage compared to an uninterrupted course of radiation.[19] Dermatologic and gastrointestinal late toxicities were also reported in 122 (42%) of 292 patients receiving chemoradiation in the UKCCCR trial.[6] Allal et al reported that morbidity correlated significantly with anatomic location of tumor and prescribed external-beam dose.[20] In addition, Hung et al reported only a 2% (3 patients) chronic toxicity in patients treated with cisplatin-based chemoradiation.[21] It is unknown if the lack of late toxicity experienced by patients treated in our series, as well as patients in RTOG 92-08, was secondary to the mandatory treatment break or other treatment-related factors.[16]

This retrospective review accentuates the fact that combined chemoradiation in treatment of anal cancer is effective in terms of local control and sphincter preservation. Five-year estimates of disease-free survival, OS and colostomy-free survival in patients treated with our mandatory treatment-break protocol were surprisingly comparable to those of most nonmandatory treatment-break protocol series; however, we reported a higher local failure compared to that in RTOG 87-04. Late toxicity was low; nevertheless, treatment breaks in anal cancer should be kept to a minimum.

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