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Intensity Modulated Radiation Therapy for the Treatment of Squamous Cell Anal Cancer with Para-aortic Nodal Involvement

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Abstract

PURPOSE: Squamous cell anal carcinoma typically presents as locoregional disease, but a small proportion of patients have para-aortic nodal involvement at initial diagnosis. Although para-aortic involvement is regarded as M1, these patients could potentially be treated definitively with chemoradiation, using Intensity Modulated Radiation Therapy (IMRT).

METHODS: Between 2001 and 2007, 6 patients with squamous cell anal cancer and para-aortic nodal involvement were treated with IMRT and concurrent infusional 5-fluorouracil and cisplatin. The primary tumor was treated with a median dose of 57.5 Gy (range 54–60 Gy), involved para-aortic, pelvic, and inguinal lymph nodes were treated with a median dose of 55 Gy (range 50.5–55 Gy), and non-involved nodal regions were treated with a median dose of 45 Gy (range 43.5–45 Gy).

RESULTS: After a median follow up of 25 months, none of the patients had a recurrence at the primary tumor, pelvic/inguinal nodes, or para-aortic nodes, while 2 patients developed distant metastases to the liver. Four of the 6 patients are alive. The 3-year actuarial locoregional control, distant control and overall survival rates were 100%, 56% and 63%, respectively. Four of the 6 patients developed grade 3 acute gastrointestinal toxicity during chemoradiation.

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Actual and potential conflicts of interest do not exist.

CONCLUSIONS: IMRT and concurrent chemotherapy could potentially serve as definitive therapy in anal cancer patients with para-aortic nodal involvement. Adjuvant chemotherapy may be indicated in these patients, as demonstrated by the distant failure rates. These patients need to be followed carefully due to the potential for treatment-related toxicities.

Keywords

Intensity-modulated radiation therapy; anal cancer; chemoradiation; para-aortic lymph node

INTRODUCTION

Anal carcinoma is a relatively rare gastrointestinal malignancy with 4650 new cases expected in 2007 [1]. Squamous cell carcinoma is the most common histological form of anal carcinoma and typically presents with locoregional involvement [2]. However, in rare circumstances, patients present with distant metastatic involvement which has been associated with worse survival outcomes [2–5]. Para-aortic lymph node involvement is considered M1 disease and thus these patients are classified as stage IV according to the American Joint Committee on Cancer staging criteria [6]. Given the limited number of M1 (Stage IV) cases and the even rarer para-aortic cases reported in the literature, the optimal treatment approach for anal cancer patients with para-aortic nodal involvement has not been established.

The recent adaptation of intensity modulated radiation therapy (IMRT) to anal cancer offers a potential advancement in the treatment of anal cancer patients. Recent dosimetric and clinical studies have indicated that IMRT yields improved organ sparing, similar local control rates and lower rates of acute toxicity, compared to conventional radiation techniques [7–10]. The use of IMRT could offer the opportunity for definitive chemoradiation in anal cancer patients with para-aortic nodal involvement. The goal of this study was to determine the rates of toxicity, locoregional control, distant control and survival in anal cancer patients with para-aortic nodal involvement, treated with IMRT and concurrent chemotherapy at a single institution.

METHODS AND MATERIALS

This study included all patients (N=6) with newly diagnosed squamous cell carcinoma of the anal canal, with involvement of para-aortic lymph nodes, who were treated with IMRT and concurrent chemotherapy at M. D. Anderson Cancer Center between June 2001 and August 2007. Involvement of para-aortic lymph nodes was based on computed tomography (CT) imaging. No patient underwent a biopsy to confirm the presence of para-aortic involvement. However, in all cases, expert radiologists reported involvement of the para-aortic nodes based on the size, appearance and distribution of the nodes [11]. A review of hospital and radiotherapy records of these patients was performed. The M. D. Anderson Institutional Review Board approved this study.

Pretreatment evaluation

Pretreatment evaluation included history and physical examination including digital rectal examination, proctoscopy, chest radiograph, and abdominopelvic CT scan. All biopsies of the primary tumor were reviewed by M. D. Anderson gastrointestinal pathologists at the time of diagnosis. Staging of all patients was based on the AJCC TNM system, 6th edition [6].

Simulation and Treatment

Patients were treated with definitive concurrent chemoradiation over a 6 week period without planned breaks in therapy. All patients underwent CT-based simulation in the supine position. For each patient, three separate clinical treatment volumes (CTV's) were delineated. CTV1 included the primary anal tumor with a margin, CTV2 included any involved pelvic, inguinal and para-aortic nodes with a margin, and CTV3 included the pelvic (mesorectal, presacral, internal and external iliac) and inguinal regions, as well as the para-aortic region, at least to the level of the involved nodes. The primary tumor (CTV1) was treated with a median dose of 57.5 Gy (range 54–60 Gy), involved para-aortic, pelvic, and inguinal lymph nodes (CTV2) were treated with a median dose of 55 Gy (range 50.5–55 Gy), and the nodal regions at risk (CTV3) were treated with a median dose of 45 Gy (range 43.5–45 Gy). Radiation therapy was administered in 27–30 fractions, with CTV1 receiving 183–200 cGy fractions, CTV2 receiving 183–187 cGy fractions and CTV3 receiving 150–167 cGy fractions. All patients were treated with IMRT, using 6 MV photons, with a median of 16 (range 11–18) beams. Five of the six patients completed the entire prescribed course using IMRT, while one patient was switched to a four-field approach for the last 6 fractions, after completing 21 fractions of IMRT treatment, due to grade 3 acute gastrointestinal toxicities. Figure 1 demonstrates the representative target volumes and isodose curves for the pelvic and para-aortic nodal regions.

During the 6 week course of radiotherapy, all patients received concurrent chemotherapy with 5-fluorouracil (5-FU) and cisplatin via protracted venous infusion, 5 days each week. The 5-FU dose was 250 mg/m²/day and the cisplatin dose was 4 mg/m²/day, in each patient.

Follow-up

Patients were seen on a weekly basis during the 6 week treatment phase. After treatment was completed, patients were seen every 4–6 weeks until complete response was confirmed. Then follow-up was at 3–4 months for the first 2 years, and every 6 months thereafter. The median follow-up was 25 months (range 6–40 months). In addition to a history and physical exam at each follow-up visit, patients had an annual chest X ray and abdominopelvic CT scan. Biopsies were performed on patients when clinically suspicious persistent lesions or mucosal ulcerations were found on physical examination or imaging. No patient was lost to follow-up. All follow-up information evaluated for this study was obtained from the hospital and radiotherapy records.

Statistical Analysis

All statistical analyses in terms of locoregional control, distant control, and overall survival were estimated by Kaplan-Meier actuarial methodology [12]. Locoregional failure was

defined as recurrence in the pelvis, inguinal, or para-aortic regions regardless of distant disease progression. Distant disease progression was defined as any tumor recurrence outside the treated pelvis, inguinal, and para-aortic fields regardless of the locoregional control. The presence of distant disease progression was confirmed based on pathology reports for patients that underwent biopsy for suspicious radiological findings on follow-up CT scans. Acute and late toxicity was evaluated and graded at each patient encounter using the Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE). All data was computed using SPSS (SPSS for Windows, Rel. 15.0.0 2006. Chicago: SPSS, Inc.)

RESULTS

Patient Characteristics

Between 2001 and 2007, 6 patients met the inclusion criteria of squamous cell carcinoma of the anal canal with para-aortic involvement, treated with definitive IMRT and concurrent chemotherapy. The ages of the patients ranged from 48 to 74 years, with a median age of 51 years. Five of the six patients were female and all six patients were Caucasian. The median size of para-aortic lymph nodes was 1.8 cm (range 1.3–2.3 cm). All six patients had multifocal pelvic and/or inguinal adenopathy, in addition to para-aortic adenopathy.

Recurrence and Survival

Following chemoradiation, 5 patients had a marked decrease in the size of the para-aortic nodes, while 1 patient had a stable para-aortic node. After a median follow-up of 25 months (range 6–40 months), none of the patients had a recurrence at the primary tumor, pelvic/inguinal nodes, or para-aortic nodes. Hence, the 3-year actuarial locoregional control rate was 100%. Two patients developed distant metastases to the liver, 4 and 34 months after chemoradiation, respectively. The 3-year actuarial distant control rate was 56%.

Four of the 6 patients are alive, with follow-up intervals of 9, 35, 38, and 40 months. One patient died due to distant metastases 15 months after completing chemoradiation, and one patient who had chronic Hepatitis C died due to complications from end stage liver disease 6 months after completing chemoradiation. The 3-year actuarial overall survival rate was 63%.

Toxicity

Four of the six patients developed grade 3 acute toxicity during chemoradiation. The specific grade 3 toxicities included nausea/vomiting (N=4), diarrhea (N=4), dehydration (N=3), small bowel obstruction (N=2), neutropenia (N=2), anemia (N=2) and leukopenia (N=1). All four patients with grade 3 toxicity required hospitalization, and the hospitalizations were primarily for gastrointestinal toxicity. Five of the six patients had grade 2 skin toxicity but there were no occurrences of grade 3 or greater skin toxicity.

The radiation treatment course was interrupted in 3 patients (breaks of 1 day, 1 day, and 2 breaks of 3 days, respectively). Five of the six patients completed the entire prescribed course of IMRT, while one patient was switched to a four-field approach for the last 6 fractions after completing 21 fractions of IMRT treatment. Chemotherapy was interrupted in 2 patients for 3 and 8 days, respectively, and chemotherapy was discontinued during the

second week in one patient. Late toxicities included grade 3 radiation proctitis in 1 patient and grade 3 pancytopenia in 1 patient.

DISCUSSION

Para-aortic involvement has historically been regarded as metastatic or M1 disease in patients with squamous cell anal carcinoma. However, our study indicates that such patients could potentially be treated with a definitive approach. In this series of 6 patients with para-aortic nodal involvement treated with IMRT and concurrent chemotherapy, no patient had a locoregional failure in the pelvic or para-aortic region. Furthermore, the actuarial overall survival rate (63%) also appeared promising. To our knowledge, our study represents the first effort to propose a definitive treatment for anal cancer patients with para-aortic nodal involvement.

Although IMRT and concurrent chemotherapy resulted in excellent locoregional control, two of the 6 patients developed distant metastases, and the 3-year actuarial distant control rate was only 56%. Adjuvant chemotherapy could potentially improve distant control in these patients. However, the role of adjuvant chemotherapy in anal cancer remains unknown, and there is no clear evidence that adjuvant chemotherapy improves outcomes. The recently completed Anal Cancer Trial II (ACT II) has investigated the role of adjuvant chemotherapy, but the results of this study are not yet available [13]. Nevertheless, since patients with para-aortic nodal involvement appear to have a high rate of distant failure, these patients could potentially benefit from adjuvant systemic therapy.

Four of the six patients in this study developed grade 3 acute toxicity during chemoradiation. The most common toxicities included nausea/vomiting and diarrhea. The rate of acute gastrointestinal toxicity in this study appears much higher than the 15% grade 3+ gastrointestinal toxicity reported in anal cancer patients treated with IMRT to the pelvis alone [10]. Treatment of the para-aortic region in addition to the pelvic region requires the use of large radiotherapy fields, resulting in radiation dose to normal structures such as small bowel. While IMRT can reduce radiation dose to normal structures, the rate of acute toxicity was high in this study, in spite of using IMRT. Better optimization of IMRT treatment plans may help in reducing acute and late toxicity. In this study, we used dose constraints to minimize the volume of small bowel receiving ≥ 45 Gy. However, recent studies have shown that the risk of acute toxicity is associated with the volume of small bowel receiving relatively low doses of radiotherapy, such as 5 Gy or 15 Gy [14,15]. Hence, IMRT plans should be designed not only to minimize the volume of small bowel receiving high doses of radiotherapy, such as 45–50 Gy, but also to reduce the volume of small bowel at low dose levels. Moreover, patients need to be carefully monitored for toxicity while undergoing chemoradiation. Clinical anticipation and aggressive supportive care could potentially help mitigate toxicities in these patients. One patient in this study developed pancytopenia as a late toxicity; hence, efforts should also be made to minimize bone marrow dose while developing the IMRT treatment plans, since IMRT can potentially increase the amount of bone marrow exposed to radiation.

All patients in this study received concurrent chemotherapy with 5-FU and cisplatin. A retrospective study from our institution showed that anal cancer patients treated with concurrent 5-FU and cisplatin had outcomes comparable to that reported in patients treated with concurrent 5-FU and mitomycin C [16]. In the recently published Radiation Therapy Oncology Group (RTOG) 98–11 trial, 682 anal cancer patients were randomized to receive either induction chemotherapy with 5-FU and cisplatin followed by radiation therapy with concurrent 5-FU and cisplatin, or no induction chemotherapy and radiation therapy with concurrent 5-FU and mitomycin C [17]. Patients in the 5-FU/mitomycin C arm had a significantly lower colostomy rate than patients in the 5-FU/cisplatin arm, but there was no significant difference in the rates of overall survival or disease-free survival between the two arms. It is not known whether the difference in colostomy rate was due to the use of induction chemotherapy or due to the difference between cisplatin and mitomycin C. The ACT II trial directly compared concurrent 5-FU/cisplatin and concurrent 5-FU/mitomycin C without induction chemotherapy, and results from this trial may help clarify the optimal concurrent chemotherapy regimen for anal cancer patients [13].

Our study was retrospective and had certain inherent limitations. The follow-up was limited, and longer follow-up is warranted to determine long-term rates of locoregional control, distant control and overall survival. Para-aortic involvement was based on radiographic findings, and biopsy of the para-aortic nodes was not obtained in any of the patients. However, all 6 patients were regarded to have para-aortic nodal involvement by expert radiologists, based on the radiographic appearance, size, and/or distribution of the nodes. Positron emission tomography (PET) scans were not obtained in any of the patients. Recent studies have indicated that PET and PET-CT scans may have a role in anal cancer staging [18–20]. The number of patients in this study was small. However, we should note that anal cancer is a relatively uncommon malignancy, and anal cancer with metastatic involvement occurs in less than 10% of cases. Hence, we believe that this series of 6 patients constitutes a significant addition to the literature.

In conclusion, IMRT and concurrent chemotherapy could potentially serve as definitive treatment in patients with squamous cell anal cancer and para-aortic nodal involvement. Adjuvant chemotherapy may be indicated in these patients, as demonstrated by the distant failure rates. These patients need to be followed carefully due to the potential for treatment-related toxicities, and investigations are warranted into reducing toxicity. Finally, multi-institutional efforts are needed to determine the optimal treatments for these patients.

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Figure 1: Abdominal (a) and pelvic (b) axial CT images demonstrating the dose distribution in a patient treated with IMRT for anal cancer with para-aortic nodal involvement. The primary tumor was treated with a dose of 60 Gy, involved para-aortic and pelvic lymph nodes were treated with a dose of 55 Gy, and the nodal regions at risk were treated with a dose of 45 Gy. The primary tumor and involved para-aortic nodes are shown in red, CTV1 is shown in cyan, CTV2 is shown in green, and CTV3 is shown in blue and khaki (See text for definitions of CTV's).