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Impact of post-radiation biopsies on development of fistulae in patients with cervical cancer

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HIGHLIGHTS

- A significant association was found in our data between invasive procedures such as cervical biopsies and subsequent fistula development.
- The overall yield for cervical biopsies is low.
- Careful clinical observation is a better approach to differentiate recurrent tumor versus radiation-related change.

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ABSTRACT

Objective. In the post-radiation patient, late vascular sequelae and fibrosis predispose women to poor tissue healing, such that small tissue injuries could theoretically evolve into much larger ones such as fistulae. We sought to determine if a correlation exists between invasive procedures such as post-treatment biopsies and the subsequent development of gynecologic fistulae.

Methods. A retrospective review was performed evaluating all patients treated for cervical cancer at our institution between 1997 and 2010. Biopsies or pelvic surgeries were included if performed within the radiated field, and evaluated in a multivariate predictive model for development of gynecologic fistulae.

Results. Out of 325 total patients, 27 patients with fistulae were identified (8.2%). 14 fistulae (51.9%) were considered toxicity-related, 6 (22.2%) resulted from primary disease, and 7 (25.9%) were attributable to recurrent disease. Eighty-nine patients underwent an invasive procedure (55 biopsies and 34 pelvic surgeries). Recurrent and/or residual cancer was found in 28 (31.5%) specimens, and of the 61 patients who underwent an invasive procedure and were not found to have evidence of recurrent disease, 9 (14.8%) subsequently developed a fistula at a median 3.08 months. An elevated dose of radiation to the rectum (OR 1.001 for dose >72 Gy, $p = 0.0005$), advancing tumor stage (OR 5.38 for stage III, OR 10.47 for stage IV, $p = 0.0288$), and a post-radiation biopsy (OR 5.27, $p = 0.013$) were significantly associated with fistula development.

Conclusions. Performing a biopsy in an irradiated field is associated with a relatively low yield and significantly contributes to the risk for fistula development.

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Introduction

Fistulae are perhaps the most feared late treatment-related toxicities of radiation following the management of gynecologic malignancies. Patients suffer significant physical, social and psychological distress, which negatively impacts their quality of life due to symptoms of leaking urine or stool, persistent bleeding, increased susceptibility to infections, and pain [1–4]. This is compounded by the fact that a fistula occurring in irradiated tissue is rarely able to be successfully repaired. Most surgical treatments are palliative in the form of fecal or urinary diversion, leaving patients with a permanent colostomy or ileostomy, respectively.

Incidence rates for treatment-related fistulas are estimated between 1 and 4% for all-comers. Some series suggest that among more advanced stages rates can be as high as 22–48% [1–4]. There is no limit to the at-risk period, as fistulas occurring following pelvic radiation therapy (RT) have been documented up to 30 years following treatment [1]. Previous series have noted a variety of risk factors, but common predictors tend to include advancing tumor stage, previous pelvic RT, the use of radical surgery, active smoking, and elevated doses of RT delivered to the rectum [2,3,5,6].

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Although controversial, pelvic RT is considered a primary cause for the development of a delayed treatment-induced fistula. The poor wound-healing characteristics that increase susceptibility to fistula development can largely be attributed to the small and medium sized blood vessel sclerosis, relative tissue hypoxia, and soft tissue fibrosis that occurs following RT [7,8]. These late effects can also be responsible for the mucosal changes and occasional bowel injuries that can mimic residual/recurrent tumor. A frequent consideration is to biopsy to evaluate for recurrence. In many cases, the pathologic finding is "post-radiation change without evidence of malignancy." Most clinicians would agree that pelvic surgery following RT carries increased risk for fistulization. It may be less recognized that a biopsy in a radiated field might carry similar risk. As a tissue becomes increasingly deoxygenated and wound healing impaired, a biopsy could potentially initiate a cascade of tissue injury evolving into fistula.

A review was performed of patients treated at our institution for cervical cancer, specifically identifying those women who were diagnosed with a gynecologic fistula following pelvic RT. We sought to develop a predictive model of risk factors, particularly focusing on the impact of invasive procedures such as a biopsy or pelvic surgery.

Methods

Patient selection

A retrospective review was performed evaluating all patients treated for cervical cancer at the University of Kentucky between 1997 and 2010. Identified fistulae were diagnosed clinically and characterized as resulting from "Primary Disease," "Toxicity-Related"(if a patient completed a previous course of pelvic RT and no recurrent/residual tumor could be identified locally at the time of fistula formation or during follow-up), and "Recurrent Disease." Patients who did not have a fistula at diagnosis and received definitive treatment with pelvic RT were evaluated for risk factors predictive of fistula development.

Definitive therapy

Radiation therapy most commonly consisted of a combination of whole pelvis RT followed by intracavitary brachytherapy (ICB). Whole pelvis RT commonly consists of 45 Gy delivered using 180 cGy daily for 25 fractions. Patients with adverse features such as parametrial extension, side wall involvement, or lymph node involvement may have received an additional 5.4 to 9 Gy boost (for a cumulative pelvic dose of 50.4 to 54 Gy, respectively) using external RT. Cisplatin chemotherapy is given once a week for five weeks at a dose of 40 mg per meter squared. Low dose rate brachytherapy (LDR) was given prior to an institutional transition to high-dose rate brachytherapy (HDR) and continues to be used per attending physician's preference. At our institution, HDR treatments were initiated during the 4th week of RT, and were most commonly delivered as 5 fractions of 500 cGy each to Point A if critical dose points were considered within tolerance. For patients receiving RT at another hospital, HDR was initiated after the 5th week and dosed as above. For patients having poorer performance status, treatment delay, or an inability to travel, HDR treatments were truncated to deliver 3 fractions of 700 cGy or 4 fractions of 600 cGy to Point A. All patients included in this series received brachytherapy planned using 2-dimensional imaging. For purposes of comparing radiation doses delivered, the HDR brachytherapy fractional doses were converted to equivalent doses in 2-Gy fractions (EQD2) as previously described [9]. Complete radiation records were obtained and evaluated for all patients.

Post radiation procedures

Post-radiation procedures were identified separately as any biopsy or surgery that was performed within the irradiated field after definitive therapy. A post-radiation biopsy was included in our analysis only if it preceded the clinical diagnosis of a fistula. Biopsies obtained directly from the cervix or upper vaginal mucosa, posterior bladder wall at time of cystoscopy and anterior rectal wall at time of endoscopic exam were included. Biopsies performed at the time of fistula diagnosis to rule out recurrent malignancy were not considered in our predictive model. Surgeries included in this analysis consisted of post-radiation hysterectomy, exploratory laparotomy with bowel resection, staging and debulking, or lysis of adhesions. Any surgery performed at the time of fistula diagnosis such as a diversion was not included in the final model. For purposes of comparison, biopsies and surgeries were considered separate for the association with development of a fistula.

Statistical analysis

Clinical and pathologic variables were compared between groups using chi-square and one-way ANOVA as appropriate. Patients who developed a fistula as a result of primary disease were not included in the predictive model. A forward selection multivariate Cox-proportional hazards model was performed to identify significant predictors for fistula development following RT ($n = 21$) among the total number of irradiated patients ($n = 325$). Predictors included in this model were body mass index (BMI), cumulative doses to Point A and ICRU bladder and rectal points, smoking history, tumor stage, histologic grade, type of brachytherapy (HDR vs LDR), post-radiation biopsy, post-radiation surgery, local tumor recurrence, high risk medical comorbidities (coronary artery disease, diabetes mellitus, or chronic obstructive pulmonary disease), and the presence of a high grade (≥grade 3 or higher) acute GI or GU toxicity during treatment. Risk factors were considered significant if the 2-sided p-value was <0.05. All calculations were performed using SPSS, version 19.0 and SAS version 9.3.

Results

After a median follow-up of 55 months, 27 of 325 patients (8.2%) patients were identified who developed a fistula: 6 (22.2%) resulted from primary disease, 14 (51.8%) were toxicity-related, and 7 (25.9%) were diagnosed in the setting of recurrent disease. Fistula types included enterovaginal fistula (5 patients), vesicovaginal (7 patients), rectovaginal (8 patients), and combined vesicovaginal and rectovaginal fistula (7 patients). Baseline characteristics of these patients compared to the entire patient population can be found in Table 1. Noteworthy characteristics are as follows: nearly two-thirds of patients who developed a fistula reported current or previous smoking history; 25.9% had coexistent medical comorbidities; 92.6% presented with bulky primary tumors with maximal tumor dimensions in excess of 4 cm; almost half were of high histologic grade; and parametrial invasion was present in 85.1% of cases. Those patients with a fistula due to primary disease had the longest median interval since the last normal Papicanolou test (120 months), and those with a fistula due to toxicity or recurrent disease had a lower median BMI and presented with more advanced/bulky tumors at initial presentation. The median time interval from the final day of treatment to the development of a fistula was 52 months (range 3.6–55.7 months). This time interval differed between those patients with a fistula due to treatment toxicity (13.1 months) and recurrent disease (8.5 months).

Characteristics of primary therapy for all previously irradiated patients can be found in Table 2. The median cumulative radiation dose delivered to Point A was 83.2 Gy (range 32.4–91.5 Gy). HDR brachytherapy was used in 38.1% of patients; LDR in 47.6%, and 14.3% received external radiation alone. The median maximum point doses to the rectum and bladder were 67.3 Gy (range 32.4–82.8 Gy) and 69.8 Gy (range 32.4–78.4 Gy), respectively.

Eighty-nine patients underwent an invasive procedure following completion of RT: 55 (16.9% of all irradiated patients) underwent a biopsy and 34 (10.5%) underwent pelvic surgery. Table 3 describes the