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Clinical Investigation

Risk of Radiation-Induced Malignancy With Heterotopic Ossification Prophylaxis: A Case–Control Analysis

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Summary

The purpose of this study was to quantify the risk of radiation-induced malignancy in heterotopic ossification prophylaxis. There was no increased incidence of malignancy in individuals who were treated with radiation compared with those who were not.

Purpose: To determine the risk of radiation-induced malignancy after prophylactic treatment for heterotopic ossification (HO).

Methods and Materials: A matched case–control study was conducted within a population-based cohort of 3489 patients treated either for acetabular fractures with acetabular open reduction internal fixation or who underwent total hip arthroplasty from 1990 to 2009. Record-linkage techniques identified patients who were diagnosed with a malignancy from our state health registry. Patients with a prior history of malignancy were excluded from the cohort. For each documented case of cancer, 2 controls were selected by stratified random sampling from the cohort that did not develop a malignancy. Matching factors were sex, age at time of hip treatment, and duration of follow-up.

Results: A total of 243 patients were diagnosed with a malignancy after hip treatment. Five patients were excluded owing to inadequate follow-up time in the corresponding control cohort. A cohort of 238 cases (control, 476 patients) was included. Mean follow-up was 10 years, 12 years in the control group. In the cancer cohort, 4% of patients had radiation therapy (RT), compared with 7% in the control group. Of the 9 patients diagnosed with cancer after RT, none occurred within the field. The mean latency period was 5.9 years in the patients who received RT and 6.6 years in the patients who did not. Median (range) age at time of cancer diagnosis in patients who received RT was 62 (43-75) years, compared with 70 (32-92) years in the non-RT patients. An ad hoc analysis was subsequently performed in all 2749 patients who were not matched and found neither an increased incidence of malignancy nor a difference in distribution of type of malignancy.

Conclusion: We were unable to demonstrate an increased risk of malignancy in patients who were treated with RT for HO prophylaxis compared with those who were not.

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Introduction

Heterotopic ossification (HO) is formation of mature lamellar bone in extraosseous tissue. The exact etiology is not completely understood, but it is hypothesized that during significant trauma pluripotent cells develop into osteoblastic stem cells, which go on to form extraosseous bone (1). Several eliciting factors are associated with a higher rate of HO formation, including traumatic fractures or surgical manipulation (2-4). This extraosseous bone can be debilitating and painful, leading to loss of motion in 33% of patients, with 10% of patients developing complete ankylosis (5). The incidence varies according to etiology and body region, but 60%-90% of high-risk patients go on to develop significant HO (Brooker's grade 3-4) after surgery. Treatment options include high-dose nonsteroidal anti-inflammatory drugs (NSAIDs) or radiation therapy (RT) (6, 7). However, a long course of NSAIDs is associated with an increased risk of gastrointestinal bleeding, ulcers, and nephropathy. These are serious health problems, particularly in elderly patients, who are typically referred for treatment after total hip arthroplasty (THA) procedures. In the late 1960s, these patients were treated with single doses of radiation in the perioperative setting, where it was found to be an effective therapy for the prevention of HO if given within 72 hours of an inciting event (3, 8).

Owing to the efficacy of this treatment in the setting of acetabular fractures (9, 10), trauma patients, who are typically much younger than their arthroplasty counterparts, have also been referred to radiation oncology departments for treatment of this benign condition (11, 12). There is concern that these younger patients would be more likely to develop a secondary malignancy because their normal life expectancy allows for the long latency period needed to develop a radiation-induced cancer (13, 14). To this assess this risk, we performed an analysis of patients who developed a malignancy after hip surgery and evaluated them for an association with radiotherapy.

Methods and Materials

After institutional review board approval, a matched case−control study was conducted from January 2011 through December 2012, within a population-based cohort of patients who were either treated with open reduction internal fixation of an acetabular fracture or underwent THA from 1990 to 2009 at our institution. Record-linkage techniques were used to identify patients who were diagnosed with a malignancy before December 2012 from our state tumor registry. This database contributes to the Surveillance, Epidemiology, and End Results national tumor registry. It does not include basal or squamous cell skin cancer or carcinoma in situ of the cervix. Benign brain tumors have been included in the registry and collected since 2004. Patients with a prior history of malignancy were excluded from the cohort. For each documented case, 2 controls were selected by stratified random sampling from the cohort. Matching factors were sex, age at time of hip surgery, and duration of follow-up.

For each patient, demographic and medical record information was collected, including date of surgery, date of RT, date of death, sex, age at time of hip treatment, cancer diagnosis date, site, histology, and age at cancer diagnosis. Follow-up period was defined from the date of their hip treatment until date of death or December 2012, whichever occurred first. Latency period was defined as the time period between hip treatment and cancer diagnosis. Patients treated with radiation had dosimetry data collected, including prescription dose, site treated, photon energy used, and fractionation regimen.

Chi-squared and Student t tests were used to assess whether the total number of cancers or mean age at HO treatment differed between those who received radiation and those who did not. Conditional regression analysis was used in a nested case−control study undertaken to estimate the relative risk of developing a secondary cancer; each case patient was matched to 2 randomly selected control patients.

As mentioned, matching factors included sex, age at diagnosis + 5 years, and length of survival. For the control patients, the follow-up period with no cancer diagnosis had to be longer than the latency period in the case they were matched to. Next, to assess whether the time to cancer occurrence differed among those who received radiation and those who did not, a Cox proportional hazard model was used to control for age. A reverse Kaplan-Meier graph was created from all the patients who developed cancer to demonstrate any differences between latency periods in the radiation versus nonradiation group. For the Cox proportional hazard model and the Kaplan-Meier graph, time to cancer was defined as time from HO treatment to cancer development. Finally, to compare the cancer occurrence with the general population, the standardized incidence ratio (SIR) was calculated between the nonirradiated group and the radiation group using the cancer incidence in our state for similar age groups over the same time period as the standard population. All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Between 1990 and 2009 there were a total of 3489 patients who underwent either THA or open reduction internal fixation at our institution. Excluding patients with inadequate radiation records (2 patients), a prior history of malignancy, or less than 1 year of follow-up resulted in a final cohort of 2749 patients, with 199 (7.2%) of them having undergone RT for HO prophylaxis. Within this population there were 243 patients who were diagnosed with a malignancy after hip surgery. There were 5 patients in this group whose prolonged length of follow-up could not be