Aspirin and Warfarin are Associated with Improved Overall Survival in Medically Inoperable Endometrial Cancer Patients Treated with Radiation Therapy

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Abstract

Objective: To assess factors associated with improved survival of medically inoperable endometrial carcinoma.

Methods: Patients with endometrial cancer who were not surgical candidates, underwent primary radiation therapy. Data were collected from medical records. Survival estimates were calculated and compared.

Results: Twenty-nine of 39 patients who underwent primary radiation therapy were considered medically inoperable. Median follow up was 19 months (range 3-66). Overall survival (OS) was 38% (11 out of 29). Progression-free survival (PFS) was 34% (10 out of 29). The cancer-specific mortality was 14% (4 out 29). Fourteen of 18 deceased patients (78%) had no evidence of recurrent disease. A history of pulmonary embolism was associated with improved survival (Rate ratio of death 0.2; 95%CI, 0.01-0.98; p=0.046). Grade 3 tumors were associated with shorter survival, compared to combined grades 1 and 2 (Rate ratio of death 3.21; 95%CI, 1-8.76; p=0.05). The median OS in patients on aspirin or warfarin was 20 months (range 7-66), and 11 months (range 3-43) in patients who did not take aspirin or warfarin (Rate ratio of death: 0.35, 95%CI, 0.13-0.89; p=0.028).

Conclusion: Radiation therapy provides acceptable tumor control in patients with medically inoperable endometrial cancer. Aspirin or warfarin therapy may result in longer overall survival.

Keywords: Aspirin; Warfarin; Endometrial cancer; Radiation therapy

Introduction

Endometrial cancer is the most common gynecological cancer with an estimated 42,160 new cases and 7,780 deaths occurring in 2009 [1]. Primary treatment consists of surgery and surgical staging. However, secondary to age, obesity and comorbidities approximately 3-9% of patients are at high risk for surgical complications and are considered medically inoperable [2]. These patients have been successfully treated with primary radiation therapy administered as brachytherapy alone or in combination with external beam radiation. Current clinical evidence supporting such therapy is based on case series collected by single institutions over a period of many years [2-6]. Studies did not report comorbidities in a uniform fashion and included patients who were treated with radiation therapy primarily because of advanced age, morbid obesity, or refusal of surgery. The purpose of this study is to present a single institution experience with primary radiation therapy in patients with endometrial carcinoma considered inoperable for medical reasons only. The unexpected finding of improved survival associated with usage of anti-platelet agents and anti-inflammatory medication is analyzed with respect to recent discoveries in the role of angiogenesis in cancer growth and metastasis. Clinical data supporting this approach in selected groups are reviewed.

Materials and Methods

Following approval by the Institutional Review Board, the medical records of all patients with endometrial cancer treated at the University of Iowa Hospitals and Clinics between February 2003 and April 2008 were reviewed. Only patients who received primary radiation therapy, and who were considered medically inoperable by their Gynecologic Oncologist were included in the analysis. Patients who received radiation therapy because of extreme obesity, refusal of surgery, advanced age, and patients with incomplete records were excluded. Data regarding medical history, current medication use, performance status, clinical stage and tumor histology were collected. When the performance status was not stated in the records, it was assigned based on available information. The Satariano comorbidity index was calculated [7]. One point was given for each of the following: myocardial infarction, other types of heart disease, diabetes, other types of cancer, respiratory, gallbladder, and liver conditions. OS, PFS, and disease-specific survival were obtained on all patients.

Information on radiation therapy was collected. Treatment consisted of pelvic external beam radiation therapy, with subsequent high dose rate tandem and ovoid (T&O) brachytherapy or external beam boost. The external beam boost was delivered with either conformal fields or Intensity Modulated Radiation Therapy (IMRT).

Actuarial survival estimates were calculated using the Kaplan Meier method. Associations between prognostic variables and survival were compared using the log-rank test and rate ratios, with a p – value < 0.05 considered significant. Rates of death were calculated as the number of deaths divided by the time at risk. A rate ratio is the ratio of death in the group with the variable of interest, divided by rate of death in the

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group without it. Values >1 indicates a higher number of deaths in a group with the given risk factor. Forests' plots with comparison of rate ratios were created using a published template [8]. The low number of subjects did not allow for meaningful multivariate analysis.

Results

Thirty-nine patients were identified who received primary radiation therapy for endometrial cancer. Six patients received radiation therapy primarily because of morbid obesity, advanced age, or refusal of surgery, and were excluded. Information was incomplete in 4 patients, leaving 29 patients eligible for analysis. The patient characteristics are presented in Table 1. Median age at diagnosis was 74 (range 36-95). Median body mass index (BMI) was 42 (range 17-66). The mean GOG performance score was 2.38 ± 1.47. Twenty-seven patients were clinical stage I, one was stage II and one stage III. Median follow up was 19 months (range 3-66). OS was 38% (11 out of 29), PFS was 34% (10 out of 29). The cancer-specific mortality was 14% (4 out 29). Out of eighteen deceased patients, fourteen (78%) had no evidence of recurrence. Fourteen fatalities were related to medical conditions; only four resulted from cancer. Details of the radiation therapy are presented in Table 2. Four patients had recurrent disease, of these two had local recurrence, and two had distant metastasis. One patient with stage III had persistent disease. All but one patient (97%) were able to complete the prescribed treatment. This patient suffered an acute myocardial infarction during cardiac catheterization performed before brachytherapy. One patient had a rectal perforation 16 days after completion of her second T&O. She required colostomy and died of a stroke 23 months after the cancer diagnosis, with metastatic disease.

Patients’ comorbidities and risk factors are listed in Figure 1. All listed conditions were present at the time of diagnosis of endometrial cancer. A trend in improved OS was observed in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE), and in patients with medical conditions possibly associated with thrombosis (cerebrovascular accident, myocardial infarction (MI), congestive heart failure and arrhythmia). Those results were statistically significant for a history of PE (Rate ratio of death 0.2, 95%CI, 0.01-0.98; p=0.046) and the combined category of patients with a history of pulmonary embolism or deep venous thrombosis (Rate ratio of death 0.2, 95%CI, 0.01-0.98; p=0.046). History of DVT when analyzed separately also showed a much lower risk of death (Rate ratio 0.23), but results were not statistically significant (95%CI, 0.01-1.13, p=0.076), suggesting insufficient power to detect this relationship in such a small study. Patients with coronary artery disease listed here, were the ones without concomitant arrhythmia, history of congestive heart failure or history of myocardial infarction. Analysis of medications taken by patients at the time of cancer diagnosis revealed significantly improved overall survival in a group taking any one of the two antithrombotic drugs – warfarin or aspirin (Figure 2) (Rate ratio of death: 0.35, 95%CI, 0.13-0.89). Survival curves comparison showed early separation and steady to increasing distance between the slopes (Figure 3). Overall survival was 56% (9 out of 16 aspirin or warfarin users) and 15% (2 out 13 non users). Aspirin was given at a dose of 81 mg for 44% of patients, and at a dose of 325 mg in the remaining 56%. The warfarin cumulative weekly dose ranged from 7 to 42 mg with a mean of 23 mg ± 15.7. INR data was not available for majority of patients. No patients took heparin products.

The mean Satariano comorbidity index was 2.38 ± 1.47. There was no statistical difference in the mean score between the living and deceased (2.36 vs. 2.39 p=0.95) groups, or between patients on aspirin/warfarin and a group not on those medications (2.19 vs. 2.61 p=0.45).

![Figure 1: Patient co-morbidities and rate ratio of death.](https://via.placeholder.com/150)

![Figure 2: Patient medications and rate ratio of death.](https://via.placeholder.com/150)

![Figure 3: Survival and Aspirin/Warfarin usage.](https://via.placeholder.com/150)
Survival among patients with 0-1 score was longer than in a group with a higher index, but not statistically significant (mean: 25 vs. 19 months p=0.26).

Grade III tumors were associated with shorter survival as compared to combined grades 1 and 2 (Rate ratio of death 3.21 95% CI, 1-8.76). This result could partially be affected by our sole stage III patient, and below median survival of 10 months (persistent disease). The remaining five grade III patients died without evidence of disease with a median survival of 12 months for the entire group (range 3-28 months). There were three recurrences among eleven grade II patients (27%) and one among twelve grade I patients (8%). Of the 4 recurrences and cancer-associated deaths, 2 were on aspirin/warfarin and 2 were not.

Discussion

This study describes a group of patients with medically inoperable endometrial cancer. The criteria to diagnose “medical inoperability” has not been defined. This determination is usually established by Gynecologic Oncologists with, or without contribution from other specialties. This group of patients is very heterogenous with a variable number and complexity of comorbidities. Overall survival (OS) data reported in the literature reflects this variation, while disease-specific survival is very similar. Results range from 28% OS at 2 years for patients older than 75 from the Pittsburgh group [5], to 55% at 5 years in the same age group from St. Louis, to 78% at 5 years for patients younger than 75 from the same institution [3]. Although our results of 38% OS at 19 months appears to be similar, it is difficult to draw conclusions on how comparable the populations are. At UIHC the medically inoperable patients with endometrial cancer are older on average by 13 years than a comparable group undergoing surgery. In elderly populations the assessment of functional status by Karnofsky or the Eastern Cooperative Oncology Group (ECOG), scale does not seem to be as effective as in the adult group because comorbidities in the elderly may interfere with the performance status [9]. We selected Satariano index for two reasons: it is a well-established tool and it can be applied retrospectively. In a large study of breast cancer patients, individuals with a score of 3 or more had a 20-fold higher rate of mortality from causes other than breast cancer [7]. The Breast cancer population is similar to ours secondary with a relatively early stage at diagnosis, low recurrence rate and similar tumor interaction with steroidal hormones. Early studies on the Satariano index were subsequently validated in other populations and the index was adopted as a part of Comprehensive Geriatric Assessment (CGA) [9].

The strength of our data lies in the observation of improved survival with a history of any condition with thrombotic pathophysiology. Statistical significance was reached for history of PE and with the combined group with a history of either PE or DVT. This relationship is very strong since the ratio of death rate is only 0.2, and it was possible to observe it in such a small study.

The concept of anticoagulation in patients with cancer and no history of thrombosis have been evaluated in lung cancers, breast cancers and heterogenous groups of patients with solid tumors. Meta-analysis of eleven randomized clinical trials showed significantly decreased 1-year overall mortality with use of anticoagulation (RR 0.905, 95%CI, 0.847-0.967, p=0.003). [10]. Considered separately, only one study of 302 patients with locally advanced or metastatic solid tumors (7 gynecological cases, 19 controls) was statistically significant, showing improved median survival following a 6 week course of subcutaneous nadroparin when compared to placebo (HR 0.75 95%CI, 0.59-0.96, p=0.021) [11]. In similar situations where patients with localized prostate cancer were treated with definitive radiation, anticoagulants (warfarin, clopidogrel or aspirin) were associated with improved biochemical control (PSA level) and decreased rate of distant metastasis at 4 years of follow up (1 vs. 5% p=0.0248). In this recently published retrospective study, overall survival at 4 years was no different (92.2% anticoagulation group vs. 90.3% control, p=0.884) [12].

Anticoagulation carries considerable risk of complications. In previously mentioned meta-analysis, warfarin was associated more with major bleeding than unfractionated heparin or low molecular weight heparin (RR 2.97 p<0.0001 vs. 1.007 p=0.996 vs. 1.679 p=0.128 respectively) [10]. Low intensity treatment with warfarin (INR 1.4 to 2.8) had a comparable safety profile to aspirin in stroke secondary prevention trials in the general population [13]. There is mounting evidence that aspirin may play a role in cancer treatment. Literature has shown that aspirin can decrease the incidence of metastatic disease in adenocarcinoma via COX-2 inhibition [14] while improving cardiovascular outcomes via COX-1 [15]. COX-2 is related to tumor angiogenesis, growth, apoptosis, metastasis and local immunosuppression [14]. Survivin, which is a COX-2 dependent protein, is critical for apoptosis resistance in non-small cell lung cancer [16]. Clinical evidence supports a dual effect of Aspirin on cancer patients. A recent study in endometrial cancer showed that expression of survivin, c-erbB2 and COX-2 correlates with tumor stage, grade, myometrial invasion and survival [17]. A retrospective cohort study of breast cancer patients enrolled in Nurses’ Health Study revealed decreased breast cancer mortality if aspirin was taken 2-5 times per week (RR 0.29 95%CI, 0.16-0.52), or 6-7 d per week (RR 0.36 95%CI 0.24-0.54). Overall mortality was also reduced, but to a lesser extent (RR 0.53 95%CI, 0.37-0.76 and RR 0.54 95%CI, 0.41-0.76, respectively; test for trend, p=0.004). This led investigators to conclude that therapeutic effect was driven by aspirin affecting breast cancer mortality [18]. A retrospective study on 1353 patients with non-small cell lung cancers after surgical resection showed more than 5 % (p=0.05) increased overall survival associated with taking aspirin [19].
Our data is similar to the literature in reporting significantly improved overall survival in studied populations without detecting clinical thrombosis. In a previously cited meta-analysis of RCT of prophylactic anticoagulants in cancer, only 5 studies report incidence of thromboembolism which ranged from 2 to 7% in the placebo group [11,20-22]. Contribution of thrombosis to death is suggested by frequent observation of pulmonary embolism in post mortem studies: 18.6% in 4077 autopsies carried out between 1979-1989 [23]. In our group, only 2 patients had documented thrombotic events after initiation of radiation treatment. Out of primary radiation treatment series, only one case series of HDR brachytherapy reports thrombotic complications.

Anticoagulants may not improve survival in all patients with cancer, but there appear to be certain cancer types that may benefit more from such treatment. It is possible that the overall survival difference in our study patients may be due to the impact of aspirin/warfarin on co-morbid conditions and not necessarily its effect on the cancer. We propose that the use of aspirin/warfarin in this population should be further investigated.

A major limitation in a study of this type is the subjective determination of medical inoperability. We propose using the Satariano index to compare our data to other institutions.

In this group of medically inoperable patients with endometrial cancer, primary radiation provided acceptable tumor control. An unexpected finding was the association between aspirin/warfarin and longer overall survival.

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