Gynecologic Oncology 129 (2013) 12–17

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Did GOG99 and PORTEC1 change clinical practice in the United States?

Emily M. Ko [a,c,*], Michele Jonsson Funk [b], Leslie H. Clark [a], Wendy R. Brewster [a,b,c]

[a] Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, NC, USA
[b] Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC, USA
[c] Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, USA

HIGHLIGHTS

- The rate of adjuvant radiation in the US did not increase after publication of PORTEC1 and GOG99.
- There is significant heterogeneity of use of radiation among states following publication of GOG99.
- In the US, the use of brachytherapy increased and external beam decreased after GOG99 publication.

ARTICLE INFO

Article history:
Received 20 December 2012
Accepted 23 January 2013
Available online 29 January 2013

Keywords:
Endometrial cancer
Adjuvant radiation
Early stage
GOG99
PORTEC

ABSTRACT

Objective. To assess the practice of adjuvant radiation (RT) for endometrial cancer in the United States following the publication of the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC1), and Gynecologic Oncology Group-Adjuvant Radiation for Intermediate Risk Endometrial Cancers (GOG99).

Methods. A retrospective cohort study using the NCI SEER database compared the use of RT pre and post publication of PORTEC1 (1996–99 v 2000–03) and GOG 99 (2000–03 v 2004–07). Criteria for intermediate (IR) and high-intermediate (HIR) risk categories as defined by PORTEC1 and GOG99 were applied. Chi-squared statistics and adjusted multivariable Poisson models were used.

Results. RT did not increase for HIR (RR 1.05, 95%CI 0.99, 1.11) or IR groups (RR 1.0, 95% CI 0.95, 1.05) following GOG99 publication, or for HIR (RR 1.01, 95% CI 0.86, 1.19) or IR groups (RR 0.88, 95% CI 0.77–1.00) following PORTEC1 publication. Radiation rates changed heterogeneously across the country without a discernible pattern of cause. Among radiated patients, brachytherapy use increased, whereas external beam use decreased after GOG99 publication.

Conclusions. As the debate regarding the utility of adjuvant radiation in early stage endometrial cancer continues, we found that overall, clinicians had not adopted GOG99 or PORTEC1 results into their clinical practice in the years immediately after publication. However, we did identify significant variation in practice by geographic location. Given that barely half the women deemed highest risk for recurrence received radiation, these findings illustrate that clinical practice reflects the continued controversy surrounding adjuvant radiation in the treatment of endometrial cancer.

Introduction

Two significant phase III randomized-controlled trials, PORTEC1 (Post Operative Radiation Therapy in Endometrial Carcinoma) and GOG99 (Gynecologic Oncology Group Trial of Adjuvant Radiation in Intermediate Risk Early Stage Endometrial Cancers) demonstrated decreased recurrence rates following adjuvant radiation use in patients with early-stage endometrial cancer. PORTEC1, conducted in Europe, found a lower 5-year recurrence rate in their intermediate risk (IR) group (4% vs 14%, $p<0.001$) and a slightly greater difference in their high-intermediate risk (HIR) group (5% vs 18%, p value not reported). [1] GOG99, conducted in the US, found a decreased cumulative incidence of recurrence (CIR) of 2% versus 6% (HR 0.46; 90%CI 0.19, 1.11) over 4 years in the IR group, with an even greater benefit in the HIR subset with a CIR of 13% versus 27% (HR 0.42; 90%CI .0.21, 0.83) [2].

Since publication of these two sentinel trials, PORTEC1 in 2000 and GOG99 in 2004, there has been much debate regarding the application of adjuvant radiation in women with early-stage endometrial cancer [3,4]. The absolute risk reduction of an already low recurrence rate, particularly among IR women, has been deemed to have questionable clinical value in light of the potential increased use of resources and resultant cost. However, within the HIR population, there may be stronger evidence of a decreased recurrence rate with the use of adjuvant radiation, leading us to expect an uptake of radiation use in this population.

* Corresponding author at: University of North Carolina, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, CB 7572, Chapel Hill, NC 27599-7572, USA. Fax: +1 919 843 5387.
E-mail address: emko@email.unc.edu (E.M. Ko).

0090-8258/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ygyno.2013.01.020

Therefore, in the heat of a continued clinical debate, we specifically sought to characterize radiation use in the immediate years following publication of PORTEC1 and GOG99 as a reflection of physicians' adoption of evidence-based literature into clinical practice. Our primary objective was to evaluate the change in radiation following these publications, with a hypothesis that increased radiation would occur in the HIR population. Our secondary objective was to explore the changes in pattern of the type of radiation used, since subsequent trials investigating brachytherapy versus external beam including PORTEC2 and ASTEC were currently under enrollment during the time covered by our study.

Methods

We obtained data on endometrial cancer patients diagnosed between 1996 and 2007 from the Surveillance Epidemiology and End Results (SEER) program of the United States National Cancer Institute [5]. Our data included surgical and radiation treatment, pathology, stage, and demographics including census-defined state and county of treatment. Since all information in the SEER database is de-identified by NCI, the university's institution review board granted an exemption for this study.

The study population included women diagnosed with stage I and II endometrial cancer from January 1, 1996 through December 31, 2007, divided into four cohorts each, defined by the four years before and after publication of PORTEC1 and GOG99. We defined staging by using the American Joint Committee on Cancer (1992) definition that is consistent with the 1988 FIGO system, and histology based on the International Classification of Diseases for Oncology codes (ICD 03 SEER Site Histology Validation List, 2007). All women had undergone hysterectomy.

Inclusion criteria from the original PORTEC1 and GOG99 clinical trials were applied, as summarized in Table 1 [1,2]. Additionally, we made a few modifications in selecting patients who qualified for inclusion in our PORTEC1 and GOG99 cohorts. Since the percent of myometrial invasion was not available in the SEER database, we used the 'clinical stage variable' as defined by uterine myometrial invasion (IA: no invasion, IB: myometrial invasion<50%, IC: myometrial invasion>50%) as a surrogate measure for depth of myometrial invasion. Patients with uterine stage IC were considered to meet criteria for myometrial invasion to the outer third. High-grade histology included SEER grading of 2, 3, and 4 (anaplastic). Lymphovascular invasion was not available and therefore could not be incorporated in the selection criteria. Patients who had undergone any lymph node dissection were included in the GOG99 cohorts; patients who had not undergone any lymph node dissection were included in the PORTEC1 cohorts.

Table 1
Clinical trial inclusion criteria of PORTEC1 and GOG99.

PORTEC1 inclusion criteria
Intermediate risk (IR)
• Endometrial adenocarcinoma of any histologic type
• Stage I based on uterine factors
• Grade 1 histology and myometrial invasion of >=50%;
• Grade 2 histology with any myometrial invasion; and
• Grade 3 histology with myometrial invasion<50%.
High-intermediate risk (HIR)
• Age>60 years with grade 1 or 2 histology and myometrial invasion>50%
• Age>60 with grade 3 histology and myometrial invasion<50%.
GOG 99 inclusion criteria
Intermediate risk (IR)
• Endometrial adenocarcinoma of any histology type except serous or clear-cell
• Positive myometrial invasion of any degree[a]
• All histologic grades
• Full surgical staging including bilateral retroperitoneal pelvic lymph node dissection
High-intermediate risk (HIR)
• Age<50 years old and:
1) grade 2 or 3 histology
2) positive lymphovascular invasion
3) myometrial invasion to the outer third
• Age 50–69 years, with 2 of 3 of the above listed factors.
• Age 70 years or more, with 1 of 3 of the above listed factors.

[a] Based on FIGO staging prior to 2008, GOG99 included endometrial cases with any myometrial invasion, defined as stages IB, IC, IIA (occult) and IIB (occult).

All statistical tests were conducted using SAS 9.0 (Cary, North Carolina). We used student t-tests and the Chi-squared statistic for unadjusted comparisons, and multivariable Poisson regression to estimate adjusted relative risks with 95% confidence intervals (CI). The model was adjusted for age, race, stage, grade, and the geographic region where the patient was treated. We used a Breslow–Day test for homogeneity of the odds ratios to assess for heterogeneity among state differences in radiation rates between before and after cohorts. We created interaction terms per state to assess the rate of radiation use of each state (individual state effect) within a single adjusted model accounting for overall calendar period effect on use of radiation. Two-tailed p values<0.05 were considered statistically significant, with alpha = 0.05.

Results

GOG99 cohort

GOG99 high-intermediate risk

We identified a total of 4724 HIR patients; 1960 were in the pre-group and 2764 in the post-group. Demographic information is presented in Table 2. The proportion of women who received adjuvant radiation did not differ significantly after publication of GOG99 in the unadjusted (48.2 pre vs. 50.9% post, RR 1.06, 95%CI 1.00–1.12) or adjusted models (RR 1.05, 95%CI 0.99–1.11) (Table 2). However, our secondary analysis revealed that of those who received radiation, fewer women received external beam (77.6% to 65.0%, p<0.0001), more received brachytherapy (52.9% to 59.3%, p=0.002), and fewer received combination radiation (31.9% to 24.7%, p=0.0001) (Fig. 1). After adjusting for all confounders, increasing age, high stage (IC, II), high grade (3 and 4) and census region were all independently associated with adjuvant radiation (Table 3).

Although the overall adjusted radiation rate did not differ pre versus post GOG99, significant heterogeneity existed among states (p<0.001). In the pre period, radiation varied greatly from 33.3% in Utah to 62.1% in Iowa. The largest increase was seen in Utah (RR 1.68, 95% CI 1.12–2.54) and the largest decrease in Hawaii (RR 0.63, CI 0.36–1.12). There did not appear to be a relationship between the amounts of radiation used before publication to the change in radiation (increase or decrease) following publication (Table 4). For example, states such as Utah (who radiated a relatively lower proportion of eligible women) and Connecticut (who radiated a higher proportion) both increased the use of radiation significantly after publication. Radiation use did not cluster by US census-defined regions, but rather varied widely by individual state practices (Table 4).

GOG99 intermediate risk

We identified 11,996 IR patients, including 4658 from 2000 through 2003, and 7338 from 2004 through 2007. Demographics of this cohort were similar to those of the HIR cohort (Table 2). Compared with the HIR group, the overall radiation rate was lower (30 v 50%). The proportion of women receiving adjuvant radiation did not change after GOG99 publication in the unadjusted (32.1 pre vs 31.0% post, RR 0.97, 95% CI: 0.92–1.02) or adjusted models (RR 1.0, 95% CI 0.95–1.05) (Table 2). Similar to HIR, in our secondary analysis, we found a decrease in the use of external beam therapy from 71.5% to 58.3% (p<0.001), an