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Extent of pelvic lymphadenectomy and use of adjuvant vaginal brachytherapy for early-stage endometrial cancer

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HIGHLIGHTS

- ICBT is replacing WPRT in adjuvant radiotherapy for stage I endometrial cancer
- Pelvic node counts among lymphadenectomy cases have been significantly increased
- Higher sampled pelvic node counts were associated with increased chance of ICBT use

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ABSTRACT

Objective. To examine trends of adjuvant radiotherapy choice and to examine associations between pelvic lymphadenectomy and radiotherapy choice for women with early-stage endometrial cancer.

Methods. The Surveillance, Epidemiology, and End Results Program was used to identify surgically treated stage I-II endometrial cancer between 1983 and 2012 (type 1 n = 79,474, and type 2 n = 25,020). Piecewise linear regression models were used to examine temporal trends of intracavitary brachytherapy (ICBT) and whole pelvic radiotherapy (WPRT) use, pelvic lymphadenectomy rate, and sampled node counts. Multivariable binary logistic regression models were used to identify independent predictors for ICBT use.

Results. There was a significant increase in ICBT use and decrease in WPRT use during the study period. ICBT use exceeded WPRT use in 2003 for type 1 stage IA, and in 2007 for type 1 stage IB and type 2 stage IA diseases. In addition, number of sampled pelvic nodes significantly increased over time in type 1–2 stage I-II diseases (mean, 7.0–12.7 in 1988 to 15.2–17.6 in 2012, all $P < 0.001$). On multivariable analysis, extent of sampled pelvic nodes was significantly associated with ICBT use for type 1 cancer: adjusted-odds ratios for 1–10 and >10 nodes *versus* no lymphadenectomy in stage IA (1.38/2.40), IB (2.75/6.32), and II (1.36/2.91) diseases. Similar trends were observed for type 2 cancer: adjusted-odds ratios for stage IA (1.69/3.73), IB (2.25/5.65), and II (1.36/2.19) diseases.

Conclusion. Our results suggest that surgeons and radiation oncologists are evaluating the extent of pelvic lymphadenectomy when counseling women with early-stage endometrial cancer for adjuvant radiotherapy.

1. Introduction

In 2016, endometrial cancer remains the most common gynecologic malignancy in the United States, projecting more than 60,000 newly diagnosed cases [1]. The majority of endometrial cancer is early-stage disease resulting in good prognosis, and surgery remains the mainstay of the treatment consisting of total hysterectomy and adnexectomy with possible lymphadenectomy in selected cases [2]. Patients with early-stage endometrial cancer whose tumors exhibit risk factors for disease relapse in the pelvis benefit from receiving adjuvant radiotherapy, given that vaginal cuff and pelvis are the two most common anatomical sites of recurrence in women with early-stage endometrial cancer [3,4].

Based upon mounting evidence, including a randomized study demonstrating the comparative effectiveness for local disease control and reduced radiation-related adverse effects in vaginal intracavitary brachytherapy (ICBT) compared to whole pelvic radiotherapy (WPRT) for early-stage endometrial cancer (PORTEC2 trial) [5], the most recent American Society for Radiation Oncology (ASTRO) guidelines recommend the use of ICBT as the preferred option for type 1 stage IB and type 2 stage IA endometrial cancer [6]. However, WPRT continues to be recommended for type 2 stage IB and type 1–2 stage II diseases [6].

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These recommendations were also endorsed by the American Society of Clinical Oncology (ASCO) in year 2015 [7].

While ICBT irradiates the vaginal cuff, it does not sterilize the pelvic lymphatic chains. Given this important difference in treatment field for radiotherapy between ICBT and WPRT, patterns of practice for adjuvant radiotherapy may be affected by the extent of pelvic lymphadenectomy; however, the data have been missing to link this association. The aims of this study was to examine time-trends of adjuvant radiotherapy choice (ICBT *versus* WPRT) and to examine associations between the extent of pelvic lymphadenectomy and radiotherapy choice for women with stage I-II endometrial cancer.

2. Materials and methods

2.1. Data source and eligibility

The Surveillance, Epidemiology, and End Results (SEER) Program is a population-based tumor registry launched in 1973, supported and managed by the National Cancer Institute in the United States [8]. The SEER Program covers approximately 27.8% of the US population from 11 States and 7 areas. The SEER data are publicly available and deidentified, and the University of Southern California Institutional Review Board exempts this study. The STROBE guidelines were used to outline the observational study [9].

SEER*Stat 8.2.1 was used to extract the data set from SEER18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases (1973–2012). Cases recorded in the section for "Corpus Uteri/Uterus NOS" limited to malignancy and female sex were generated. Within the extracted dataset, stage I-II endometrial cancer cases with known pelvic lymphadenectomy status at hysterectomy and adjuvant radiotherapy information between 1983 and 2012 were included in the study. Data from 1973 to 1982 were removed due to lack of information on the surgical procedure. Women who received radiotherapy prior to the hysterectomy, uterine sarcomas, and metastatic tumors to the uterus were excluded. Variables ascertained from the database were patient demographics, tumor information, and treatment pattern.

2.2. Clinical Information

Patient demographics included age at diagnosis, calendar year at hysterectomy, ethnicity, marital status, and registration area. Tumor information included cancer stage, histologic subtype, tumor grade, tumor size, and pelvic lymph node status. Among the cases that had pelvic lymphadenectomy, number of sampled lymph nodes was abstracted. Treatment patterns included type of hysterectomy, pelvic lymphadenectomy, and postoperative radiotherapy. Adjuvant radiotherapy type was grouped as none, WPRT, and ICBT.

2.3. Definition

Type 1 endometrial cancer was defined as grade 1 and 2 endometrioid types [10]. Grade 3 endometrioid, serous, clear cell, undifferentiated, carcinosarcoma, squamous, adenosquamous, and mixed histology types were defied as type 2 endometrial cancer. Recorded cancer stage was re-classified into AJCC 7th staging classification schema. ICD-0-3 SEER site/histology validation list and the WHO histological classification were used for grouping histologic subtypes as shown previously (Table S1) [11].

2.4. Statistical consideration

The primary interest of analysis was to examine a time-trend of the use of adjuvant radiotherapy and lymphadenectomy for stage I-II endometrial cancer. The secondary interest of analysis was to examine associations of ICBT use and pelvic lymphadenectomy. On univariable analysis, Student *t*-test for continuous variables and chi-square test for ordinal/categorical variables were used as appropriate. Binary logistic regression models were used for multivariable analysis to determine independent contributing factors for ICBT. In this model, covariates for patient demographics, tumor characteristics, and treatment patterns were entered in the final model. Magnitudes of statistical significance were expressed with adjusted-odds ratio (aOR) and 95% confidence interval (CI).

For a time-trend analysis of adjuvant therapy and lymphadectomy per calendar year, Joinpoint Trend Software (version 4.2.0.2) provided by the National Cancer Institute was used to determine the potential changes in temporal trends [12]. Time duration was grouped every one year to provide percent frequency or mean value of collected variables. The results were analyzed with linear segmented regression test, and log-transformation was performed to determine annual percent change of the slope, expressed as annual percent change (APC) and 95%CI [13]. All statistical analyses were two-tailed, and a *P*-value of <0.05 was considered statistical significant. Statistical Package for Social Sciences (version 22.0, Chicago, IL, USA) was used for the analysis.

3. Results

Selection schema is shown in Fig. 1. There were 104,494 women with surgically-treated stage I-II endometrial cancer with known pelvic lymphadenectomy status, including 79,474 (76.1%) women with type 1 cancer and 25,050 (23.9%) women with type 2 cancer. Patient characteristics are shown in Table S2. The majority of women were aged >60, White, married, and Western US residents. The majority of tumors had stage IA disease and grade 1 endometrioid histology. For adjuvant radiotherapy, WPRT and ICBT use were given in 14,496 (13.9%) and 7689 (7.4%) cases, respectively. There were 56,278 (53.9%) women who underwent pelvic lymphadenectomy.

Women with type 2 cancer were more likely to be older, Black, and single compared to type 1 cancer (all, $P<0.001$; Table S3). Type 2 cancer were more likely to be stage IB-II disease and had a larger tumor size compared to type 1 cancer (both, $P<0.001$). Women with type 2 cancer were more likely to receive radical surgery and adjuvant radiotherapy (both, $P<0.001$).

3.1. Type 1 cancer: trends of adjuvant radiotherapy and lymphadenectomy

For type 1 stage IA cancer (n = 64,626), use of adjuvant radiotherapy was generally low (7.2%). During the study period, there was a significant increase in ICBT use (APC 6.7, 95%CI 4.0–9.5, $P<0.001$) and a significant decrease in WPRT use (APC −8.3, 95%CI −9.6 to −7.1, $P<0.001$). ICBT use rate exceeded WPRT use rate in year 2003 (Fig. 2A). In year 2012, ICBT use and WPRT use rates were 9.0% and 2.2%, respectively. Rates of women who underwent pelvic lymphadenectomy increased until year 2008 with the rate being 51.3% (APC 5.9, 95%CI 5.4–6.4, $P<0.001$).

Similarly, among 10,636 cases of type 1 stage IB disease, ICBT use continued to increase (APC 14.1, 95%CI 12.2–16.1, $P<0.001$) and WPRT use continued to decrease (APC −7.5, 95%CI −8.9 to −6.1, $P<0.001$) during the study period, and ICBT use rate exceeded WPRT use rate in year 2007 (Fig. 2B). In year 2012, ICBT use and WPRT use rates were 37.5% and 11.9%, respectively. Pelvic lymphadenectomy rates also continued to increase during the study period, reaching to 76.7% in year 2012. For type 1 stage II disease (n = 4,212), ICBT use started significantly increasing in year 2001 or later (APC 14.7, 95%CI 10.1–19.4, $P<0.001$), and the ICBT use rate was similar to the WPRT rate as of year 2012 (37.0% *versus* 39.0%, Fig. 2C).

3.2. Type 2 cancer: Trends of adjuvant radiotherapy and lymphadenectomy

Among 16,671 women with type 2 stage IA disease, ICBT use rate increased significantly after year 1993 (APC 12.3, 95%CI 10.8–13.7, $P<0.001$), and WPRT use rate decreased significantly after year 1997

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