RESEARCH ARTICLE

Survival Rate of Early Stage Endometrioid Adenocarcinoma of Endometrium Treated at Srinagarind Hospital

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Abstract

Purpose: To evaluate the survival outcome of early stage endometrioid adenocarcinoma of the endometrium with risk factors for locoregional recurrence treated with combined pelvic external beam radiotherapy (EBRT) and vaginal brachytherapy (VBT) after comprehensive surgery. Materials and Methods: Post-operative radiotherapy by pelvic EBRT and VBT for early stage endometrioid endometrial carcinoma resulted in excellent pelvic control with acceptable complications. This study showed no significant relationships between age, stage, histologic grade and LVSI and overall survival rate. Results: The 5-year overall survival rate (OS) of early stage endometrioid type of endometrial carcinoma was 85.7%. Acute toxicity occurred in 38.1% of the patients, all of whom were grade 1 or 2. Total late toxicity developed in 42.9% of study group, in which 36.99% of them were grade 1-2 and 4.76% were grade 3-4. Conclusions: Post-operative radiotherapy by pelvic EBRT and VBT is acceptable for early stage endometrioid endometrial carcinoma, independent of age, stage, histologic grade and LVSI.

Keywords: Endometrial adenocarcinoma - survival - radiotherapy - brachytherapy - survival

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Introduction

Adenocarcinoma of the endometrium is the third most common malignant neoplasm of the female genital tract. In Thailand, 3,958 new cases of endometrial carcinoma were diagnosed between 2004 and 2006 (Khuhaprema et al., 2012). Most of patients were classified as early stage disease (stage I or II) with excellent results by surgery alone. The 5-year survival rate for stage I/II was 83-85% (Algan et al., 1996; Creasman et al., 1997). The Gynecologic Oncology Group (GOG) reported a 5-year survival rate of 93% for stage I disease without any risk factors (Keys et al., 2004). The early stage disease with risk factors was considered to require adjuvant radiotherapy. The risk for local recurrence was related to age, depth of myometrial invasion, histologic grade and lymphovascular space invasion (Aalders et al., 1980; Grigsby et al., 1992; Podczaski et al., 1992; Morrow et al., 1994; Keys et al., 2004).

Radiotherapy has been used as adjuvant treatment for some early stage endometrial carcinoma with risk factors. This combined modality significantly reduced the loco-regional recurrence rate (Bliss et al., 1992; Carey et al., 1995; Rush et al.,1995; Algan et al., 1996; Creutzberg et al., 2000; Keys et al., 2004; Nout et al., 2010). The PORTEC2-trial demonstrated that external beam radiotherapy and vaginal brachytherapy in stage I endometrial carcinoma with high-intermediate risk factors were equally effective (Nout et al., 2010).

The objectives of this study were to determine the survival rates and complications of early stage endometrial carcinoma patients treated with external-beam radiotherapy and vaginal brachytherapy.

Materials and Methods

Patients

Between January 1997 and December 2007, there were 386 patients with endometrial carcinoma who were treated by radiotherapy in Srinagarind hospital. The inclusion criteria were: 1) stage IA-IIB endometrioid type of endometrial carcinoma who had undergone comprehensive surgery followed by external-beam radiotherapy (EBRT) and vaginal brachytherapy (VBT); 2) pathological reports were reviewed to determine that indicated sufficient risk factors were present to warrant consideration for adjuvant treatments; 3) none of these patients had received adjuvant chemotherapy. Exclusion criteria were: 1) patients who had no comprehensive staging surgery; 2) advanced disease; 3) other or mixed histology; 4) concurrent malignancy; 5) Patients who had previous pelvic or abdominal irradiation.

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There were 31.35% early stage (I-II) diseases (121/386 cases) and 26.42% advanced stage (III-IV) diseases (102/386 cases). Of those patients with early stage diseases who were treated by comprehensive surgery including extensive surgical staging and postoperative radiotherapy (PORT), 69.42% (84/121cases) were endometriod adenocarcinoma and 30.58% (37/121cases) were non-endometriod adenocarcinoma.

There were 42.23% (163/386 cases) who received incomplete or no surgical staging and were excluded from this study.

The staging was classified according to the FIGO 1988 pathologic staging system (FIGO, 1988). This project has been approved by the Human Ethic Committee of Khon Kaen University (HE 561029).

Radiotherapy

Radiotherapy was started as soon as possible, usually between 4-8 weeks after surgery. The treatment protocol included a combination of pelvic EBRT and VBT. Most of VBT regimens were two sessions of high-dose-rate Iridium-192 brachytherapy which performed one week apart by 6-7Gy/fraction at a depth of 0.5 cm to the upper 3 cm of vagina, after completion of EBRT, The applicators used for VBT were either the vaginal cylinder or vaginal colpostat.

Radiotherapy technique

Whole pelvic irradiation was used as the technique of EBRT in every patient. After conventional simulation, the target volume was defined to include the tumor bed, the upper two thirds of vagina and the pelvic lymph nodes. The para-aortic lymph nodes were not included in the treatment fields. The superior border was placed at the L5-S1 interspace, the inferior border was at the inferior margin of the obturator foramen or below the vaginal involvement margin plus 2 centimeters depending on which one was lower. The lateral borders were placed at the widest opening of bony pelvis plus 1.5-2.0 centimeters. No midline shields were applied for the whole course of pelvic irradiation.

Statistics

The data of patients' demographics, pathologic characteristics, radiotherapy treatment, recurrence, current living status and treatment-related complications were collected from medical records. Treatment-related complications were documented according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.02 (National Cancer Institute, 2009). The prognostic factors including age, histologic grade, lymphovascular space invasion were analyzed by bivariate analysis using the log-rank test. Variable significance in univariate analysis was then subsequently analyzed by a multivariate analysis using the Cox-proportional hazards model. Overall survival rates (OS) were calculated from the date of treatment completion to the date of death or date of known living status. Kaplan-Meier curves were generated from the survival data using STATA version 10.0. A p value of ≤0.05 was considered to be statistically significant.

Results

Patients and tumor characteristics

The patient and tumor characteristics of the entire treatment group are summarized in Table 1.

Treatment

The mean time interval between surgery and radiotherapy was 55.15±27.92 days. Most of the patients were treated with teletherapy 50Gy/25 fractions, 5 fractions per week to the whole pelvis, followed by brachytherapy. The common brachytherapy regimens were 6Gy×2 fractions, 6Gy×4 fractions and 6Gy×3 fractions due to doctor's opinions. Radiation dose at a depth of 0.5 cm submucosa of upper 3 cm vagina was prescribed for all regimens in each fraction. The mean total radiation treatment time was 60.80±30.18 days. The treatment data are summarized in Table 2.

Survival

Mean follow-up time was 71.68±42.96 months (mean±SD). All survival data are shown in Table 3 and

Table 1. Patients and Tumor Characteristics

Patients and tumor characteristics		No.	%
No. of patients		84	100
Age	Median (range)	55.05 (26.79-80.88)	
Age (years)	<50	22	26.19
	≥50	62	73.81
Karnofsky performance status (KPS)	100%	4	4.76
	90%	59	70.24
	80%	21	25.00
Initial hemoglobin (gm/dl)	Mean±SD	12.22±1.07	
Tumor stage	IA	-	-
	IB	21	25.00
	IC	25	29.76
	IIA	13	15.48
	IIB	25	29.76
Histologic grade	1	37	44.05
	2	27	32.14
	3	20	23.81
LVSI	Absent	20	23.81
	Present	35	41.67
	Unknown	29	34.52

Table 2. Treatment Characteristics

Treatment characteristicss		N	%
Interval between surgery and radiotherapy (days)	Mean±SD	55.15±27.92	
Total radiation treatment time (days)	Mean±SD	60.80±30.18	
Radiation fraction (Fx) and Total Dosage, external beam			
2Gy/Fx, total dose 42Gy		1	1.19
2Gy/Fx, total dose 48Gy		1	1.19
2Gy/Fx, total dose 50Gy		80	95.24
1.8Gy/Fx, total dose 50.4Gy		2	3.38
Brachytherapy Regimens	6Gy×2Fx	25	29.76
	6Gy×4Fx	16	19.05
	6Gy×3Fx	13	15.48
	3Gy×4Fx	8	9.52
	8Gy×2Fx	7	8.33
	5Gy×2Fx	6	7.14
	8Gy×1Fx	3	3.57
	7Gy×2Fx	2	3.38
	4Gy×2Fx	2	3.38
	8Gy×3Fx	1	1.19
	5Gy×3Fx	1	1.19

Figure 1-2.

Treatment-related complications

The most acute treatment-related complication was diarrhea grade 1-2 (29.76%) while the most late complication was proctitis grade 1-2 (22.62%). There were 4.76% of grade 3-4 cystitis in acute complications and 3.57%of grade 3-4 proctitis in late complications. Treatment-related complications are summarized in Table 4.

Discussion

It is currently accepted that adjuvant radiotherapy in early stage (I-II) endometrial carcinoma with risk factors can improve locoregional control compared with surgery alone (Aalders et al., 1980; Bliss et al., 1992; Grigsby et al., 1992; Podczaski et al., 1992; Morrow et al., 1994; Carey et al., 1995; Rush et al., 1995; Algan et al., 1996; Creutzberg et al., 2000; Keys et al., 2004; Nout et al., 2010).

Algan et al. (1996) reported a 5-year overall survival and disease free survival for stage I and II endometrial carcinoma patients treated with PORT of 83-85%. Similar outcomes were also described by Creutzberg et al. (2000). Their randomized controlled trial demonstrated a 5-year overall survival rate of 81% for stage IB G2-3 or IC G1-2 endometrial carcinoma and significantly reduced the locoregional recurrence rate (LRR) from 14% to 4%. Rush et al. (1995) demonstrated that there was no pelvic failure following EBRT. In addition, Podczaki et al. (1992) reported that relapse of early stage endometrial carcinoma mainly occurred locally.

In this retrospective study, the 5-year overall survival rate was 85.7% which is comparable to other published reports (Hanprasertpong et al., 2008; Manchana and Nipon, 2008; Tangjitgamol et al., 2010; Wilairat and Benjapibal, 2012).

This study showed no association between age, stage, histologic grade or LVSI and overall survival rate. There were many studies demonstrating the benefit of PORT for reducing pelvic and vaginal recurrence from 18% to 3% in patients with risk prognostic factors (Morrow et al., 1994; Keys et al., 2004). The risk factors in their studies were age, tumor differentiation grade, presence of LVSI and outer third myometrial invasion. The reviewed studies showed an analogous relationship of risk factors for relapse rate (Aalders et al., 1980; Kucera et al., 1990; Grigsby et al., 1992; Morrow et al., 1994; Creasman et al., 1997). This present study showed no significant relationships of age, stage, histologic grade and LVSI to OS rate.

Weiss et al. (1999) reported 47.8% and 28.8% cases of mild grade gastrointestinal and genitourinary tract out of 65.4% of the total acute toxicity. In addition, the late toxicities were found to be 8.8% with grade 1-2 and 1.8% with grade 3-4. The severe complications included rectal ulcer and rectovaginal fistula. Nori et al. (1994) showed 9.5% of grade 1-2 with late complications and Kucera et

Table 3. Survival Data

Factors		5-year survival rates (%)	95%CI	p value
Total	Overall survival, 5 year	85.71	75.14-91.22	-
Age	<50	91.3	69.49-97.75	
(years)	≥50	83.61	71.67-90.82	0.081
Stage	IB	85.71	61.97-95.16	
	IC	84	67.81-93.67	
	IIA	100	-	
	IIB	80	58.44-91.15	0.972
Histologic grade	1	97.3	82.32-99.61	
	2	74.07	53.19-86.70	
	3	80	55.11-91.98	0.163
LVSI	Absent	100	-	
	Present	88.57	72.36-95.56	
	Unknown	72.41	52.34-85.13	0.071

Table 4. Treatment-Related Complications

		No.	%
Acute complications			
Diarrhea	Grade 1-2	25	29.76
	Grade 3-4	-	-
Cystitis	Grade 1-2	3	4.76
	Grade 3-4	-	-
	Skin; moist desquamation	3	4.76
Late complications*			
Proctitis	Grade 1-2	19	22.62
	Grade 3-4 (one recto-vaginal fistula)	3	3.57
Cystitis	Grade 1-2	11	13.10
	Grade 3-4 (vesico-vaginal fistula)	1	1.19
	Vaginal stenosis	11	13.10
	Skin fibrosis	4	4.76
	Lymphatic obstruction	2	2.38

*some patients had more than 1 complication

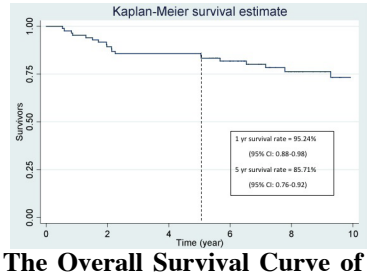

Figure 1. The Overall Survival Curve of the Entire Treatment Group

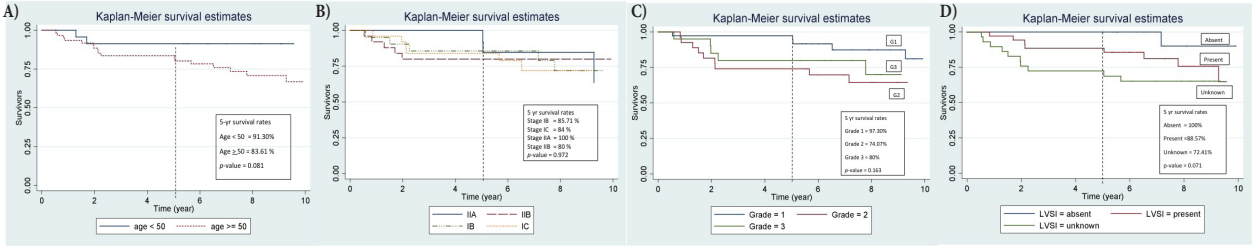

Figure 2. The Survival Curves by A) Age; B) Stage; C) Histologic Grade and D) Lymphovascular Space Invasion (LVSI)

al. (1990) reported cystitis and proctitis in 12.6% of their analyzed group.

This present study demonstrated a total acute complication rate of 38.1%, all of them were grade 1-2 for the gastrointestinal tract (29.76%), dysuria (4.76%) and moist desquamation (3.57%). For late complications, there were 22.62% with grade 1-2 proctitis and 13.09% with grade 1-2 cystitis. Vaginal stenosis was found in 11 cases (4.76%). Severe complications with persistent rectal bleeding were found in 3 cases (3.57%); rectovaginal fistula,1case, vesicovaginal fistula,1 case and lymphatic obstruction of lower extremity,1case. Most of the complications were manageable.

Although the combined radiation treatment had shown good results for decades, some later studies using single radiation technique (either EBRT or VBT) revealed similar or slightly poorer results but fewer complications. Bliss and Cowie (1992) reported a higher incidence of vaginal recurrence (10% vs none) in patients receiving EBRT without VBT but a lower incidence of bowel toxicity (2.5% vs 18%). Nout et al. (2010) demonstrated a 5-year locoregional relapse rate, vaginal or pelvic recurrence,or both, at 5.1% for VBT and 2.1% for EBRT without a different survival rate. The incidence of acute complications of grade 1-2 gastrointestinal toxicity in the VBT group were lower than in the EBRT group (12.6% vs 53.8%).

In conclusion, this retrospective study in the early stage endometrioid type of endometrial carcinoma showed comparable overall survival rates and toxicities to other studies.

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