**ADJUVANT RADIOTHERAPY FOR ENDOMETRIAL CANCER WITH CERVICAL
STROMAL INVOLVEMENT: A PATTERNS OF PRACTICE SURVEY IN AUSTRALIA AND
NEW ZEALAND**

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RT for endometrial cancer with cervix involvement survey

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ABSTRACT

Introduction: The purpose of this study is to describe the patterns of practice in Australia and New Zealand for post-operative radiotherapy in endometrial cancer with cervical stromal involvement.

Methods and materials: A ten-item survey including five clinical case scenarios in endometrial cancer with cervical stromal invasion was emailed to Royal Australian and New Zealand College of Radiologist (RANZCR) radiation oncologists in 2018. Responses were analysed to determine relative frequency distributions and preferred adjuvant treatment modalities for the clinical case scenarios.

Results: A total of 65 respondents initiated the survey with 27 respondents treating more than 11 endometrial cancer cases annually. Only 31 respondents answered all five clinical case scenarios. Preferred adjuvant radiotherapy modalities varied for the Stage II cases between vault brachytherapy (VB), pelvic external beam radiotherapy (EBRT) or a combination. For the stage IIIA and IIIC1 cases, the majority recommended pelvic EBRT with or without VB boost (79% and 77%), and of these, most combined with chemotherapy (61% and 88%). For 4 of the 5 case scenarios, when pelvic EBRT was offered, most recommended a VB boost.

Conclusion: This patterns of practice survey suggests variability in adjuvant radiotherapy recommendations in endometrial cancer with cervical involvement, particularly in cases where there is lack of randomised data and discrepancies in consensus guidelines.

Keywords: brachytherapy; endometrial cancer; radiation oncology; survey.

Article type : Radiation Oncology Original Article

INTRODUCTION

Uterine cancers are the most common gynaecological malignancy in Australia and New Zealand.^{1,2} Primary management is surgery with total hysterectomy, bilateral salpingo-oophorectomy (BSO) with or without lymph node management and adjuvant treatment recommendations are based on clinicopathological prognostic factors.^{3,4}

Cervical stromal involvement has historically been considered an unfavourable prognostic factor in endometrial cancer.⁵⁻⁷ However, these tumours generally have other known poor prognostic features such as high tumour grade, deep myometrial invasion and lymphovascular space invasion (LVSI), making it difficult to attribute a higher risk of recurrence and lower overall survival to cervical invasion alone.^{3,7,8} There is a lack of randomised evidence to guide adjuvant treatment in this group of patients, likely related to low prevalence. Approaches vary between vaginal vault brachytherapy (VB), external beam radiotherapy (EBRT) or a combination of both, with or without chemotherapy.^{3,4,9} Therefore, the optimal adjuvant treatment approach for patients with endometrial cancer with cervical stromal involvement remains unclear.⁹

The Gynaecology Oncology Radiation Oncology Collaboration (GOROC) is a special interest group of the Royal Australian and New Zealand College of Radiologists (RANZCR). In 2018, GOROC conducted a survey to establish the patterns of practice of adjuvant radiation therapy use in endometrial cancer with cervical stromal involvement amongst radiation oncologists in Australia and New Zealand.

METHODS

A ten-item electronic survey was developed by the GOROC executive members which included five questions about the respondent's involvement with gynaecological cancer radiotherapy and five clinical scenarios to study individual treatment preferences (Table 1).

The five clinical case scenarios related to patients with endometrial cancer managed with surgery and found to have cervical stromal involvement. Survey participants were asked for their preferred adjuvant treatment approach.

Following approval by the Dean of the RANZCR Faculty of Radiation Oncology (FRO), the survey was sent via email to all active RANZCR FRO Fellow, Life and Educational Affiliate members in March 2018 using SurveyMonkey (SurveyMonkey Inc., San Mateo, CA, USA), with one email reminder follow-up in mid April and survey closure in May 2018. The survey was completed anonymously and voluntarily. No reimbursement was offered.

Descriptive analysis was conducted using Stata version 15.1 (StataCorp, College Station, Texas, USA), with results presented as counts and percentage frequencies. Comparisons across groups were assessed using the chi-squared or Fishers' Exact test, with a p-value of less than 0.05 considered to indicate statistical significance.

RESULTS

A total of 65 of 463 RANZCR members (14%) responded to the survey, of which only 20 (31%) were GOROC members. Of the respondents, 39 (65%) personally treated endometrial cancers, of which 19 were not GOROC members. Forty-six (71%) respondents offered VB at their centre. Four GOROC members did not have brachytherapy at their centre, while 8 respondents who treated endometrial cancers at a centre offering VB were not GOROC members.

Sixty-two respondents provided an indication of how many endometrial cancer patients they personally treated with radiotherapy annually. Of these, 6 (10%) respondents treated more than 30 endometrial cases per annum, 21 (34%) treated 11-30 cases per annum, 7 (11%) treated 6-10 cases per annum and 28 (45%) treated 5 or less cases per annum.

When asked how many endometrial cancer patients each respondent's centre treated with radiotherapy annually, 59 responses were obtained. Of these, 21 (36%) respondents came from centres that treated more than 30 cases per annum, 22 (37%) came from centres that treated 11-30 cases per annum, 10 (17%) came from centres that treated 6-10 cases and 6 (10%) came from centres that treated 5 or less endometrial cases per annum.

Clinical Case Scenarios

Case 1: FIGO Stage II Grade 1

There were 40 responses to Case 1. The majority (65%, 26 respondents) preferred adjuvant VB in this case (Figure 1). Of these, 3 offered chemotherapy in combination with brachytherapy. One respondent preferred small field EBRT, 7 respondents (18%) preferred standard pelvic EBRT and 2 of these respondents preferred concurrent and adjuvant chemotherapy with radiation. Five respondents (13%) preferred pelvic EBRT and VB boost, while 1 respondent preferred observation.

Case 2: FIGO Stage IIIA Grade 1

There were 39 responses to Case 2. The majority (31/39, 79%) preferred adjuvant pelvic EBRT, and 65% (20/31) of these respondents offered VB boost whilst 19/31 (61%) respondents preferred combination with chemotherapy (Figure 2). Five respondents (13%) preferred small field EBRT, and 2 of these preferred combination with chemotherapy. Two respondents (5%) preferred para-aortic (PA) and pelvic EBRT and 1 of these preferred the addition of VB boost (no chemotherapy). One respondent preferred a combination of radiotherapy and chemotherapy, but radiotherapy modality was not specified.

Case 3: FIGO Stage II Grade 3

There were 35 responses to Case 3. The majority (66%) preferred adjuvant pelvic EBRT with vaginal VB boost. Of these, 13 (57%) preferred adjuvant EBRT combined with chemotherapy. Seven respondents (20%) preferred adjuvant pelvic EBRT without VB boost with 4 respondents combining with chemotherapy. Four respondents (11%) preferred VB without EBRT (Figure 3). For the 18 responses for combined chemotherapy, preferred timing of chemotherapy relative to radiotherapy was mixed between before radiotherapy (5 respondents), after (4 respondents), concurrent (1 respondent) and concurrent and sequential (8 respondents).

Case 4: FIGO Stage II Grade 2

There were 31 responses to Case 4. Adjuvant therapy preferences were VB alone (29%), small field EBRT alone (13%), pelvic EBRT (26%) and pelvic EBRT with VB boost (32%). Four respondents preferred the addition of chemotherapy with pelvic EBRT (Figure 4).

Case 5: FIGO Stage IIIC1 Grade 2

There were 31 responses to Case 5. The majority (24/31, 77%) preferred adjuvant pelvic EBRT with or without VB boost. Three-quarters (18/24) of these respondents preferred VB boost and 21 (88%) respondents preferred combination with chemotherapy. Five respondents (16%) preferred EBRT targeting PA and pelvic nodes (Figure 5). Two respondents preferred a combination of radiotherapy and chemotherapy, but radiotherapy modality was not specified. Of the 27 respondents who preferred combination with chemotherapy, 15 respondents preferred concurrent and sequential chemotherapy, 8 preferred chemotherapy before radiotherapy, 3 preferred after radiotherapy and 1 preferred concurrent with radiotherapy.

Comparison between higher versus lower volume caseload

Consistency of preferred adjuvant treatment modalities was no better amongst higher case volume radiation oncologists (>10 endometrial cancer patients treated annually) compared with lower case volume radiation oncologists (≤ 10 endometrial cancer patients treated annually) in any of the five clinical cases (Table 2). The spread of recommendations for adjuvant treatment were similar amongst the two groups for Cases 2, 4, and 5 ($p = 1.000$). For Case 1, VB alone was recommended by less higher case volume radiation oncologists (56.5%) compared with lower case volume radiation oncologists (76.5%). For Case 3, a VB boost was added to EBRT by less higher case volume radiation oncologists (52.2%) compared with lower case volume radiation oncologists (64.7%). However, these differences were not statistically significant.

DISCUSSION

This patterns of practice survey demonstrates a wide range of practice amongst radiation oncologists in Australia and New Zealand regarding adjuvant radiotherapy for endometrial

cancer with cervical stromal invasion, particularly in areas where there is lack of phase III evidence and heterogeneity in consensus recommendations.

The European Society for Medical Oncology (ESMO), European Society of Gynaecological Oncology (ESGO) and European Society of Radiotherapy and Oncology (ESTRO), the American Society for Radiation Oncology (ASTRO) and National Comprehensive Cancer Network (NCCN) have published consensus guidelines to direct adjuvant radiotherapy decisions for endometrial cancer.^{3,4,10}

For FIGO stage II disease, the ESMO-ESGO-ESTRO guidelines recommend adjuvant VB for surgically node negative, grade 1-2, LVSI negative tumours whilst they recommend limited field EBRT with consideration of brachytherapy boost if surgically node negative Grade 3 or LVSI positive. Chemotherapy is investigational for these patients. In the absence of surgical nodal staging, EBRT with consideration of VB boost and sequential adjuvant chemotherapy is recommended.³ The ASTRO guidelines, on the other hand, recommend pelvic EBRT for endometrial cancer with cervical stromal invasion and suggest VB boost may not be necessary unless risk factors for vaginal recurrence are present.⁴ NCCN also recommends EBRT as the preferred modality for Stage II and/or VB, with or without systemic therapy. VB is also an option for low grade disease with negative surgical staging or minimal invasion. Observation is also felt to be an option in NCCN guidelines for patients who have had a radical hysterectomy with negative margins.¹⁰ There are retrospective studies that suggest VB alone may be suitable in selected Stage II patients.^{8,9}

In the survey, 65% of respondents preferred the use of VB in FIGO Stage II, grade 1, surgically node negative disease with no LVSI (Case 1). 33% preferred either small field or pelvic EBRT with or without a brachytherapy boost. 1 respondent preferred observation. However, for the patient with FIGO Stage II, grade 2, LVSI negative and surgically node negative disease (Case 4), the preferred adjuvant radiation modality was divided between adjuvant VB (29%), pelvic EBRT (26%) and pelvic EBRT with brachytherapy boost (32%). For the patient with FIGO stage II, grade 3 disease with extensive LVSI and surgically node negative (Case 3), 86% of respondents preferred adjuvant pelvic EBRT, in keeping with the ASTRO and NCCN guidelines, however, 77% of these respondents also preferred a VB boost after EBRT. Only 1 respondent preferred small field EBRT.

For Stage III disease, the ESMO-ESGO-ESTRO and ASTRO guidelines recommend EBRT and chemotherapy, whilst NCCN guidelines recommend systemic therapy, and/or EBRT with or without VB. None of the guidelines specifically examine cervical stromal invasion in

Stage III disease.^{3,4,10} Both ESTRO-ESGO-ESTRO and ASTRO guidelines discuss the controversies around the addition of a VB boost in combination with EBRT, with paucity of prospective randomised data comparing EBRT with or without VB boost. There are, however, retrospective studies that report on VB boost after adjuvant EBRT with excellent locoregional control and low vaginal recurrence rates.¹¹⁻¹³ Its use is common enough that prospective trials often allow a VB boost after EBRT in the study design.⁴

In the survey, 79% of respondents to the patient with FIGO Stage IIIA disease with cervical stromal invasion (Case 2) preferred adjuvant pelvic EBRT with (65%) or without (35%) VB boost. However, only 61% (19/31 respondents) recommended combination of radiotherapy with chemotherapy. For the patient with Stage IIIC1 disease with cervical involvement (Case 5), 94% recommended some form of EBRT (with the remaining 6% not specifying radiation modality) and 87% of these respondents preferred a combination with chemotherapy, in keeping with consensus guidelines. 68% preferred the addition of VB boost.

The use of combined EBRT and chemotherapy in advanced endometrial cancers is widely supported by prospective randomised studies and reflected in the published guidelines. De Boer et al.¹⁴ demonstrated improved 5 year overall survival and failure free survival in their Post Operative Radiation Therapy in Endometrial Cancer 3 (PORTEC 3) study with combined chemoradiotherapy in high risk Stage I and Stage II-III endometrial cancers versus radiotherapy alone, with greatest benefit seen in Stage III disease and those with serous carcinomas. Matei et al.¹⁵ in the Gynecologic Oncology Group (GOG) 258 study showed similar recurrence free survival and overall survival rates in Stage III-IVA endometrial cancers treated with adjuvant chemotherapy alone versus combined chemoradiotherapy, however, nodal and vaginal failures were significantly lower with the combined chemoradiotherapy arm. Although combined modality adjuvant therapy is widely employed in advanced endometrial cancers, there remains debate regarding optimal sequencing of EBRT and chemotherapy. PORTEC 3 and GOG 258 used a concurrent and adjuvant approach, however, there are studies that suggest alternative sequencing strategies such as the “sandwich” approach^{16,17} (3-4 cycles of chemotherapy, EBRT then further 2-3 cycles of chemotherapy) or upfront chemotherapy followed by EBRT may be acceptable.¹⁸

Although the majority of respondents preferred combination chemotherapy with radiotherapy in Stage III disease, there was a variation in sequencing preference in the Stage IIIA case (Case 3) and in the Stage IIIC case (Case 5), although concurrent and sequential was the

more favoured timing in both cases (44% and 55% respectively). In Stage II disease, where chemotherapy remains investigational, there was even less uniformity amongst respondents.

This study has several limitations including the small number of participants and the inclusion of radiation oncologists with limited experience in the management of gynaecological cancers. However, the results of the study provide a current assessment of practice patterns in Australia and New Zealand with useful information on the trends of radiotherapy preference in endometrial cancer with cervical stromal invasion. Areas with more robust evidence such as the use of a combined modality approach in Stage III endometrial cancer showed more homogeneous treatment preferences, however, large differences in respondent preference were seen in areas of controversy, such as the use of VB boost or timing of chemotherapy.

CONCLUSION

Adjuvant radiation therapy has an important role in the management of endometrial cancers, although there remain areas with limited evidence to guide practice. This survey demonstrates heterogeneity in preferred adjuvant radiotherapy modalities, particularly for Stage II disease. The role of VB boost and optimal timing of chemotherapy is still being determined. Further prospective research is required to provide more guidance on the optimal adjuvant therapy pathways for endometrial cancer with cervical stromal invasion.

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Table 1: Survey questions

1. Are you a member of GOROC?
2. Do you personally treat endometrial cancers?
3. Does your centre offer vaginal brachytherapy?
4. How many endometrial cancer patients do you treat with radiation per annum?
5. How many endometrial cancer patients does your centre treat with radiation per annum?
Clinical case scenarios
Case 1 Age: 62 Presentation: Post-menopausal bleeding Imaging: US - thickened endometrium D&C: atypical complex hyperplasia with possible endometrioid adenocarcinoma Surgery: TAH, BSO, SNB Pathology: Grade 1 endometrioid adenocarcinoma with 4/9mm myometrial invasion. No LVSI. Carcinoma extended to upper end of endocervical canal with a small deposit 0.2 mm deep, composed of a few glands. Stromal involvement confirmed. Margins clear. Right sentinel node specimen showed benign fatty tissue only FIGO Stage II Grade 1 Co-morbidities: overweight, hypertension, previous surgery for ovarian cyst and bladder repair
Case 2 Age: 67 Surgery: TAH, BSO, PLND Imaging: MRI - Stage IIIA (serosa) pre-op with cervical involvement suspected and possible left parametrium involvement

CT - Para-aortic nodes normal and chest normal

Pathology: Grade 1 endometrioid adenocarcinoma extending to serosal surface, cervical stromal involvement, parametrial margin 0.2mm, cervical radial margin 3mm with endocervical and ectocervical margins 8mm. No LVSI. 0/14 lymph nodes (LN), washings negative

FIGO Stage IIIA Grade 1

Co-morbidities: BMI 36

Case 3

Age: 58

Surgery: TLH, BSO, PLND

Imaging:

MRI - Not supplied

CT - nodes normal; chest - 2 tiny non-specific lung nodules, for re-imaging

Path: G3 endometrioid adenocarcinoma, 6/11mm myometrial invasion, with extensive LVSI, plus focal cervical stromal invasion, 0/15 pelvic LN

FIGO Stage II Grade 3

Co-morbidities: nil

Case 4

Age: 79

Surgery: TAH, BSO, PLND

Imaging:

US - pedunculated lobulated mass plus additional mass

MRI - 3 malignancies in uterus extending beyond junctional zone, outer myometrium, cervix probably not involved, plus cyst outside on pelvic sidewall, likely ovary – no solid component; irregular left inguinal LN (unable to be found on US guided FNA)

Clinical pre-op stage IB

Pathology: Grade 2 endometrioid adenocarcinoma extending nearly to serosal surface, no LVSI, cervical stromal involvement present, ovaries and tubes uninvolved, 0/9 LN, well clear margins (20mm) but 0.1mm to serosa

FIGO Stage II Grade 2

Co-morbidities: BMI 30; hypertension, hyperlipidaemia, previous appendicectomy and ovarian cystectomy

Case 5

Age: 62

Presentation: 3 months post-menopausal bleeding

Imaging: Pelvic US - thickened endometrium 18mm

CT abdomen/pelvis - suspicious 11mm left external Iliac LN; CT lung clear

No MRI

Surgery: TLH, BSO, omentectomy, washings, pelvic LN sampling, para-aortic LN intra-operatively benign but not sampled

Pathology: Grade 2 endometrioid adenocarcinoma of endometrium, 12/15mm myometrial invasion with focal LVSI and cervical stromal involvement. 2/6 pelvic LN (2/2 left obturator). Margins, tubes, ovaries, omentum and washings clear
FIGO Stage IIIC1 Grade 2

BSO = bilateral salpingo-oophorectomy; D&C = dilatation and curettage; FIGO = International Federation of Gynaecology and Obstetrics; FNA = fine needle aspirate; GOROC = Gynaecology Oncology Radiation Oncology Collaboration; LN = lymph node; LVSI = lymphovascular space invasion; PLND = pelvic lymph node dissection; SNB = sentinel node biopsy; TAH = total abdominal hysterectomy; TLH = total laparoscopic hysterectomy; US = ultrasound

Table 2: Comparison of preferred adjuvant treatment modalities based on number of endometrial cancer patients treated annually

Case 1 - by number of endometrial patients treated				
Radiotherapy	≤10	>10	Total	p-value
VB only	13 (76.5)	13 (56.5)	26	0.592
EBRT	3 (17.7)	5 (21.7)	8	
EBRT + VB	1 (5.9)	4 (17.4)	5	
RT not specified	0	1 (4.4)	1	
Total	17	23	40	
Case 2 - by number of endometrial patients treated				
Radiotherapy	≤10	>10	Total	p-value
VB only	0	0	0	1.000
EBRT	7 (41.2)	10 (43.5)	17	
EBRT + VB	9 (52.9)	12 (52.2)	21	
RT not specified	1 (5.9)	1 (4.4)	2	
Total	17	23	40	
Case 3 - by number of endometrial patients treated				
Radiotherapy	≤10	>10	Total	p-value
VB only	2 (11.8)	2 (8.7)	4	0.274
EBRT	1 (5.9)	7 (30.4)	8	
EBRT + VB	11 (64.7)	12 (52.2)	23	
RT not specified	3 (17.7)	2 (8.7)	5	
Total	17	23	40	
Case 4 - by number of endometrial patients treated				
Radiotherapy	≤10	>10	Total	p-value
VB only	4 (23.5)	5 (21.7)	9	1.000
EBRT	5 (29.4)	7 (30.4)	12	
EBRT + VB	4 (23.5)	6 (26.1)	10	
RT not specified	4 (23.5)	5 (21.7)	9	
Total	17	23	40	
Case 5 - by number of endometrial patients treated				
Radiotherapy	≤10	>10	Total	p-value
VB only	0	0	0	1.000
EBRT	3 (17.7)	5 (21.7)	8	

EBRT + VB	9 (52.9)	12 (52.2)	21
RT not specified	5 (29.4)	6 (26.1)	11
Total	17	23	40

EBRT = external beam radiotherapy; RT = radiotherapy; VB = vault brachytherapy;

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