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Original Research

Relapse Frequency and Pattern Following Adjuvant Radiotherapy for Intermediate and High-Intermediate Risk Endometrial Cancer Based on Retrospective ESGO-ESTRO-ESP Risk Classification

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Abstract

Background: The management of early-stage endometrial cancer (EC) consists of surgery followed by tailored adjuvant therapy, largely based on the risk of loco-regional recurrence. We evaluated the frequency and site of first relapse in patients who received vaginal brachytherapy (VBT) or pelvic external beam radiotherapy (EBRT) for early-stage EC. These data were stratified retrospectively according to the European Society of Gynaecological Oncology–European Society of Radiotherapy and Oncology–European Society of Pathology (ESGO-ESTRO-ESP, 2020) intermediate risk endometrial cancer (IR-EC) and high-intermediate risk endometrial cancer (HIR-EC) classifications. **Methods**: The central radiotherapy prescribing system within the West of Scotland Cancer Network was analyzed to identify International Federation of Gynaecology & Obstetrics (FIGO) Stage I–II EC patients who commenced VBT, at a dose of 2100 cGy for 3 fractions, and/or EBRT, at 4500 cGy for 25 fractions, between 1st January 2017 and 31st December 2019. Clinical follow-up was conducted until death or for a maximum of five years (data lock 31st December 2022). Imaging was performed if recurrence was suspected. Statistical analysis was implemented using R statistical software (v4.4.1). **Results**: In total, 282 patients were identified. The median age was 69 years (range: 37–92 years), and the median follow-up was 33 months (range: 0–68 months). Stage distribution: IA (25.2%), IB (57.4%), and II (17.4%). The pathology subtype was predominantly endometrioid (93.6%), but 6.4% of patients had non-endometrioid histology with no myometrial invasion. IR-EC patients comprised 51.1% of the series; all received VBT and no adjuvant chemotherapy. The HIR-EC cohort comprised 48.9% of the series; just over half received EBRT, and adjuvant chemotherapy was delivered to 15.9%. By the end of the study, 37 (13.1%) patients had relapsed, and 41 (14.5%) had died, 22/41 (53.7%) of which were attributable to EC. Recurrences were documented in 11.1% of the IR-EC patients and 15.2% of the HIR-EC patients. Vaginal, pelvic, and distant relapses per risk group and treatment were: 2.1%, 7.6%, and 6.9% in IR-EC (VBT-treated), respectively; 3.1%, 16.9%, and 6.2% in the HIR-EC (VBT-treated), respectively; 0%, 6.9%, and 9.6% in the HIR-EC (EBRT-treated), respectively. None reached statistical significance ($p = 0.34$, Fisher's exact test). Salvage therapy for locoregional recurrence was performed in 3.5% (10/282) of patients, and virtually all pelvic relapses were symptomatic. **Conclusions**: Vaginal relapse rates were very low (1.8%). However, pelvic recurrences occurred in 16.9% of the HIR-EC (VBT-treated) patients, suggesting that external beam radiotherapy should be considered to optimize loco-regional control in this group.

Keywords: endometrial cancer; vaginal brachytherapy; external beam radiotherapy; relapse; salvage; follow up

1. Introduction

The management of Stage I-II endometrial cancer (EC) consists of surgery followed by tailored post-operative therapy, largely based on risk of locoregional recurrence. Historically, pathological risk factors were identified in the Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) [1] and Gynecological Oncology Group (GOG) 99 trials [2], namely grade 3, age older than 60 years, outer 50% myometrial invasion, and presence of lymphovascular space invasion (LVSI). The resultant definition of high-intermediate risk endometrial cancer (HIR-EC) in PORTEC-2 directed the choice of adjuvant radiation for the following groups of patients: (1) age greater than 60 years, $\geq$50% myometrial invasion, and grade 1 or 2 disease; (2) age greater than 60 years, $<$50% myometrial invasion and grade 3 disease; (3) stage IIA endometrial cancer based on International Federation of Gynaecology & Obstetrics (FIGO) 1998 classification (any age, apart from grade 3 tumours with $\geq$50% myometrial invasion) [3]. Vaginal brachytherapy (VBT) was adopted as the standard of care as vault relapse rates were non-inferior to external beam radiotherapy (EBRT) and the late toxicity profile was more favourable [3]. In 2016, the combined European Society for Medical Oncology–European Society of Gynaecological Oncology–European Society of Radiotherapy and Oncology (ESMO-ESGO-ESTRO) joint guideline on EC was published and considered the benchmark for optimiz-

ing and standardizing management of EC across Europe [4]. Evaluation of risk criteria re-defined the intermediate-risk (IR-EC) and HIR-EC groups, and this is a continually evolving process. IR-EC was described as FIGO 2009 stage I low grade endometrioid pathology, with outer 50% myometrial invasion, and LVSI focal or negative, or grade 3 endometrioid pathology with inner 50% myometrial invasion and LVSI focal or negative. Essentially, IR-EC is broadly representative of the PORTEC-2 population with a key feature being the absence of substantial LVSI. Conversely, LVSI positivity in the context of stage I endometrioid pathology is synonymous with HIR-EC. VBT was recommended for patients with IR-EC, especially if aged $\geq$60 years, to optimize vaginal control rates, but EBRT or VBT (+/– chemotherapy) could be considered for HIR-EC depending on the precise combination of clinical, pathological, and surgical factors, including whether pelvic lymph node dissection (PLND) or sentinel node staging was performed [4].

In the advent of the Cancer Genome Atlas (TCGA) programme, the identification of four separate EC subgroups–*p53* mutant, mismatch repair (MMR) deficient, DNA polymerase epsilon (POLE) hyper-mutated, and no specific molecular profile (NSMP)–challenged the traditional histopathology classification of EC [5]. The prognostic significance of these four groups is reproducible across multiple series and molecular profiling has the advantage of being less subject to inter-observer variation. Updated European guidelines have since been produced, European Society of Gynaecological Oncology–European Society of Radiotherapy and Oncology–European Society of Pathology (ESGO-ESTRO-ESP) [6], taking genotype into account. A complex algorithm previously based on FIGO stage, tumour grade, pathology subtype, depth of myometrial invasion, presence or absence of LVSI, and nodal status unknown (Nx) or node negative (N0) status is now subdivided into whether molecular profiling is available or not. IR-EC is no longer restricted to endometrioid EC, providing there is no myometrial invasion. Although the mainstay of HIR-EC still consists of stage I endometrioid cancers with substantial LVSI, this category has been extended to encompass stage II tumours of endometrioid subtype. As before, VBT alone (or observation) remains the adjuvant treatment of choice for IR-EC (even for aggressive subtypes), but the optimal post-operative management of HIR-EC might require a more intensified or multimodality approach based on intricate assessment of individual patient factors [6].

In the UK, the British Association of Gynaecological Pathologists (BAGP) recommend reflex testing for at least MMR and *p53*, and preferably POLE, on all EC cases at diagnostic biopsy [7]. This practice is being increasingly implemented across all centres, facilitated by regional genomic hubs in national health service (NHS) England & Wales, and a similar infrastructure in Scotland is now in place. EC is the fourth most common malignancy affecting females in Scotland and the incidence is predicted to increase over the next decade [8]. The West of Scotland Cancer Network (WOSCAN) provides oncology input to approximately half of the Scottish population. All gynaecological oncology radiotherapy and/or systemic treatment is performed at a single tertiary referral centre. Over 100 patients are referred for adjuvant therapy for EC every year. A significant proportion are socioeconomically deprived with high body mass index and multiple medical comorbidities, which can influence the choice of therapy. We evaluated the use of VBT and/or EBRT in our population based on ESGO-ESTRO-ESP 2020 IR-EC and HIR-EC risk criteria and documented the frequency and pattern of first relapse in both groups of patients.

2. Materials and Methods

The central radiotherapy prescribing system at WOSCAN was interrogated to identify patients who commenced VBT, 2100 cGy in 3 fractions, or EBRT, 4500 cGy in 25 fractions, between 1st January 2017 and 31st December 2019. Inclusion criteria consisted of FIGO (2018) stage I–II endometrioid EC (or stage IA non-endometroid EC in the absence of myometrial invasion). Re-staging according to FIGO 2018 was performed on all those who were diagnosed during the first half of the study when FIGO 2009 was in use. Patient demographics, including clinical and pathological data, and treatment details were collated from the corresponding medical records. Retrospective risk classification–IR-EC and HIR-EC–was applied based on ESTRO-ESGO-ESP 2020 Consensus Guidelines [6]. Molecular profiling was not available during the period of investigation.

High dose rate VBT was delivered by a vaginal cylinder with Iridium-192 source loading confined to the upper 4 cm and prescribed to 5 mm depth. In the absence of EBRT, 2100 cGy in 3 fractions is administered over two weeks. Otherwise, 1200 cGy in 3 fractions is delivered following EBRT to the pelvis. EBRT was planned on computed tomography (CT) images utilsing RapidArc technique. Set up consisted of an empty rectum and comfortably full bladder. Clinical target volume to the lymph nodes (CTVn) encompasses the obturator and iliac chains up to the level of the L4/L5 interface. The clinical target volume to the central pelvis (CTVcp) is delineated as the superior 2.5 cm vagina and parametrial tissue. Appropriate margins are added to create corresponding planning target volumes (PTV); adaptive plans are then formulated based on predicted rectal motion. Daily cone beam CT technology permits the selection of "plan of the day" with optimal PTV coverage to avoid geographical miss. Standard dose fractionation at WOSCAN consists of 4500 cGy in 25 fractions prescribed to the isocentre over 5 weeks.

Adjuvant chemotherapy, consisting of Carboplatin area under the curve (AUC) 5 and Paclitaxel 175 mg/m^2,

Table 1. Patient demographics.

Clinical Characteristic	All n = 282	IR-EC (VBT) n = 144	HIR-EC (VBT) n = 65	HIR-EC (EBRT) n = 73
Age (years)				
Median (range)	69 (37–92)	69 (43–92)	67 (37–88)	69 (31–80)
<60	61 (21.6%)	27 (18.8%)	17 (26.2%)	17 (23.3%)
60–69	99 (35.1%)	50 (34.7%)	21 (32.3%)	28 (38.4%)
70–79	100 (35.5%)	54 (37.5%)	20 (30.8%)	26 (35.6%)
≥80	22 (7.8%)	13 (9.0%)	7 (10.7%)	2 (2.7%)
FIGO stage				
IA	71 (25.2%)	56 (38.9%)	15 (23.1%)	-
IB	162 (57.4%)	88 (61.1%)	23 (34.5%)	51 (69.9%)
II	49 (17.4%)	-	27 (41.5%)	22 (30.1%)
Grade				
1–2	197 (69.9%)	102 (70.8%)	52 (80%)	43 (58.9%)
3	85 (30.1%)	42 (29.2%)	13 (20%)	30 (41.1%)
Pathology subtype				
EEC	264 (93.6%)	126 (87.5%)	65 (100%)	73 (100%)
Non-EEC	18 (6.4%)	18 (12.5%)	-	-
LVSI				
Present	106 (37.6%)	-	46 (70.1%)	60 (82.2%)
Absent	176 (62.4%)	144 (100%)	19 (29.2%)	13 (17.8%)
PLND				
Yes	34 (12.1%)	21 (14.6%)	11 (16.9%)	2 (2.7%)
No	248 (87.9%)	123 (85.4%)	54 (83.1%)	71 (97.3%)
Chemotherapy				
Yes	22 (7.8%)	-	10 (15.4%)	12 (16.4%)
No	260 (92.2%)	144 (100%)	55 (84.6%)	61 (83.6%)

Abbreviations: EBRT, external beam radiotherapy; EEC, endometrioid endometrial cancer; FIGO, International Federation of Gynaecology & Obstetrics; HIR-EC, high-intermediate risk endometrial cancer; IR-EC, intermediate risk endometrial cancer; LVSI, lympho-vascular space invasion; PLND, pelvic lymph node dissection; VBT, vaginal brachytherapy.

was considered in patients with grade 3 (G3) tumours and substantial LVSI. Up to 6 cycles were delivered prior to EBRT and/or VBT. Clinical follow up, consisting of vaginal and abdominal examination, was performed 4–6 monthly until death or 3–5 years had elapsed (data lock 31st December 2022). Imaging was requested, primarily CT thorax/abdomen/pelvis and/or magnetic resonance imaging (MRI) pelvis, if recurrence was suspected. First site of relapse was recorded as vagina only, pelvis only, distant only, or a combination. Frequencies were compared descriptively. Statistical analysis was performed using R statistical software (v4.4.1; R Foundation for Statistical Computing, Vienna, Austria). Categorical data was compared using the Fisher exact test as part of the gtsummary package. Multivariate logistic regression analysis was performed using the glm function from the stats package, to model risk factors for relapse. Ethical approval was not required due to the retrospective nature of this study. All data was managed appropriately in accordance with Caldicott guidelines.

3. Results

A total of 282 patients were identified. The median age was 69 years; just over 20% of the cohort were aged <60 years and less than 10% were 80 years or older. Patient demographics pertaining to the entire cohort and a breakdown based on risk group are illustrated in Table 1. The proportion of patients with IR-EC and HIR-EC was 51.1% (144/282) and 48.9% (138/282), respectively. Within the HIR-EC group, 47.1% (65/138) received adjuvant VBT and 52.9% (73/138) received EBRT to the pelvis, all of whom completed 4500 cGy in 25 fractions over five weeks. Additional VBT was delivered to the 22 HIR-EC patients with cervical involvement. The majority of patients had stage I, grade 1–2 endometrioid EC, and/or no LVSI. Rates of grade 3 EC and positive LVSI were highest in the HIR-EC group who received EBRT; 41.1% (30/73) and 82.2% (60/73), respectively. The proportion of HIR-EC patients with the combination of a grade 3 tumour plus LVSI was 20.3% (28/138). Of note, 12.5% (18/144) of the IR-EC patients had non-endometrioid high-risk pathology subtype; all had EC confined to a polyp with no evidence of myometrial invasion. Pelvic lymph node dissection (PLND) was performed in 12.1% (34/282) of cases; nodal staging was least frequently applied in the HIR-EC group who received EBRT at just 2.7% (2/73). Unknown nodal status/lymphovascular space invasion (Nx/LVSI) positive sta-

tus was recorded in 71.7% (99/138) of HIR-EC patients (41/65 VBT-treated and 58/73 EBRT-treated). Adjuvant chemotherapy, consisting of 3-weekly carboplatin + paclitaxel (median 4 cycles, range 1–6), was administered to less than 10% of the cohort and only in those with HIR-EC features.

After median follow up of 33 months (range 0–68 months), the relapse rate was 13.1% (37/282) overall. Deaths occurred in 41 cases, 22 of which were attributed to EC. Relapses more frequently developed in patients with HIR-EC compared with IR-EC (15.2% *vs.* 11.1%), stage II EC as opposed to stage I EC (22.4% *vs.* 11.2%), grade 3 compared with grade 1–2 tumours (16.5% *vs.* 11.7%), and in those with positive LVSI rather than none or focal LVSI (16.9% *vs.* 10.8%). There was also a slightly higher recurrence rate in younger patients aged <60 years (16.4%) compared with the population aged 60 years and above (12.2%). See Table 2.

Table 2. Relapse rate based on clinical characteristics.

Characteristic	Relapse
Risk group	
Intermediate	16/144 (11.1%)
High-intermediate	21/138 (15.2%)
Age (years)	
<60	10/61 (16.4%)
≥60	27/221 (12.2%)
Grade	
1–2	23/197 (11.7%)
3	14/85 (16.5%)
Pathology subtype	
Endometrioid	34/264 (12.9%)
Non-endometrioid	3/18 (16.7%)
FIGO Stage	
I	26/233 (11.2%)
II	11/49 (22.4%)
PLND	
Yes	13/34 (38.2%)
No	24/248 (9.7%)
LVSI	
Present	18/106 (16.9%)
Absent	19/176 (10.8%)
Chemotherapy	
Yes	8/22 (36.4%)
No	29/260 (11.2%)

Abbreviations: FIGO, International Federation of Gynaecology & Obstetrics; LVSI, lympho-vascular space invasion; PLND, pelvic lymph node dissection.

The pattern of first relapse is demonstrated in Table 3. Vaginal failure rate was very low at 1.8% (5/282) and there were no vaginal recurrences, isolated or otherwise, in HIR-EC patients who received EBRT. Pelvic recurrences were highest in the VBT-treated HIR-EC group at 16.9% (11/65) whereas distant recurrences were most prevalent in the EBRT-treated HIR-EC group at 9.6% (7/73). Overall, differences in relapse rates within the cohorts did not reach statistical significance (p = 0.34). In addition, multivariate logistic regression analysis was attempted to model factors that influence relapse whilst controlling for confounding factors. However, the number of events in this dataset were too few to create a model including all relevant factors: age (<60 years *vs.* ≥60 years); grade (G1/2 *vs.* G3); stage (I *vs.* II); LVSI status (presence *vs.* absence); and, treatment (VBT *vs.* EBRT). The McFadden's R^2 values for the models were suboptimal (<0.05) indicating low predictive ability. Within the IR-EC cohort, relapse was documented in 3/18 cases with non-endometrioid pathology (all of whom developed distant metastases). The adjusted relapse rates based on IR-EC patients with endometrioid pathology only were vaginal 2.4%, pelvic 7.9%, distant 5.6%, and overall 10.3%.

As the pelvic failure rate was more than doubled in the HIR-EC patients who received VBT compared with those who received EBRT, we examined this group in more detail in order to ascertain whether EBRT was underutilized. As the previous ESMO-ESGO-ESTRO guideline (which was in use during the time period in question) and the current adaptation are not identical, we focused on the Nx group with positive LVSI as EBRT is recommended in this context in both versions [4,6]. Of the 41 Nx/LVSI positive VBT-treated patients, EBRT was considered in over 90% (37/41), but VBT was selected due to a combination of patient factors and clinician preference, as shown in Table 4. Across both HIR-EC cohorts, LVSI was present in 18/21 patients who relapsed (10/12 in the VBT-treated group and 8/9 in the EBRT-treated group).

The majority of patients with isolated locoregional recurrence presented with symptoms between scheduled hospital appointments, with a single exception. The most common symptoms consisted of pelvic pain, vaginal bleeding, and lower limb swelling. Salvage therapy was deemed feasible in 10/16 cases with relapse confined to the pelvis (based on extent of disease and patient fitness), predominantly by radical radiotherapy or chemoradiotherapy, but exenterative surgery was recommended in one patient who developed peri-urethral recurrence following adjuvant EBRT for HIR-EC. Pelvic control was achieved in 7 of these 10 patients at the time of last follow up (1–24 months post salvage treatment), but only 5/10 were disease-free.

4. Discussion

To summarise, in this retrospective series, clinical outcomes were very favourable in patients with stage I IR-EC who received adjuvant VBT with extremely low rates of vaginal recurrence detected after median follow up of just under three years. However, VBT was associated with a higher frequency of pelvic relapse in stage I/II HIR-EC pa-

Table 3. Site and frequency of relapse.

Relapse	All n = 282	IR-EC (VBT) n = 144	HIR-EC (VBT) n = 65	HIR-EC (EBRT) n = 73	*p*-value[1]
Isolated vaginal	3 (1.1%)	1 (0.7%)	2 (3.1%)	-	0.20
Total vaginal	5 (1.8%)	3 (2.1%)	2 (3.1%)	-	0.35
Isolated pelvic	16 (5.7%)	6 (4.2%)	8 (12.3%)	2 (2.7%)	0.04
Total pelvic	27 (9.6%)	11 (7.6%)	11 (16.9%)	5 (6.9%)	0.09
Isolated distant	10 (3.5%)	5 (3.5%)	1 (1.5%)	4 (5.5%)	0.49
Total distant	21 (7.4%)	10 (6.9%)	4 (6.2%)	7 (9.6%)	0.76
Overall	37 (13.1%)	16 (11.1%)	12 (18.5%)	9 (12.3%)	0.34

Abbreviations: EBRT, external beam radiotherapy; HIR-EC, high-intermediate risk endometrial cancer; IR-EC, intermediate risk endometrial cancer; VBT, vaginal brachytherapy. [1]Fisher's exact test.

Table 4. Reason for selection of VBT rather than EBRT in HIR-EC Nx/LVSI positive patients.

Reason	Number of patients
	n = 41
Performance status and/or comorbidities	13 (31.7%)
Patient choice	7 (17.1%)
Clinician preference	7 (17.1%)
Synchronous malignancy	5 (12.2%)
Age	5 (12.2%)
Unclear	4 (9.7%)

Abbreviations: EBRT, external beam radiotherapy; HIR-EC, high-intermediate risk endometrial cancer; VBT, vaginal brachytherapy; Nx/LVSI, unknown nodal status/lymphovascular space invasion.

tients compared with EBRT. Salvage therapy for locoregional recurrence was performed in 3.5% (10/282) of patients in the entire cohort.

The adjuvant management of early stage EC has gradually evolved from pelvic radiotherapy in all but the lowest risk patients to de-escalation of treatment with the adoption of VBT based on the traditional PORTEC-2 definition of HIR-EC [3]. Based on current European guidelines, the majority of the PORTEC-2 population would now be described as IR-EC, and VBT alone is recommended in this group to decrease the risk of vaginal relapse, but can be omitted if age at diagnosis is less than 60 years [4,6]. At WOSCAN, VBT is offered to all patients with IR-EC, regardless of age, as evidenced by the range from 43 to 92 years. The proportion aged less than 60 years was 18.8% (27/144) and is unlikely to augment the disease control rates, especially as recurrences developed in 14.8% (4/27) of these patients. Overall, the vaginal, pelvic, and distant relapse rates of 2.1%, 7.6%, and 6.9%, in the IR-EC cohort after a median follow up of 33 months compare favourably with the PORTEC-2 results. Estimated five-year recurrence patterns in the VBT-treated arm after median follow up of 45 months were purported to be 1.8% (vaginal), 5.1% (pelvic) and 8.3% (distant) [3]. We can only speculate as to the potential longer term control rates in our series, but ten-year outcomes from PORTEC-2 were not significantly higher than the previously reported findings; vault recurrence 3.4%, pelvic recurrence 6.3% (most combined with systemic metastases), and distant recurrence 10.4% [9]. The majority of failures in PORTEC-2 were distant, but in our series, there was a slightly higher proportion of pelvic recurrences, out with the vaginal vault, compared with that of the trial population. Over time, the pattern may become more divergent as most locoregional recurrence tend to occur early, within two years [10]. As PLND was only performed in 14.6% of our patients with IR-EC we may have inadvertently included a small number of patients with occult stage IIIC EC. Likewise, systematic lymphadenectomy was not routinely undertaken in the trial [3]. Alternatively, it is feasible that underlying pathological and/or molecular subtype contributed to frequency and pattern of recurrence. Unfortunately, molecular testing was not introduced in WOSCAN until early 2022 and this information was therefore not available during the period of the study. Of note, three of the nine distant failures had non-endometrioid pathology, albeit confined to a polyp, despite data suggestive of favourable outcomes if there is no myometrial invasion [11]. However, this group have generally been excluded from randomized trials and several retrospective/population based studies, predominantly focused on high grade serous EC, advise caution in offering VBT alone [12,13]. Excluding all of the non-endometrioid cases from the IR-EC cohort resulted in similar relapses rates. Of the recurrences in IR-EC VBT-treated patients with endometrioid pathology, more than half had grade 1–2 tumours. Although aberrations in *p53* are typically associated with grade 3 tumours, this is not invariable. Low grade

EC may possess *p53* mutations which can negatively impact on loco-regional control [14–17]. If molecular testing had been performed routinely, it is possible that a minority of the IR-EC patients would have been classified as high-risk and managed more aggressively.

Comparison of the two groups of HIR-EC patients revealed a higher overall failure rate in the VBT-treated cohort, most of whom had pelvic recurrence. Again, rates of PLND were low, at just under 10% for all HIR-EC patients, although lymphadenectomy was more likely to have been performed in the VBT-treated cohort (16.9% *vs.* 2.7%). We may have under-staged a proportion of patients and it is of interest to note that almost 40% of patients who had undergone PLND developed a recurrence, suggesting that only the highest risk patients were fully staged. There are plans to implement sentinel node biopsy imminently in order to more accurately characterize the N0 population especially as European guidelines now recommend surgical staging in HIR-EC (and consideration in IR-EC) [6]. However, we suspect that LVSI status is also important. Almost 85% of relapses in the VBT-treated group developed in those with substantial LVSI. This is already known to be a risk factor for loco-regional recurrence [18,19] and EBRT is recommended in Nx patients with positive LVSI [4,6]. Moving forward, we are more likely to strongly consider EBRT in this group, although careful risk-balance analysis is required particularly in elderly patients over 80 years [20], and a substantial proportion had comorbidities or contra-indications that precluded EBRT to the pelvis, including prior radiation. At the time of the investigation, the GOG249 trial had completed recruitment and results were awaited, but a number of patients were treated with a similar protocol off study due to clinician preference as they were deemed to be at high risk of distant relapse. GOG249 randomised patients with FIGO 2009 stage IB grade 3 endometrioid EC, stage II endometrioid EC, or stage I/II serous/clear cell EC to EBRT or three cycles of carboplatin + paclitaxel chemotherapy and VBT [21]. Five-year outcomes revealed no difference in relapse-free or overall survival. However, despite 89% undergoing PLND, pelvic and para-aortic failures were significantly more frequent in the non-EBRT arm (9% *vs.*4%) [21], demonstrating the importance of EBRT in loco-regional control. Interestingly, virtually all of the relapses in our EBRT-treated cohort occurred in the presence of LVSI, compounding this pathological feature as a potential risk factor for recurrence, although we were not able to demonstrate statistical significance. The use of chemotherapy was low in our series (approximately 15% in both HIR-EC cohorts) and therefore the numbers are too small to draw any conclusions, but intensification of treatment over and above EBRT may be required in certain sub-groups. Indeed, the ESGO-ESTRO-ESP guidelines reflect this and suggest that chemotherapy may be considered in patients with grade 3 tumours and/or the presence of LVSI [6].

Overall, the number of vaginal relapses across the entire cohort was exceedingly small. Also, the number of salvageable relapses (vaginal and/or pelvic) was 3.5%, and almost exclusively detected due to symptomatic presentation. This calls into question the value of regular hospital based follow up after adjuvant treatment for IR-EC and HIR-EC. There is no European consensus on patient initiated follow up (PIFU) in EC [22], although intensive hospital based surveillance schedules have no proven impact on survival or quality of life [23,24] and have significant cost implications [24]. In the UK, however, the British Gynaecological Cancer Society (BGSC) published a guideline on the use of patient initiated follow up (PIFU) in gynaecological malignancies in 2020 just prior to the onset of the coronavirus disease 2019 (COVID-19) pandemic [25]. PIFU is considered appropriate for IR-EC, but only recommended for HIR-EC after an initial two-year period of clinical monitoring. It could be argued that HIR-EC patients have a higher risk of both recurrence and late toxicity, but this series indicates that the recurrence profile in patients who undergo pelvic EBRT for HIR-EC is very similar to those who receive VBT for IR-EC. We did not record toxicity but significant grade 3 or higher late effects in patients who receive EBRT +/– chemotherapy for EC is less than 5% [26]. Providing patients are adequately counselled and educated, it is our belief that HIR-EC patients can immediately be considered for PIFU following appropriate holistic needs assessment.

The major strength of this series is the sizeable number of patients treated over a 3-year period at a tertiary referral center. This provides a comprehensive comparison of descriptive recurrence frequencies but a larger cohort with a higher number of events would be required to perform robust multivariate logistic regression analysis to determine the most important factors that influence relapse. Whilst the management of IR-EC was uniform, the selection of adjuvant therapy for HIR-EC was subject to evolving single institution guidelines and clinician bias (and patient preference) and may have skewed the results. The rate of PLND was low and sentinel node staging was not performed during the period under observation, therefore potentially resulting in underestimation of true FIGO stage. We fully acknowledge that molecular profiling was not available; these data would provide a valuable insight into both the recurrence rate and pattern of relapse. Also, histopathology was not centrally reviewed; inter-obsever variation is reported to be common in gynaecological oncology pathology [27,28].

Moving forward, there continues to be much interest in further refinement of risk stratification in EC in order to reduce over- and under-treatment and improve cost-effectiveness. Various retrospective studies and subset analysis highlight the importance of molecular markers as both prognostic and predictive tools in the adjuvant setting [29–32]. In early stage disease, EBRT appears to more effective than VBT in achieving loco-regional control in *p53* abnormal EC, yet VBT is not inferior to EBRT in the

NSMP subtype [31]. At present, not all international guidelines rely solely on molecular risk stratification [33] and, ultimately, prospective randomized data is required. Trials incorporating molecular integration risk profiles such as PORTEC-4 (NCT03469674) and Refining Adjuvant Treatment IN Endometrial Cancer Based on Molecular Features (RAINBO) (NCT05255653) may provide invaluable information in support of the advancing treatment algorithms in EC.

5. Conclusions

In conclusion, the vaginal recurrence rate following VBT for IR-EC in WOSCAN recapitulated that of the PORTEC-2 trial population and reinforces the ESGO-ESTRO-ESP recommendation. We were unable to confirm that the variables age, grade, stage, LVSI status, and treatment were a statistically significant predictor of relapse. Pelvic failure, however, was more common in HIR-EC patients who received VBT rather than EBRT, suggesting that EBRT is important in optimising loco-regional control, at least in certain sub-groups. Indeed, EBRT is now strongly considered at our institution for HIR-EC in accordance with ESGO-ESTRO-ESP 2020 guidelines, especially in Nx/LVSI positive patients. We plan to repeat the analysis after a 3-year period since implementing molecular profiling has elapsed. Additionally, salvageable recurrence rates are low in IR-EC and HIR-EC, strengthening the case towards more widespread adoption of PIFU in early stage EC.

Abbreviations

CT, computed tomography; EC, endometrial cancer; EBRT, external beam radiotherapy; IR-EC, intermediate-risk endometrial cancer; HIR-EC, high-intermediate risk endometrial cancer; LVSI, lymphovascular invasion; PLND, pelvic lymph node dissection; VBT, vaginal brachytherapy; HIR-EC, high-intermediate risk endometrial cancer; FIGO, International Federation of Gynaecology & Obstetrics; GOG, Gynecological Oncology Group; PORTEC-1, Post Operative Radiation Therapy in Endometrial Carcinoma 1; MMR, mismatch repair; NSMP, no specific molecular profile; PTV, planning target volumes; MRI, magnetic resonance imaging.

Availability of Data and Materials

The data cannot be provided on request due to data confidentiality rules pertaining to NHS patients.

Author Contributions

KG and AS designed the retrospsective audit. RH, AK, NR interpreted the data. LH, AW, and CD collated the data. DC performed statistical analysis. KG, LH, DC and AW analyzed the results. KG wrote the manuscript. All authors interpreted the data, contributed to editorial changes in the manuscript and read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

NHS Research Ethics Committee approval is not required for retrospective audit of service evaluation. The data is sourced from The West of Scotland Cancer Network (WOSCAN) and has been handled appropriately. Since individual patients are not identifiable, informed consent is not required.

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Conflict of Interest

The authors declare no conflict of interest.

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