Southern African Journal of Gynaecological Oncology 2016; 8(1):10-15
http://dx.doi.org/10.1080/20742835.2016.1175708

South Afr J Gynaecol Oncol
ISSN 2074-2835 EISSN 2220-105X

RESEARCH

Lymphovascular space invasion in early-stage endometrial cancer: adjuvant treatment and patterns of recurrence

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Background: In early-stage endometrial cancer, lymphovascular space invasion (LVSI) is an independent predictor of relapse of disease and poorer survival. Nevertheless, adjuvant treatment for LVSI-positive patients is variable.
Methods: Early-stage endometrial cancer patients with LVSI, treated in Melbourne between 2000 and 2010, were retrospectively reviewed. Outcomes of patients observed after hysterectomy were compared with those who had had adjuvant EBRT or VBT.
Results: A total of 95 patients met the inclusion criteria. After surgery, 40 patients were observed, 48 patients received adjuvant EBRT and 7 adjuvant VBT. Nineteen patients developed recurrent disease (20.0%), of which 12.5% were in the observation group, 27.1% in the EBRT group and 14.3% in the VBT group (*p*-value 0.217). Fewer vaginal recurrences and more distant recurrences were found in both the RT groups (*p*-value 0.636 and 0.648 respectively). Multivariate analysis for overall survival (OS) and cancer-related survival (CRS) revealed a non-significant decrease of hazards in both the radiotherapy (RT) groups when compared with the observation group.
Conclusions: In patients with LVSI, adjuvant RT was not shown to reduce recurrence rates or improve OS or CRS. Previous reports have suggested that LVSI may be as important as nodal status for the risk of distant recurrence, therefore the use of systemic therapy should be further investigated.

Keywords: adjuvant radiotherapy, early-stage, endometrial cancer, lymphovascular space invasion, patterns of recurrence

Introduction

In developed countries, endometrial cancer is the most common malignancy of the female genital tract.[1] Because of the early appearance of symptoms, most patients have early-stage disease at presentation.[1] Therefore, the overall survival is good. Early-stage disease is defined as stage I and II endometrial cancer without local or regional spread of the tumour and without distant metastasis.[2] However, depending on pathologic factors, up to 3–30% of early-stage patients will develop loco-regional recurrent disease and 5–6% will develop distant recurrence.[3] The risk stratification is performed using pathologic factors such as age over 60 years, serous and clear cell histology, grade 3 histology and tumour invasion in the outer half of the myometrium. This will lead to low-risk, low-intermediate risk, high-intermediate risk and high-risk patients.[4] The standard treatment for endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic lymphadenectomy. In patients at high risk for recurrence, para-aortic lymph node dissection will be added and surgery is followed by adjuvant radiotherapy (RT) or chemotherapy.[5] A number of studies have shown lymphovascular space invasion (LVSI) to be a risk factor as well, as it is an independent predictor of early relapse of disease and poorer survival.[5–9] LVSI is identified in about 15% of early-stage patients and it does not necessarily equate to positive lymph nodes.[10] In node-negative patients, the presence of LVSI gives a high-intermediate risk. It may even be a more powerful prognostic marker than grade and histological subtype.[9] Nevertheless, adjuvant treatment for LVSI-positive patients is not well defined and therefore treatment at present is variable. The role of adjuvant RT in early-stage endometrial cancer has changed over the past years.[4] In the PORTEC trials and GOG-99 study, external beam radiotherapy (EBRT) and vaginal vault brachytherapy (VBT) have both been shown to reduce the risk for loco-regional recurrence in the presence of high risk factors.[10–12] However, these studies showed no proof of benefit in overall survival, and EBRT is known to be associated with significant morbidity and a reduction in quality of life.[13] It is therefore necessary to select patients appropriately to increase therapeutic gains while lessening treatment-related morbidities.[5] The PORTEC trials showed significantly less morbidity for VBT compared with EBRT while they were equally effective in preventing loco-regional recurrence.[4,11] However, patients with LVSI may still harbour tumour emboli at some distance from the vaginal vault where VBT may not be effective.[9] The aim of this study was to examine the patterns of recurrence of stage I and II endometrial cancer patients with LVSI, comparing patients treated with no adjuvant treatment after hysterectomy with those who had adjuvant EBRT or adjuvant VBT.

Materials and methods

Patient selection

Patients treated between 2000 and 2010 in Melbourne, Australia at the department of Gynaecologic Oncology, Mercy Hospital for Women and the department of Radiation Oncology, Peter MacCallum Cancer Centre, were retrospectively reviewed. Only endometrial cancer patients with surgical stage I or II and LVSI were included. Selection of stage was done according to the 2009 criteria of the International Federation of Gynaecology and Obstetrics (FIGO). Patients with carcinosarcoma, small cell or neuroendocrine histology were excluded from the study. Those with synchronous malignancies were also excluded. Lymphadenectomy was not required for surgical staging. After surgery, patients were either observed or treated with adjuvant EBRT or VBT.

Histopathology features

Histopathology features were collected from either anatomical pathology files at the Mercy Hospital for Women, or the patient database at the Peter MacCallum Cancer Centre. Every histological specimen was previously reviewed and discussed in multidisciplinary tumour board meetings.

Treatment policy

All patients analysed were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). The decision to perform lymphadenectomy was left to the discretion of the surgeon. Patients were referred to the Peter MacCallum Cancer Centre for adjuvant RT if indicated according to the FIGO guidelines.[2] As mentioned in the introduction, there was not a well-defined protocol for LVSI-positive patients and treatment varied according to individual practitioners. In cases of adjuvant treatment with EBRT, by protocol a dose of 45 to 50.4 Gy in 1.8 Gy fractions was given to a pelvic field using a 4-field box technique. In cases of VBT, a 3-cm margin around the vaginal vault was boosted to a dose of 30 Gy in 5 fractions.

Outcome

The primary outcome of this study was patterns of recurrence by adjuvant therapy. All recurrences were grouped as first or subsequent recurrence after surgery and were noted as vaginal, pelvic, para-aortic or distant. Recurrences that occurred in the same site were not included. Secondary outcomes were recurrence-free survival (RFS), overall survival (OS) and cancer-related survival (CRS).

Statistical analysis

Analysis was done by the intent to treat division of groups in case a patient did not complete her RT. In cases where patients were treated with adjuvant EBRT in combination with VBT or chemotherapy, they were grouped and analysed with the EBRT group. For baseline patient characteristics between groups, data were analysed using the Kruskal–Wallis test in the case of ordinal data and the chi-square test for categorical and dichotomous data. Multivariate Cox proportional-hazard analyses were conducted to estimate the hazard ratios (HR) of RFS, OS and CRS associated with treatment. The five-year survival outcomes were estimated and displayed using the Kaplan–Meier method. All analysis was done using IBM SPSS edition 22.0™ (IBM Corp, Armonk, NY, USA).

Ethics

The research proposal was reviewed and approved by the Expedited Review Working Party of Mercy Health Human Research Ethics Committee (HREC). This decision was undertaken as directed by the National Statement on Ethical Conduct in Human Research 2007 (updated December 2013).

Results

Clinical and pathologic characteristics

We identified 95 stage I and II endometrial cancer patients with LVSI that met the inclusion criteria. Clinical and pathologic characteristics of patients per adjuvant treatment group are listed in Table 1. Of the 95 included patients, 40 patients were observed (42.1%); 48 patients received adjuvant EBRT (50.5%) and 7 patients received adjuvant VBT (7.4%) after surgery. Two patients received a combination of adjuvant EBRT and VBT and 4 patients received a combination of adjuvant EBRT and chemotherapy. Two patients did not complete their EBRT treatment. The mean age was 68 years (SD 12.0) and the median follow-up was 48 months (range 0–131 months). Both the RT groups had a significant longer duration of median follow-up compared with the observation group (for EBRT and VBT 53 and 92 months respectively, compared with 26 months for the observation group). After a median of 48 months, 47 patients (49.5%) were lost to follow-up. Lymphadenectomy was performed in 34 cases (35.8%) of which 23 (67.6%) were comprehensive. All nodes were shown to be disease free. Of patients who had lymphadenectomy, 23 received adjuvant RT (67.6%). As a result of no performed randomisation, not all prognostic factors were evenly divided between adjuvant treatment groups. More patients with stage II and outer half myometrial invasion were treated with adjuvant RT. Histology, grade, cervical involvement and mean tumour size were divided evenly between treatment groups.

Patterns of recurrence

Recurrence rates per adjuvant treatment group are listed in Table 2. In total, 19 patients developed recurrent disease (20.0%), of which 5/40 were in the observation group (12.5%), 13/48 in the EBRT group (27.1%) and 1/7 in the VBT group (14.3%) (p-value 0.217). Twenty-five first recurrence sites were documented in which 5 were vaginal (20.0%); 11 were pelvic (44.0%); 3 were para-aortic (12.0%) and 6 were distant (24.0%). Patterns of recurrence between adjuvant treatment groups showed fewer vaginal recurrences in both RT groups (7.5% for the observation group, 4.2% for the EBRT group, 0% for the VBT group (p-value 0.636)). It must be noted that one of the two vaginal recurrences in the EBRT group occurred in a patient that did not complete her EBRT treatment. Still, there were too few vaginal recurrences in total for reliable analysis. Rates of para-aortic and distant recurrences were slightly higher in both the RT groups (p-value 0.219 and 0.648 respectively). From the 19 recurred patients, 6 patients developed recurrences in multiple sites (31.6%).

Recurrence-free survival

Table 3 shows the multivariate Cox proportional-hazards model for RFS. For each variable, the first was used as the reference category. Multivariate analysis revealed an HR of 1.09 for EBRT and 0.86 for VBT of developing recurrence (p-value 0.888 and 0.892 respectively). Endocervical involvement (HR 7.05) was the only statistical significant adverse prognostic factor for RFS (p-value 0.022). Figure 1 displays the Kaplan–Meier curves for RFS in months per treatment group. Because of the big fall in numbers followed for longer than 5 years, we displayed only the first 60 months. Some 26% of recurrences occurred within 12 months, 52.6% within 24 months and 89.5% within 48 months of initial therapy. The 24-month estimated cumulative incidence of recurrence was 9.5% for the observation group, 13.6% for the EBRT group and 14.3% for the VBT group (p-value 0.50).

Overall survival and cancer-related survival

Mortality rates by treatment group are listed in Table 2. A total of 27 patients died from any cause (28.4%) whereas 13 patients died from recurrent endometrial cancer (13.7%). Altogether, 52% of deaths were due to causes other than endometrial cancer of which 7/11 were in the observation group (63.6%), 7/15 in the EBRT group (46.7%) and 0% in the VBT group. Multivariate Cox proportional-hazards analysis of OS (Table 4) revealed a non-significant decrease in hazard among patients treated with EBRT (HR 0.45) or VBT (HR 0.23) when compared with the observation group (p-value 0.114 and 0.196 respectively). A non-significant decrease in hazard among patients treated with EBRT and VBT was also seen for CRS (HR 0.77, p-value 0.731 and HR 0.63, p-value 0.706 respectively). Apart from age over 60 years there were no other significant adverse prognostic factors for OS and CRS.

Table 1: Patient characteristics by adjuvant treatment group

Characteristic	Total		Observation		EBRT		VBT		*p*
	(*n* = 95)		(*n* = 40)		(*n* = 48)		(*n* = 7)		
	No.	%	No.	%	No.	%	No.	%	
Mean (SD) age in years	68 (12)		70 (12)		67 (11)		61 (11)		0.154
Age in years									0.165
< 60	26	27.4	11	27.5	11	22.9	4	57.1	
≥ 60	69	72.6	37	72.5	37	77.1	3	42.8	
Median (range) follow-up in months	48		26		53		92		**< 0.001**
	(0–131)		(0–131)		(0–126)		(11–123)		
Lymphadenectomy	34	5.8	11	27.5	19	40.4	4	57.1	0.236
Histology									0.719
Endometrioid	76	80.0	33	82.5	37	77.1	6	85.7	
Clear cell	3	3.2	0	0	3	6.3	0	0	
Serous	6	6.3	3	7.5	3	6.3	0	0	
Mixed	10	10.5	4	10.0	5	10.4	1	14.3	
Stage									**< 0.001**
Ia	34	35.8	22	55.0	7	14.6	5	71.4	
Ib	44	46.3	13	32.5	29	60.4	2	28.6	
II	17	17.9	5	12.5	12	25.0	0	0	
Grade									0.091
1	24	25.3	9	22.5	13	27.1	2	28.6	
2	30	31.6	18	45.0	9	18.8	3	42.9	
3	41	43.2	13	32.5	26	54.2	2	28.6	
Myometrial invasion, %									**< 0.001**
< 50	38	40.0	23	57.5	10	20.8	5	71.4	
≥ 50	57	60.0	17	42.0	38	79.2	2	28.6	
Cervical involvement	20	21.0	6	15.0	13	27.1	1	14.3	0.346
Mean (SD) tumour size in mm	40.3		35.9		43.5		42.9		0.162
	(18.6)		(19.7)		(17.2)		(19.1)		

Table 2: Recurrence and mortality rates by adjuvant treatment group

Characteristic	Total		Observation		EBRT		VBT		*p*
	(*n* = 95)		(*n* = 40)		(*n* = 48)		(*n* = 7)		
	No.	%	No.	%	No.	%	No.	%	
Recurrence									
Total	19	20.0	5	12.5	13	27.1	1	14.3	0.217
Vaginal	5	5.3	3	7.5	2	4.2	0	0	0.636
Pelvic	11	11.6	3	7.5	8	16.7	0	0	0.249
Para-aortic	3	3.2	0	0	3	6.3	0	0	0.219
Distant	6	6.3	2	5.0	3	6.3	1	14.3	0.648
Death by any cause	27	28.4	11	27.5	15	31.3	1	14.3	0.640
Cancer-related death	13	13.7	4	10.0	8	16.7	1	14.3	0.663

Figures 2 and 3 demonstrate the Kaplan–Meier survival curves. Because of the big fall in numbers followed for longer than 5 years, we have displayed only the first 60 months. The 48-month Kaplan–Meier estimates for OS were 76.6% for the observation group, 86.2% for the EBRT group and 85.7% for the VBT group (*p*-value 0.138). For CRS the 48-month estimates were 88.5% for the observation group, 90.3% for the EBRT group and 85.7% for the VBT group (*p*-value 0.809). The 5-year OS and CRS for all patients was 80.3% and 89.2% respectively. Analysis without the four patients who received EBRT together with chemotherapy revealed no significant differences in baseline patient characteristics, patterns of recurrence and survival outcomes.

Table 3: Multivariate Cox proportional-hazards model for recurrence-free survival

Characteristic	Recurrence-free survival		
	HR	95% CI	*p*
Age (years)			
< 60			
≥ 60	2.57	0.48–13.7	0.269
Grade			
1			
2	1.14	0.27–4.77	0.857
3	1.56	0.48–5.10	0.460
Myometrial invasion			
< 50%			
≥ 50%	2.41	0.48–11.699	0.284
Cervical involvement			
No involvement			
Endocervical	7.05	1.32–37.56	**0.22**
Stromal	1.26	0.42–3.79	0.683
Adjuvant treatment			
Observation			
EBRT	1.09	0.33–3.56	0.888
VBT	0.86	0.09–7.88	0.892

Note: First = Reference category.

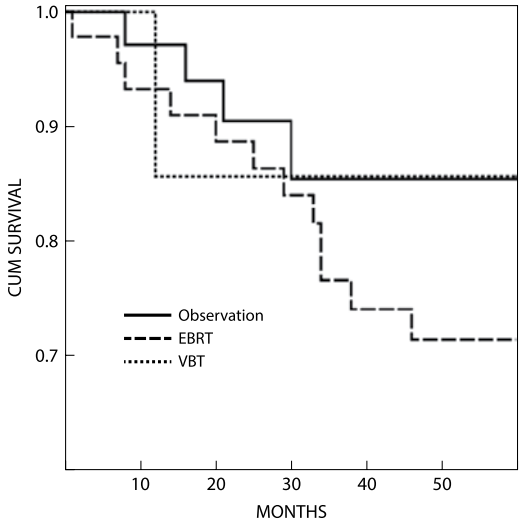

Figure 1: Recurrence-free survival by adjuvant treatment group.

Discussion

With this study we looked at stage I and II endometrial cancer patients with LVSI. We found an overall recurrence rate of 20.0%, of which 12.5% were in the observation group and 25.5% in the RT groups. We showed that neither EBRT nor VBT had a statistically significant impact on these relapse rates. Looking at patterns of recurrence, we found fewer vaginal recurrences and more distant recurrences in the EBRT and VBT groups. These results were not statistically significant. In multivariate analysis for OS and CRS we revealed a non-statistical decrease of hazard in both the EBRT and VBT group when compared with the observation group.

Because of its retrospective nature, the risk of selection bias is a limitation of this study. For example, 52% of all deaths were due to causes other than endometrial cancer. In the observation group 63.6% of deaths were due to other causes. This could be a manifestation of selection bias as the observation group had a high percentage of high-risk or high-intermediate risk factors. Nevertheless, not all serous carcinomas or stage 2 or grade 3 were treated with adjuvant therapy if lymph node status was negative. The patients were treated on their merits and were not excluded from adjuvant treatment because of morbidity. Analysis without the 10 patients who decided not to be treated with adjuvant radiotherapy revealed that 11 out of 22 (50%) of all deaths were due to causes other than endometrial cancer. In the observation group 2 out of 6 deaths (33.3%) were due to other causes. Further analysis without these 10 patients did not reveal any different outcome.

Another limitation of the study is that the addition of high-risk histology could cloud the role that LVSI has on recurrence. Therefore we performed analysis without the 19 patients with clear cell and serous histology as well. This showed that there were no recurrences or deaths in the VBT group. Compared with the observation group there were fewer vaginal recurrences in the EBRT group but more para-aortic and distant recurrences. The results were not statistically significant. Multivariate Cox proportional-hazards analysis revealed an HR of 1.13 for EBRT of developing recurrence (*p*-value 0.875). Multivariate Cox proportional-hazards analysis of OS revealed a non-significant decrease in hazard among patients treated with EBRT (HR 0.34) when compared with the observation group (*p*-value 0.091) and an HR of 0.52 for CRS (*p*-value 0.489). These results are not different from the results found in the analysis with the high-risk histology patients included.

Simpkins et al. and van der Putten et al. both retrospectively investigated the recurrence rates between adjuvant treatment groups in early-stage LVSI-positive patients. Simpkins et al.[14] found an overall recurrence rate of 23%. They concluded that adjuvant RT improved pelvic control, but did not impact

Table 4: Multivariate Cox proportional-hazards model for overall survival and cancer-related survival

Characteristic	Overall survival			Cancer-related survival		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (years)						
< 60						
≥ 60	9.30	1.04–83.17	**0.046**	6.29	0.58–68.00	0.130
Grade						
1						
2	0.77	0.21–2.81	0.693	1.02	0.53–6.82	0.984
3	1.22	0.42–3.58	0.715	1.85	0.36–9.42	0.461
Myometrial invasion						
< 50%						
≥ 50%	1.40	0.35–5.60	0.638	0.78	0.12–4.95	0.789
Cervical involvement						
No involvement						
Endocervical	1.77	0.35–8.99	0.493	3.63	0.62–21.36	0.155P
Stromal	0.74	0.26–2.12	0.577	0.66	0.12–3.56	0.633
Adjuvant treatment						
Observation						
EBRT	0.45	0.17–1.21	0.114	0.77	0.17–3.52	0.731
VBT	0.23	0.03–2.12	0.196	0.63	0.06–6.88	0.706

Note: First = Reference category.

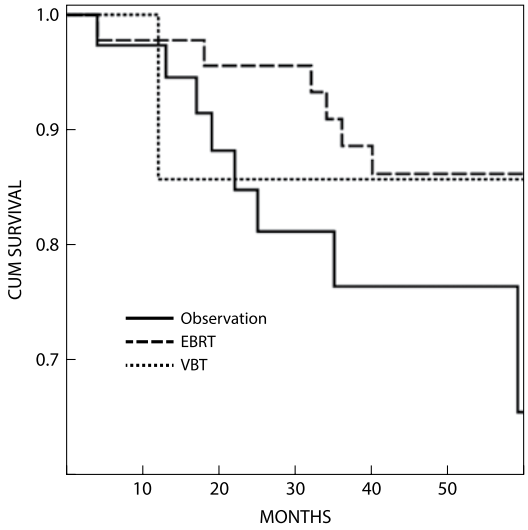

Figure 2: Overall survival by adjuvant treatment group.

recurrence rates, CRS and OS, due to secondary distant failures. Van der Putten et al.[15] found an overall recurrence rate of 22.2%. They stated that, despite adjuvant RT, a high overall and distant recurrence rate was observed in patients with 2–3 risk factors.

An important issue for this study is the assessment of LVSI, which is highly variable among pathologists with marked inter-observer variability. LVSI could easily be overestimated when retraction artefact, artefactual vascular involvement or micro-cystic elongated fragmented (MELF) myometrial invasion is present.[16] On the other hand, LVSI could be overlooked when using standard haematoxylin-and-eosin staining alone.[17] The chance of finding LVSI increases when using markers that are used to assist in identifying it such as CD31 and D2–40.[16] When multiple pathology departments are involved in a study, the reliability of the assessment of LVSI could be variable.

Two-thirds of the patients who underwent pelvic lymphadenectomy received RT (67.6%). As only stage I and II cancers were included, there were no metastases to the lymph nodes, which puts the role of lymphadenectomy in doubt. Lymph-node metastasis is usually found in patients with uterine risk factors that could justify adjuvant treatment, irrespective of the nodal status.[18] As the probability of lymph-node involvement is low, avoidance of unnecessary lymphadenectomy is mandatory bearing in mind the invasive nature.[18]

Considering the current and previous studies,[14,15] it may be that adjuvant RT does not improve recurrence rates in patients with LVSI. This is most likely due to distant recurrences. The theory behind these distant recurrences is that tissue disruption and inflammatory reactions due to surgery and RT cause increased lymph flow. In case of LVSI, as for positive lymph nodes, this increased lymph flow will lead to higher nodal failure and distant failures.[9] Kwon et al.[19] suggest that high-risk factors in early-stage endometrial cancer, such as LVSI, might be equally important to nodal status.[19] Narayan et al.[9] found that lymph node involvement was found to be a predictor for RFS and OS, but only in combination with LVSI. As LVSI might be equally important to nodal status in the risk of developing distant failures, the use of systemic therapy in these patients should be further studied.

Although systemic therapy is currently only considered in late-stage endometrial cancer and in serous and clear cell histology types, the use in early-stage has previously been investigated. In 2011 a systematic review and meta-analysis[20] looked at nine RCTs that focused on the effect of chemotherapy following the primary treatment of early endometrial cancer. This revealed that postoperative platinum-based chemotherapy reduces the risk of

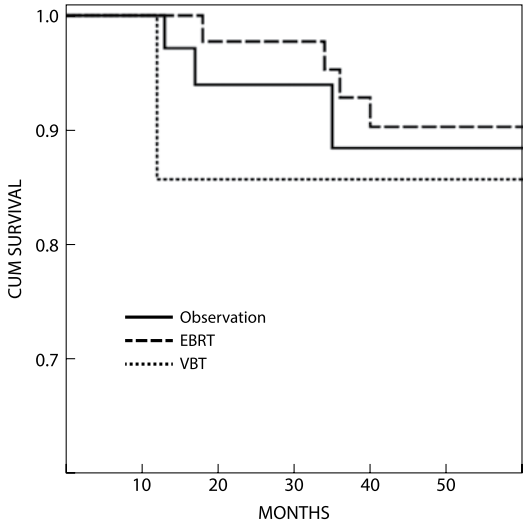

Figure 3: Cancer-related survival by adjuvant treatment group.

developing a distant recurrence compared with RT (RR 0.79, 95% CI 0.68–0.92). For pelvic recurrences the trend suggested that chemotherapy may be less effective than RT (RR 1.28, 95% CI 0.97–1.68) but it may have added value when used with RT (RR 0.48, 95% CI 0.20–1.18). Furthermore they stated that platinum-based chemotherapy was associated with a small benefit in RFS (RR 0.75, 95% CI 0.64–0.89) and OS (RR 0.74, 95% CI 0.64–0.89) irrespective of RT. However, there was insufficient agreement between the reporting of trials to make any meaningful comments about serious adverse events and the authors stated that chemotherapy should only be reserved for high-risk patients.

As for LVSI-positive patients, Hirai et al.[21] analysed 54 patients and compared the outcome of patients treated with adjuvant chemotherapy with those who had observation. They found a non-statistical significant benefit in 5-year OS (89% vs. 64%, *p*-value 0.05) and a statistical significant benefit in 10-year OS (89% vs. 56%, *p*-value 0.02). They stated that no severe toxicities occurred. Nevertheless these findings need to be confirmed in independent prospective studies.

Hopefully the current PORTEC 3 trial will help with the adjuvant management decisions for these patients. So far, they have released toxicity data for those on the intervention arm. This has reported increased side effects from chemotherapy, including neuropathy. The side effects resolved within 24 months.

Acknowledgement – The authors thank Christine Smith, data manager at the Mercy Hospital for Women, for her assistance and Dr Richard Hiscock for his assistance with the statistical analysis.

Conflicts of interest – None.

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Received: 07-08-2015 Accepted: 05-04-2016