Malignant extra-ovarian endometriosis: a case series of ten patients and review of the literature

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/AJO.13178](https://doi.org/10.1111/AJO.13178)

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Conflict of Interest Statement

I declare that there are no conflicts of interest. This research has not received any financial support.

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Article type : Original Manuscript

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Key Words

Endometriosis; Malignant endometriosis; Endometriosis associated ovarian cancer; Endometriosis associated cancer; Malignant extra-ovarian endometriosis; Malignant transformation of endometriosis

Manuscript word count: 2598

Abstract word count: 245

Table count: 2

ABSTRACT

Background

The malignant transformation of endometriosis within the ovary is a recognised condition. There is less literature surrounding the malignant transformation of extra-ovarian endometriosis (MEOE).

Aims

We report our experience with MEOE in 10 patients and present a review of the literature regarding this rare malignancy.

Materials and Methods

For this retrospective case series, patients were identified from a practice-based database. Where required operative notes and pathology reports were reviewed.

Results

Ten patients diagnosed with MEOE between 1991 and 2014 were identified. In each case the tumour was localised to the pelvis and centred on the pouch of Douglas, broad ligament, obturator fossa, parametrium and rectovaginal septum. Tumour histology was endometrioid adenocarcinoma (6), clear cell carcinoma (2), and adenosarcoma (2). Five patients had a history of endometriosis and four had received oestrogen only hormone replacement therapy after hysterectomy and bilateral salpingo-oophorectomy.

Treatments included surgery (1), surgery and radiotherapy (1), surgery and chemotherapy (1), surgery, radiotherapy and chemotherapy (3), and radiotherapy and chemotherapy (4). Maintenance hormonal therapy was also used in 3 patients. Curative doses of radiotherapy 45 Gy. Or more resulted in-field control in five patients. Six patients have no evidence of disease at a mean follow up

period of 15 years (5.5-24 years). Severe G3 long-term bladder morbidity occurred in 3 patients after radical surgery and radiotherapy.

Conclusion

MEOE is a rare condition for which treatment needs to be individualised. Multicentre studies and registries will hopefully define optimal treatment.

INTRODUCTION

Endometriosis is a common gynaecological condition characterised by the presence of endometrial glands and stroma outside the uterus. It is estimated to be present in 5-15%¹ of women in the reproductive age group, 25–80 % of infertile women, 2–5% of postmenopausal women, and 40%–80% of women with pelvic pain.²

Although endometriosis is considered to be a benign condition, this condition shares many pathological characteristics with malignant tumours, including tissue invasion and damage, neo-angiogenesis and spread to distant sites³. Furthermore, there are several epidemiological studies

that demonstrates that endometriosis is associated with an increased risk of various malignancies^{4,5}. The incidence of malignant transformation ranges between 0.7-1% of patients with endometriosis⁶. Malignant transformation in the ovary accounts for about 80% of endometriosis associated malignancies⁷ with the remaining 20% occurring in extra-ovarian sites.

The malignant transformation of endometriosis within the ovary was first described by Sampson⁸ in 1925. He proposed that three criteria should be fulfilled for the diagnosis of malignant transformation within endometriosis to be made. These criteria included (1) demonstration of both cancerous and benign endometrial tissue in the tumour, (2) histology of the neoplasm is compatible with an endometrial origin, (3) no other primary tumour sites can be found. Scott⁹ later proposed a fourth criterion, namely demonstration of a dysplastic phase between the benign endometriosis and the carcinoma.

Endometriosis-associated ovarian cancer (EAOC) is typically of endometrioid or clear cell type histology. It is characterised by an early onset of disease, reported to occur on average 5.5 years earlier than those with non-endometriosis associated ovarian cancers.¹⁰ Furthermore, EAOC usually represents a low-stage, and low-grade disease, which is associated with a more favourable outcome.¹¹ EAOC is staged and treated according to standard guidelines for ovarian cancer.¹²

Women diagnosed with malignant extra-ovarian endometriosis (MEOE) are reported to be 10-20 years younger than those with ovarian or endometrial cancer.¹³ The histopathology of MEOE is primarily represented by endometrioid carcinoma (69.1%), sarcoma (25%) and clear cell carcinoma (4.5%).¹⁴ MEOE is a rare condition and there are very few case series in the literature¹⁵. Most recent papers appear as individual case reports describing MEOE in various sites, including abdominal wall scars mainly after caesarean section¹⁶, rectovaginal septum, pouch of Douglas, uterosacral ligament, pelvic side wall, bladder¹⁷ and gastrointestinal¹⁸. MEOE is a rare condition and its management has not been standardised.¹⁹

The purpose of this study is to report our experience with ten cases of MEOE, especially management and long-term outcomes and to review the literature on this ill-defined disease entity.

MATERIALS AND METHOD

This study was approved by the Ethics Committee of Epworth HealthCare (EH 2017-211). The practice-based prospectively maintained database of a gynaecological oncologist was searched for all patients with a diagnosis of MEOE. We included patients that had an extra-ovarian malignancy amongst a background of benign endometriosis, and patients with an extra-ovarian malignancy of endometrial origin and a history of endometriosis, and/or a history of endometriosis for whom no other primary tumour site had been found.

Information was collected regarding the patient's age, parity, past medical history including history of endometriosis, family history, past or present use of hormone replacement therapy (HRT), operative findings, pathology results, further management and follow up. All patients gave informed consent for their treatment and had pathology review and presentation at a multi-disciplinary team meeting.

Radiotherapy (RT) intent was curative when the planned external beam dose was 45 Gy. or more. Recurrence was defined as the diagnosis of cancer after a cancer-free interval. Progression was defined as worsening disease, when there was no cancer free interval after diagnosis. Recurrence and progression were measured from the date of diagnosis of MEOE. In-field control was defined as permanent control of tumour within the treated RT field. Complications were graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Schema.²⁰

A review of the literature was performed using Medline/Pubmed and Embase. This search was conducted by using the keywords "malignant endometriosis", "extra ovarian endometriosis" and "endometriosis associated cancer."

RESULTS

Ten patients with MEOE were identified. These cases were diagnosed during the years 1991 to 2014.

Table 1 summarises the patient and tumour characteristics. The mean age at diagnosis was 45.3 years (range 34 to 56). Six patients were nulliparous and five had undergone prior treatment for endometriosis. Four had undergone a hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) for the management of endometriosis (cases 4, 7, 8 and 9) all four of whom had taken oestrogen only hormone replacement therapy (HRT) following their TAH and BSO. The interval from completion of TAH and BSO to MEOE was 4, 12, 3, 9 years respectively.

Pain was the most common presenting symptom, occurring in the pelvis, buttocks and hips. Severe neurological pain (from compression on the obturator nerve and sciatic nerve) occurred in cases 8 and 10. Patients also presented with altered bowel habit and abnormal uterine bleeding (AUB). The CA125 level was measured in 6 cases and it was elevated in five. In all 10 patients, the malignancy was confined to the pelvis at initial diagnosis and distant extra-pelvic spread was not detected. The most common location was the pouch of Douglas (POD), followed by the broad ligament and obturator foramen. Other locations include the parametrium and rectovaginal septum. Tumour size ranged from 6 to 13 cm (median 9cm).

Table 2 summarises the pathology, management and outcomes. Six malignancies were endometrioid adenocarcinoma (two G1, one G2, and three G3), two were low-grade adenosarcoma, and two were high-grade clear cell.

Treatment was individualised according to the location and size of their disease. Six patients underwent surgery with the objective of complete removal of the tumour. There was no macroscopic residual tumour in one (case 1), macroscopic residual disease in four (cases 2, 5, 7 and 9) and involved margins in one case (case 3).

Initial management was surgical in six patients. After surgery, one patient received no further treatment (case 1) as they had an encapsulated tumour with negative surgical margins. Case 9 received post-operative chemotherapy and had a complete response lasting nine years. Four patients received postoperative external beam pelvic RT either alone (case 7) or combined with cisplatin based concurrent chemotherapy (case 3 and 5). In three cases the dose of RT ranged from 45-59 Gy. in 22-30 fractions, but in case 2 the RT was ceased before 45 Gy. because of acute toxicity.

Initial management was non-surgical in four patients in whom the diagnosis had been made by core biopsy. Case 4 received neo-adjuvant chemotherapy (NACT) followed by RT after showing a partial response to Caelyx and case 6 showed a complete response to chemo-RT. Response in each case was determined clinically and by PET/CT imaging. Two patients with advanced local disease (cases 8,10) received platinum-based chemotherapy and palliative RT but neither showed a definite response to this treatment. Case 10 also received hormonal treatment with medroxyprogesterone acetate (MPA dose 200mg bd but had progressive disease).

Six patients are NED 5.5-24 years after initial diagnosis (mean 15 years). All four patients with grade 1 or low-grade tumours are NED compared with two of the six with grade 2, 3 or high-grade tumours. Four have remained free of recurrence. Their initial treatment had been surgery only (case 1), concurrent cis-platin chemo-RT (case 5, 6), and postoperative RT only (case 7). Both patients with low-grade adenosarcomas (cases 2,7) received long-term hormonal maintenance therapy with MPA (200mg BD). Case 7 also received Tamoxifen (20mg daily). They are NED after 23.5 and 24 years respectively.

Two patients developed a late recurrence at the vaginal vault (case 2) and in a para-aortic lymph node (case 4) and both are currently NED 14 and 3 years after treatment of the recurrence. Two patients who developed late recurrence in the upper abdomen and liver (case 3) and POD (case 9) were treated with chemotherapy. Case 3 had a partial response lasting 6 months and case 9 had a further complete response lasting 9 months; however both subsequently died of their disease.

In-field control was achieved in the five (cases 3,4,5,6,7) who received 45 Gy. or more of RT of whom three (cases 3,5,6) had also received concurrent cis-platin based chemo-RT. Case 2 had not received a curative dose of RT and suffered a late in-field recurrence at the vaginal vault after 10 years. In-field control was not achieved in the two patients with extensive local disease (cases 8,10) who received palliative RT and chemotherapy.

Three patients who had undergone complex/radical surgery followed by RT, experienced late radiation cystitis (G3). One patient has had multiple hospital admission for subacute small bowel obstruction (G3) probably due to adhesions and radiation enteritis but surgical intervention has not been required. One patient developed a disease-related colo-vesical fistula.

DISCUSSION

Whilst endometriosis is a common condition, endometriosis associated malignancies are relatively uncommon, and the ability of the clinician to predict which patients will go on to develop a malignancy within endometriosis and the management of these patients remains elusive.⁵ Nezhat et al.²¹ suggest that some characteristics of women with endometriosis that warrant ongoing follow-up includes women with a long-standing history of endometriosis, endometriosis-associated infertility or infertility treatment, or women with ovarian endometrioma. Our study supports this recommendation, as six of our patients had a long history of endometriosis with prior treatment, and six were nulliparous.

The management of patients with benign endometriosis may include observation, hormonal treatment or surgical excision. Nezhat et al.² advocate complete surgical resection of all endometriotic foci in women undergoing surgical treatment, with tissue evaluation of ovarian endometriomas to rule out malignancy. The benefits of serial surgery to excise visible lesions needs to be balanced by the risks of major operative morbidity due to adhesions and other anatomical distortions. Furthermore, there is no definitive data that demonstrates early surgical treatment of limited implants is associated with a reduced risk of disease progression and malignancy.²² Nezhat et al.⁵ also recommend ongoing hormonal treatment aimed at reducing the risk for recurrent endometriosis and endometriomas, as oral contraceptive use is associated with 80% lower occurrence of ovarian cancer in women with endometriosis who use the drug for more than 10 years,²³ however it's efficacy in reducing malignant transformation in extra ovarian endometriosis is speculative.

Caution should be taken when prescribing unopposed oestrogen hormone replacement therapy (HRT) in women with a history of endometriosis as there has been an association noted between

women with malignant endometriosis and unopposed oestrogen HRT, even in those women who have had a TAH BSO²⁴. This risk factor was evident in our case series as four of six patients with known endometriosis had received unopposed oestrogen HRT.

There are a limited number of cases of MEOE in the literature, and its diagnosis is often based on circumstantial information. Most cases fulfil Sampsons⁸ three criteria for the diagnosis of malignant change in ovarian endometriosis. Only a minority of cases demonstrate a dysplastic transition from benign to malignant endometriosis as required by Scott's criteria⁹. The literature review by Benoit et al²⁵ found that dysplastic transition is found in only 36-42% cases. This led Mostoufizadeh²⁶ to regard that the co-existence of a neoplasm and endometriotic tissue is sufficient to indicate an endometriotic origin. A history of endometriosis adds to the circumstantial evidence, especially when the malignancy has arisen in a site of known endometriosis. The issue is further confounded in patients who have received radiotherapy prior to surgical resection which can have a significant impact on tumour morphology as occurred in two cases (5 and 7) in which no residual malignancy was identified. We believe that it is time for Sampson's and Scott's criteria be expanded to include patients with a history of endometriosis.

Due to the rarity of MEOE, therapeutic management has not been not standardised.¹⁹ Primary surgical treatment should be performed when feasible which aims to completely resect all disease and obtain staging biopsies of peritoneal surfaces and lymph nodes.²⁵ Surgical resection may be challenging especially when the malignancy is located deep in the POD or rectovaginal septum and its infiltrative nature often results in residual disease after surgery. Ulrich et al.²⁷ advocate radical surgery followed by radiation therapy as the treatment of choice.

Radiation therapy is effective in this condition and in-field control of disease was achieved in all 5 of our patients whose total dose of RT was 45 Gy. or more. We recommend that RT should be used when the surgical resection is incomplete.

The role of chemotherapy is less clear. Published reports such as that by Heaps et al.¹⁵ suggest that that chemotherapy is ineffective in the treatment of ME, but most of their cases in their case-series and literature review predated the introduction of cisplatin. In a literature review conducted by Benoit et al²⁵, they concluded that the effect of chemotherapy is minimal given its limited efficacy in

endometrial cancer. In our series 5 patients with measurable disease received chemotherapy; there was one complete and two partial responses. Larger numbers are required before any conclusions about the effectiveness of chemotherapy can be drawn.

The place of chemo-radiotherapy is also not clear. It has been postulated that ME behaves more like endometrial carcinoma^{19, 25}. The recently published PORTEC-3²⁸ phase 3 trial of women with high-risk endometrial cancer compared adjuvant chemotherapy during and after pelvic RT (chemoradiotherapy) versus pelvic RT alone. In that study chemo-radiotherapy did not improve 5-year overall survival although it did increase failure-free survival. but it has some appeal in MEOE which is usually localised in the pelvis at the time of presentation. Two cases (5 and 6) in our series presented with large masses in the RVS and/or POD and both had prolonged complete responses to concurrent platinum based chemo-RT and are still alive with NED. Its role should be explored further as MEOE masses are usually large and localised in the pelvis at the time of presentation.

Heaps et al.¹⁵ recommended the use of progestin therapy in all cases of cancer arising in endometriosis. Hormone receptor testing to assess suitability for hormonal treatment was advocated by Brooks et al. and although this has theoretical appeal, there is currently no strong evidence that it is useful. In our study two patients with adenosarcomas received long-term maintenance progesterone treatment following initial treatment and are long-term disease-free survivors, but again there is no high-level evidence to support its use.

There is a fine balance between aggressive treatment of primary disease and recurrent disease versus the risk of major therapeutic morbidity.³⁰ In our series, four patients experienced serious complications to the bladder and/or bowel. These were often due to a combination of RT and surgery.

The prognosis for malignant transformation within MEOE confined to the genital tract, correlates well with stage.¹⁵ In the literature, patients with isolated disease of endometrioid histology, had an 82–100% 5-year survival. However, disseminated intraperitoneal disease has a very poor associated prognosis, with a 0–12% 5-year overall survival^{15, 29} In our case-series none of our patients had tumour spread at the time of diagnosis and the five-year overall survival was 80%.

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297 The limitations of this study relate to small sample size, accrual of patients over a long period of time
 298 and the individualisation and heterogeneity of treatments. Following these patients over a very long
 299 period has enabled us to report our long-term treatment outcomes. We cannot dogmatically define
 300 the optimal treatment of this rare disease and it would be very difficult for any one institution to
 301 accrue the necessary numbers. One way to progress would be to establish a multi-institutional
 302 registry of pathology, management and outcomes. More research needs to be done on this rare
 303 and challenging gynaecological malignancy.

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Table 1. Clinical details of patients up to the time of diagnosis of malignant endometriosis.

Pt	Age	History of endometriosis (and treatment) and other gynaecological history	Past Medical History	HRT	Parity	Symptoms, signs and CA125 level at diagnosis	Location of malignancy
1	42	No	None relevant	Nil	P2	Abdominal bloating and mass. CA125 not done	Right pelvis; 9.5cm.
2	50	No	None relevant	Nil	P3	Pelvic pain. Ca 125 not done.	POD
3	48	No	Later developed breast DCIS aged 62 years	Nil	P0	Vaginal bleeding and discharge; ulcer in L vaginal fornix; CA125 not done.	POD and parametrium; 6cm.
4	56	TAH/BSO aged 52 years for benign endometriosis in L. ovary, residual endometriosis in POD. Removal of benign endometrioma in POD, anterior resection and loop ileostomy aged 53 years. Treated with Zoladex x 6 months.	None relevant	Oestrogen only for 1.1 years	P0	LIF pain and L sacro-iliac pain. CA125 57u/ml.	POD; mostly cystic; fluid cytology positive; 13cm.
5	54	TAH/BSO aged 42 years for fibroids and adenomyosis. Endometriosis was not noted.	None relevant	Oestrogen only for 9 years.	P4	Pelvic pain. CA125 84u/ml.	RV septum; 6cm.
6	41	No	Infertility	Nil	P0	Constipation and pelvic pain CA125 243u/ml.	POD and RV septum; 9cm.
7	34	Long history of endometriosis and infertility. TAH/BSO aged 31 years for severe endometriosis	None relevant	Oestrogen only for 3 years	P0	Pelvic pain	POD; 8cm.

8	35	Laparotomy, exploration of right obturator fossa, drainage of endometrioma excision of endometriosis right USL aged 29 years. Treated with Zoladex x 6 months. Then progestogen.	None relevant	Nil	P0	Pain R hip. CA125 19u/ml.	R broad ligament, obturator foramen, bony pelvis; >10cm.
9	49	Hormonal treatment from age 26 years with progestogen. RSO for endometrioma aged 30 years. LSO aged 35 years. TAH aged 40 years.	Breast DCIS aged 46 years. Myeloma aged 49 years.	Oestrogen only 11 years.	P0	Pelvic pain CA125 42u/ml.	POD; 6cm.
10	44	CT guided drainage of endometriosis from obturator internus aged 39 years.	None relevant	Nil	P2	Pain L buttock CA125 548u/ml.	L hemipelvis, obturator foramen, bony pelvis; partly cystic; 13cm.

Abbreviations

POD – Pouch of Douglas; USL – utero sacral ligament; LIF

TAH – total abdominal hysterectomy

BSO – Bilateral salpingo-oophorectomy

LSO/RSO – L and R salpingo-oophorectomy

RV = rectovaginal RV septum

Table 2. Pathology, treatment and outcomes after the diagnosis of malignant endometriosis.

No.	Pathology	Primary debulking surgery	Radiation therapy	Chemotherapy	Hormonal treatment	Recurrence/clinical course	Outcome
1	Endometrioid ca; G1	Debulking pelvic mass, no residue. Ovaries normal, not removed.	None	None	None	No further problems	Patient well with NED at 10.4 years.
2	Adenosarcoma; low-grade	TAH/BSO. Ovaries normal. Residual tumour in POD.	Pelvic EBRT (incomplete due to acute toxicity), vault BT	Cisplatin, doxorubicin, ifosfamide after RT	MPA	Recurred after 10 years at vaginal vault. Upper vaginectomy, further EBRT. Complications: radiation cystitis, non-functioning bladder managed by ISC. G3.	Patient well with NED at 24 years.
3	Endometrioid ca; G3	RHBSO and upper vaginectomy. Involved margins.	Pelvic EBRT, Cisplatin chemo-RT	Carboplatin, paclitaxel after RT	None	Recurred after 14.3 years in left upper quadrant of abdomen and liver. Treated with MPA; progressive disease over 3 months. Then carboplatin, paclitaxel with only partial response for 6 months and then carboplatin, caelyx with no response.	Died from progressive disease at 16.1 years.
4	Clear cell ca	Not done	Pelvic EBRT (after NACT)	NACT prior to RT with Carboplatin, paclitaxel then partial response to caelyx	None	Recurred at 8.5 years in para-aortic LN. Para-aortic LN debulking. Carboplatin and paclitaxel chemotherapy then EBRT to PA region.	Patient well with NED after 11.5 years.

5.	Endometrioid ca; G1	Vaginal evacuation of rectovaginal tumour.	Pelvic EBRT, (concurrent cisplatin)	None	None	PET scan after 4 months showed possible persistent disease in the RVS. Vaginectomy, anterior resection, loop ileostomy and Martius flap. Residual benign endometriosis but no cancer. Complications: radiation cystitis, recurrent UTIs. G3.	Patient well with NED at 15.0 years.
6	Endometrioid ca; G3	Not done	Pelvic EBRT, (concurrent cisplatin)	Gemcitabine after RT. Complete response to chemo-RT	None	No further problems.	Patient well with NED at 5.5 years.
7	Adenosarcoma; low-grade	Debulking pelvic masses and femoro-femoral artery bypass graft.	Pelvic EBRT	None	Tamoxifen, MPA	Laparotomy and drainage of collection with colostomy after 11 months, no cancer, only fibrosis. Complications: RT cystitis with urinary incontinence requiring ISC. Recurrent SBO. Surgery not required. G3.	Patient well with NED at 23.5 years.
8	Endometrioid; G3	Not done	Palliative EBRT to R hemi-pelvis and buttock	NACT with Carboplatin, paclitaxel prior to RT	None	Progressive disease in R hemipelvis and bony pelvis.	Died of progressive disease at 10 months.

9	Clear cell ca	Debulking tumour mass	None	Carboplatin, paclitaxel after initial surgery. Complete response.	None	Recurred at 6.0 years with pelvic mass. Retreated with carboplatin, paclitaxel; interval debulking. Complications: paraneoplastic occipital infarct after 1 cycle of chemotherapy. Disease-related colovesical fistula; G4	Died of progressive disease at 8.2 years
10	Endometrioid adenocarcinoma; G2	Not done	Palliative EBRT to L hemipelvis and buttock	Carboplatin, paclitaxel before, during and after RT	MPA	Progressive disease in pelvis, bony pelvis, retro-peritoneal LNs and lungs.	Died of progressive disease at 24 months.

Abbreviations:

NED = no evidence of disease

NACT= neo-adjuvant chemotherapy

ISC = intermittent self-catheterisation;

LN = lymph node;

RVS = rectovaginal septum;

POD = cul-de-sac;

MPA = medroxyprogesterone acetate, usual dose 200mg bd

BT = brachytherapy; EBRT = external beam RT

TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy

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Title:

Malignant extra-ovarian endometriosis: A case series of ten patients and review of the literature.

Date:

2020-08

Citation:

Poon, C. & Rome, R. (2020). Malignant extra-ovarian endometriosis: A case series of ten patients and review of the literature.. Aust N Z J Obstet Gynaecol, 60 (4), pp.585-591.
<https://doi.org/10.1111/ajo.13178>.

Persistent Link:

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