Gynecologic Oncology 124 (2012) 185–191

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Editorial

The role of peritoneal cytology at risk-reducing salpingo-oophorectomy (RRSO) in women at increased risk of familial ovarian/tubal cancer

Risk-reducing salpingo-oophorectomy (RRSO) is the mainstay of managing women at increased risk of familial ovarian cancer and use of strict surgical protocols with serial sectioning of the specimen is increasingly the norm. The role of cytology obtained from peritoneal washings has received less attention, with even commentaries by some authoritative experts omitting to remark on this point [1]. As a result, practice varies among surgeons and institutions, with some published series reporting cytological findings at RRSO [2–4], a number omitting to mention this [5,6], and recently one suggesting it is not necessary [7]. This is an important issue for clinical practice which requires addressing. Cytology is likely to impact management decisions if early stage or pre-invasive disease is discovered at RRSO. We present a summary of the current literature (Tables 1–3), and put forward the rationale for cytology to be included as routine in RRSO protocols.

Relevant papers were identified through an exhaustive search of the online database PubMed, using the search terms 'RRSO', 'salpingo-oophorectomy', 'oophorectomy', 'prophylactic salpingo-oophorectomy', 'risk-reducing' and 'BRCA' in different combinations. Additional papers were also identified and included where appropriate through examining the reference lists of the initially identified papers. Three initial series [8–10] were excluded as they were followed by subsequent papers [11–13] in which previously published data had been repeated. Five series were excluded as details of occult lesions and stages of disease were not available [13–17]. Of the remaining series those reporting early stage/pre-invasive disease are summarised in Tables 1–3.

Potential change in stage and subsequent management

Positive cytology can lead to upstaging of Stage I microinvasive disease with prognostic and therapeutic implications. In the published literature on RRSO, we found 45 cases of stage-1 invasive fallopian tube/ ovarian cancers (Table 1) [3–5]. These included 5 women who had positive cytology, 16 with negative cytology and 24 women for whom cytology was not done/reported. A number of series pre-date the use of a serial sectioning of the fallopian tube fimbria (SEE-FIM) protocol [18] and it is possible that the true incidence of occult early stage cancers may be higher than this.

In five of the 21 (23.8% CI, 8.2, 47.2) who had cytology done, positive findings led to upstaging of disease from stages Ia to Ic (Table 1). Four of these five cases were invasive fallopian tube cancers. Three of these women received chemotherapy and in two of these, where follow-up details were available, the disease recurred at 13 and 17 months. In the remaining two patients, no details were reported (Table 1). Despite the microscopic nature of these stage 1 invasive lesions, positive cytology may define a higher risk cohort with guarded prognosis that requires adjuvant chemotherapy. With respect to adjuvant chemotherapy, management of primary fallopian tube cancer is generally similar to ovarian cancer and comparable 5 year survival rates have been reported for stage 1a and stage 1b ovarian and fallopian tube cancers [19,20]. Decision making should be individualised through a multidisciplinary forum. It is our practice and that of others to advise adjuvant chemotherapy (carboplatin and paclitaxel) for stage 1c (any grade) or high-grade (grade 3) stage 1a and stage 1b disease [19]. The presence of positive cytology would thus affect management of Grade1/2 stage 1a/stage 1b fallopian tube or ovarian cancers. However, some authorities advocate that, chemotherapy should be considered for all stage 1 fallopian tube cancers [21]. Given the fallopian tube lumen is in direct communication with the peritoneal cavity, they propound stage Ia fallopian tube cancer has a higher predisposition for distant microscopic spread and is functionally equivalent to stage Ic ovarian cancer.

Negative cytology was found in 10 stage 1a/1b invasive tubal cancers and six stage 1a invasive ovarian cancers at RRSO (Table 1). Adjuvant chemotherapy was given in three patients (invasive tubal cancer), not given in five (three tubal and two ovarian cancers) and not reported in eight cases. Of these 16 cases, follow-up data was only available in three who did not receive chemotherapy and were disease free at 3, 24 and 30 months (Table 1). Cytology would not have impacted on staging in only two of these 16 women, both of whom had disease present on the surface of the ovary/ tubal serosa [2,3].

Details of cytology were unclear or not available for 24 cases. Reports of disease free survival ranging from 11 to 46 months is reported for seven of these cases, along with three deaths: one from disease at 4 years, and two from breast recurrence (Table 1).

In Serous Tubal Intraepithelial Carcinoma (*STIC*) lesions, positive cytology is a possible surrogate for early undetected microinvasive disease and/or predictive marker for increased peritoneal cancer risk

Accumulating evidence driven largely by findings in the high-risk population suggests that the cell of origin of a proportion of ovarian/ tubal cancers lies outside the ovary, in the extrauterine mullerian epithelium, with newer models of ovarian carcinogenesis suggesting that the tube is the most favoured site [22]. A continuum of tubal epithelial change from a putative precursor lesion (the p53 signature) [23] through carcinoma in situ (*CIS*) or Serous tubal in situ carcinoma (*STIC*) lesions to early invasive tubal carcinoma has been described [24]. It has been postulated that genotoxic injury is more likely to lead to progression of these lesions to cancer in women at high risk for disease [24]. As the currently favoured nomenclature is *'STIC'*, we subsequently use this term (instead of *'CIS'*) for all such lesions

0090-8258/$ – see front matter
doi:10.1016/j.ygyno.2011.10.017

Table 1
Occult Stage 1 invasive cancers (with or without concomitant STIC)[a] detected at RRSO.

Author	Series	Pos cases	Histology (gross)	Histology (microscopic)	Cytology	Staging surgery	Stage	Mutation status	Chemotherapy	2nd Look	Follow-up data
Stratton 1999	n = 48	Case 1	NA	Ovary ca (microinvasive serous adenoca)	NA	NA	1	BRCA	NA	NA	Colonic ca—2 yrs
Deligdisch 1999	n = 52	Case 1	NA	Ovary ca (microinvasive mod diff serous)	NA	NA	1	BRCA1	NA	NA	NA
Hartley 2000	Case report	Case 1	Normal	FTC (fimbrial)	Neg	Yes, Neg (TAH BSO followed by omentectomy + PA node dissection)	1a	BRCA1	P + C	No	NA
Paley 2001	2 case reports	Case 2	Small nodule lt. FT infundibulum	FTC (7 mm)	**Pos**	Incomplete (TAH, BSO, appendicectomy)	1c	BRCA1	P + C (6 cycles)	Neg	NA
Leeper 2002	n = 30	Case 3	Normal	FTC (8 mm)	**Pos**	Yes (post chemotherapy7 mth after TAH BSO, at 2nd look but details NA)	1c	BRCA1	P + C (6 cycles)	Neg	Rec 13 mth (post 2nd look)
Rebbeck 2002	n = 259	Case 1	NA	Ovary ca	NA	NA	1	BRCA 1	NA	NA	NA
		Case 2	NA	Ovary ca	NA	NA	1	BRCA 1	NA	NA	NA
		Case 3	NA	Ovary ca	NA	NA	1	BRCA 1	NA	NA	NA
		Case 4	NA	Ovary ca	NA	NA	1	BRCA 1	NA	NA	NA
		Case 5	NA	Ovary ca	NA	NA	1	BRCA 1	NA	NA	NA
		Case 6	NA	Ovary ca	NA	NA	1	BRCA 1	NA	NA	NA
Agoff 2002, 2004	n = 7 case reports	Case 1	Normal	FT focal CIS + FTC 7 mm + (same tube)	**Pos**	TAH BSO at primary surgery (not formally staged)	1c	BRCA1	P + C (6 cycles)	Neg 7 mth (pelvic and PA nodes Neg)	Rec 17 mth—T + C (vag dis-alive 30 mth)
		Case 4	18 cm ov cyst	FT CIS + FTC(fimbria) + (ov cystadenoma)	Neg	TAH BSO at primary surgery (not formally staged)	1a	Unknown	Not given		30 mth dis free
		Case 5	Normal	FTC (fimbria) 9 mm	Not done at pri surgery. Neg at staging	TAH BSO at primary surgery. Staging laparotomy 1mth later (details NA)	1a	Unknown	Not Given		9 yrs (brst ca-5 yr, 7 yr)
Olivier 2004	n = 90	Case 1	Normal	FTC (endometrioid adenoca) 2.5 mm	NA	Yes (details of procedure NA)	1a	BRCA 1	NA		46 mth dis free
		Case 4	Normal	Ovary ca (pap serous adenoca)	NA	Yes (details of procedure NA)	1c	BRCA 1	NA		35 mth dis free
		Case 5	Normal	Ovary ca (pap serous adenoca)	NA	Yes (details of procedure NA)	1a	BRCA 1	NA		11 mth dis free
McEwen 2004	Case report	Case 1	Normal	FTC (3 mm) with FT CIS	Neg	Not reported	1a	BRCA2	None	NA	3 mth dis free
Meeuwissen 2005	n = 133	Case 1		FTC	NA	Yes (TAH, BSO, omentectomy. No lymphadenectmoy reported)	1a	BRCA1	NA		NA
Powell 2005	n = 67	Case 1	Normal	FT CIS 2.7 mm + FTC (1.7 mm, same FT)	Neg	Omental bx Neg (details of any formal staging not reported)	1a	BRCA2	Not known		Individual case FU not known. Cohort FU median 3 years
		Case 3	Normal	FT CIS + FTC (2.2 mm, same FT)	**Pos**	Omental bx Neg (details of any formal staging not reported)	1c	BRCA1	Not known		
		Case 5	Normal	Ovary ca (Rt ovary adenoca, 0.9 mm)	Neg	Omental bx Neg (details of any formal staging not reported)	1a?	BRCA1	Not known		

		Case6	Normal	Ovary ca (serous, high grade)	Neg	Omental bx Neg (details of any formal staging not reported)	1a?	BRCA1	Not known		
		Case 7	Normal	Ovary ca (Lt ovary 3 small foci adenoca)	Neg	No omental bx (details of any formal staging not reported)	1a?	BRCA1	Not known		
Schmeler 2006	n = 65	Case 1	Normal	Ovary ca (1 mm)	?Neg	TAH BSO primary surgery (no further staging)	1a	BRCA	None		24 mths dis free
Finch 2006 JAMA	n = 490	Case 5	NA	FTC	Unclear	NA	1a	BRCA2	NA	NA	1 yr (alive)
		Case 7	NA	Ovary ca	Unclear	NA	1a	BRCA 1	NA	NA	4 yrs (deceased)
		Case 8	NA	FTC	Unclear	NA	1a	BRCA2	NA	NA	alive at 6 yr
Finch 2006 Gynecol Oncol	n = 159	Case 2	Normal	Ovary ca (serous) 1 mm (high grade)	**Pos**	NA	1c	BRCA 1	NA	NA	NA
		Case 5	1.5 cm fim nodule	FTC-fimbria	Neg	NA	1b	BRCA 1	NA	NA	NA
Medeiros 2006	n = 13	Case 1	NA	FT STIC, FTC fimbria (serous) 1.2 mm; multifocal	Unclear	Yes (at FU, details NA. upstaged to stage 3))	1a	BRCA2	NA	NA	NA
		Case 2	NA	FTC (7 mm-endometrioid adenoca fimbria)	Unclear	Yes (details NA)	1a	BRCA 1	NA	NA	NA
Laki 2007	n = 89	Case 1	NA	FTC	Neg	Unclear	1a	BRCA 1	NA	NA	12 mth (deceased, breast ca rec)
		Case 3	NA	FTC	Neg	Unclear	1a	BRCA 1	NA	NA	38 mth Dis free
Callahan 2007	n = 122	Case 5	Normal	FTC-endometrioid (fimbrial)	Neg	Yes (following BSO, operative details NA)	1a	BRCA1	P + C (1 cycle, stopped due to toxicity)	NA	NA
		Case 6	Normal	FT CIS + FTC (fimbrial, tubal serosal)	Neg	Yes (RAH, BSO, omentectomy)	1c	BRCA1	P + C	NA	NA
Domchek 2010	n = 647	Case 2	NA	Serous ca ovary	NA	NA	1	BRCA1	NA	NA	NA
		Case 3	NA	Ovary ca	NA	NA	1	BRCA1	NA	NA	NA
		Case 4	NA	Ovary	NA	NA	1	BRCA1	NA	NA	NA
		Case 5	NA	Ovary ca or FTC (unclear)	NA	NA	1	BRCA1	NA	NA	NA
		Case 6	NA	Ovary ca or FTC (unclear)	NA	NA	1	BRCA1	NA	NA	NA
		Case 7	NA	Ovary ca or FTC (unclear)	NA	NA	1	BRCA1	NA	NA	NA
Manchanda[b]2011	n = 308	Case 3	Normal	FTC- serous (Grade 2)	Neg	Yes (hysterectomy, omentectomy)	1a	BRCA1	NA	NA	NA
		Case 7	Normal	Ovary ca (Serous 5 mm, incl cyst lining,Gr 3)	Neg	Yes (Following BSO-hysterectomy, omentectomy, lymphadenectomy)	1a	BRCA 2	None	No	NA
		Case 8		Ovary ca—(Pap serous, Gr 2, 9 mm lesion 4 mm invasion & extracapsular extension)	Neg	Yes (following BSO- TLH, omentectomy, lymphadenectomy)	1c	BRCA2	C (6 cycles)	No	24 mth dis free

BSO—bilateral salpingo-oophorectomy, C—Carboplatin, ca—cancer, CIS—carcinoma in situ, dis—disease, FU—follow up, FTC—fallopian tube cancer, mth—months, NA—not available, Neg—negative, Pos—positive, P—Paclitaxel, rec—recurrence, RAH—radical abdominal hysterectomy, STIC Serous tubal carcinoma in situ, TAH—total abdominal hysterectomy, TLH—total laparoscopic hysterectomy, T—Taxotere. *(unable to provide reference links for all above studies in the reference section given journal guidelines)*.

[a] Includes those cases with histology reports of invasive ovarian and fallopian tube cancer (with or without concomitant STIC).

[b] Follow-up data previously unpublished (personal communication).

Table 2
Occult carcinoma in situ (CIS) / serous tubal in situ carcinoma (STIC) lesions[a] (without concomitant invasion) detected at RRSO.

Author	Series	Pos cases	Histology (gross)	Histology (microscopic)	Cytology	Staging surgery	Stage	Mutation status	Chemotherapy	2nd Look	Follow up
Paley 2001	2 case reports	Case 1	Normal	FT CIS 8 mm	**Pos**	Yes (LAVH, BSO primary surgery. Staging completed at 2nd look but details NA)	1c	BRCA1	P + C (6 cycles)	Negative (completion of staging, details NA)	NA
Colgan 2002	n = 35	Case 2	Normal	FT CIS	**Pos**	Unknown	1c?	BRCA1	None	–	1 year dis free
Leeper 2002	n = 30	Case 2	Normal	FT CIS 7 mm	**Pos**	Yes (LAVH, BSO primary surgery. Staging completed at 2nd look but details NA)	1c	BRCA1	P + C (6 cycles)	Negative (7 mth after primary surgery)	17 mths dis free
		Case 4	Normal	FT CIS <1 cm	Neg	Uncertain (LAVH BSO primary surgery)	0	BRCA2	P + C (3 cycles)	Not done	>14 mths dis free
Agoff 2002, 2004	n = 7 case reports	Case 2	Normal	FT CIS 8 mm	**Pos**	TAH BSO primary surgey (no formal staging)	1c	BRCA1	P + C (6 cycles)	Neg 6mth (biopsies taken but details NA)	48 mths dis free
		Case 3	Normal	FT CIS 2 mm	Neg	TAH BSO primary surgey (no formal staging)	1a	BRCA2	P + C (3 cycles)	Not done	36 mths dis free
Powell 2005	n = 67	Case 2	Intraluminal lesion	FT CIS (+12 mm luminal lesion)	Neg	Omental bx Neg. (details of any formal staging not reported)	0	BRCA2	Not known		Individual case FU not known. Cohort FU median 3 yrs
		Case 4	Normal	FT CIS (b/l multifocal)	Not done	No omental bx. (details of any formal staging not reported)	0	BRCA1	Not known		
Finch 2006 Gynecol Oncol	n = 159	Case 4	Normal	FT CIS	Neg	NA	0	BRCA 1	NA	NA	NA
Lamb2006	n = 113	Case 2		FT CIS	**Pos**	?Undertaken at 2nd look (details NA)	0	BRCA 1	P + C (6 cycles)	Neg (details NA)	Dis free
		Case 4		FT CIS	Neg	Not done	0	BRCA2	P + C (3 cycles)	NA	Dis free
		Case 6		FT CIS	Neg	Not done	0	BRCA 1	None	NA	Dis free
		Case 7		FT CIS	Neg	Not done	0	BRCA 1	None	NA	Dis free
Medeiros 2006	n = 13	Case 3		FT STIC (fimbria, serous,2 mm)	Neg	Yes (at FU, details NA)	0	BRCA2	NA	NA	NA
		Case 4		FT STIC (fimbria, serous, 1 mm)	**Pos**	Yes (at FU, details NA)	?1c	BRCA2	NA	NA	NA
		Case 5		FT STIC (ampulla, serous, 1 mm)	Neg	Yes (at initial surgery, details NA)	0	BRCA 1	NA	NA	NA
Carcangiu 2006	n = 50	Case 4		FT CIS	NA	Not reported	0	BRCA 1	None	NA	Dis free 87 mths
		Case 5		FT CIS	Neg	Not reported	0	BRCA 1	None	NA	Dis free 38 mths
		Case 6		FT CIS	Neg	Not reported	0	BRCA 1	None	NA	Dis free 7 mths

Callahan 2007	n = 122	Case 1	Normal	FT CIS (fimbrial)	**Pos**	Yes (following BSO, operative details NA)	1c?	BRCA2	P + C	NA	NA
		Case 2	Normal	FT CIS (ampullary)	Neg	Yes (following BSO, operative details NA)	0	BRCA2	P + C	NA	NA
		Case 4	Normal	FT CIS (fimbrial)	Neg	TAH at primary surgery (formal staging not reported)	0	BRCA1	P + C	NA	NA
Manchanda[b]*2011*	n = 308	Case 1	Normal	FT CIS	Neg	No	0	BRCA 1	None	None	NA
		Case 2	Normal	FT CIS	Neg	No	0	BRCA1	None	None	7 mths dis free
		Case 4	Normal	FT CIS	Neg	No	0	BRCA1	None	None	11 mths dis free
		Case 6	Normal	FT CIS	**Pos**	Yes (TLH, BSO, omentectomy)	1c	BRCA1	None	None	40 mths dis free
		Case 9	Normal	FT CIS, CIS ovary	**Pos**	No (No formal staging)	?1c?0	BRCA2	None	FU laparoscopy + washings + peritoneal bx + omentectomy Neg	24 mths dis free
		Case 10	Normal	FT CIS	Neg	No	0	BRCA2	None	None	12 mths dis free
		Case 11	Normal	FT CIS	**Pos**	Yes (TLH, BSO, omentectomy)	1c	Unknown	None	None	28 mths dis free
		Case 12	Normal	FT CIS	Neg	No	0	Unknown	None	None	48 mths dis free
		Case 13	Normal	FT CIS	Neg	No	0	Unknown	None	None	NA

BSO—bilateral salpingo-oophorectomy, bx—biopsy, C—Carboplatin, ca—cancer, CIS—carcinoma in situ, dis—disease, FU—follow up, FTC—fallopian tube cancer, mth—months, NA—not available, Neg—negative, Pos—positive, P—Paclitaxel, rec—recurrence, STIC Serous tubal carcinoma in situ, TAH—total abdominal hysterectomy, T—Taxotere. *(unable to provide reference links for all above studies in the reference section given journal guidelines)*.

[a] Includes cases where the final histological diagnosis is STIC without concomitant invasive cancer.

[b] Follow-up data previously unpublished (personal communication).

Table 3
Cases of normal histology and positive cytology detected at RRSO.

Author	Series	Pos cases	Histology (gross)	Histology (microscopic)	Cytology	Staging surgery	Stage	Mutation status	Chemotherapy	2nd Look	Follow up
Colgan 2002	n = 35	Case 3	Normal	Normal	**Pos**	Yes	?	Unknown	Yes		10 mths dis free
Finch 2006 JAMA	n = 490	Case 6	NA	Normal	**Pos**	NA	?	BRCA 1	NA	NA	Alive at 1 yr
Schmeler 2006	n = 65	Case 2	Normal	Normal	**Pos**	TAH BSO primary surgery. (Unknown if full staging undertaken at 2nd look)	?	BRCA	P + C (4 cycles)	Yes (details of procedure NA)	60 mths disease free

BSO—bilateral salpingo-oophorectomy, C—Carboplatin, dis—disease, mths—months, NA—not available, Pos—positive, P—Paclitaxel, TAH—total abdominal hysterectomy *(unable to provide reference links for all above studies in the reference section given journal guidelines)*.

reported in the literature. The natural history of *STIC* lesions is yet to be established and the evidence base for managing these women is very limited.

Of the 31 reported patients with tubal *STIC* lesions (Table 2) [3,4,18], 10 had positive cytology, of whom five received adjuvant chemotherapy (paclitaxel and carboplatin). No recurrence has been found in such cases, although the follow up reported is extremely limited (Table 2). In addition, there were three reports of women with positive cytology and normal tubal/ovarian histology at RRSO [5], two of whom subsequently received chemotherapy (Table 3). These cases of positive cytology with *STIC*/normal histology may potentially reflect undetected early microinvasive peritoneal cancer or an early micro-invasive lesion in the tube/ovary missed despite 2-3 mm serial sectioning. Additional multistep level sections of tubal and ovarian tissue blocks beyond original 2–3 mm standard protocols has been shown to further increase detection of occult cancer. The finding of positive cytology at RRSO is consistent with pelvic serous cancers arising in the tube and seeding the ovary or peritoneal surfaces, as well as cancers which may arise/be present in the peritoneum, omentum or other abdominopelvic structures. We would advocate that consideration be given to full staging surgery in women with *STIC* and positive cytology.

Five of the 18 cases of *STIC* with negative cytology also received adjuvant chemotherapy (paclitaxel and carboplatin) (Table 2). Cytology was not undertaken/not reported in three cases. The role of chemotherapy in these cases of *STIC* is not yet well defined and practice varies between institutions. Given the lack of clear evidence of benefit it has not been our practice in women with *STIC* and negative cytology to undertake further staging surgery or to routinely give chemotherapy, though this has been advocated by others [3]. Although no recurrence has been reported in these cases with negative cytology, only limited follow-up data is available in 13 cases (Table 2). However, we are aware of an unreported case of peritoneal cancer developing in one patient with *STIC* four years after risk-reducing surgery (personal communication—Drapkin R). This patient was a BRCA1 carrier who had breast cancer at age 34 and a recurrence at age 41. She underwent RRSO at the age of 44. Peritoneal cytology was not performed at the time, and serial sectioning of the ovaries and tubes showed no tumor. She presented with a pelvic mass and ascites at age 50 and was diagnosed with a stage IIIc peritoneal carcinoma. As part of an epidemiologic study, the paraffin blocks of her BSO were subsequently step sectioned and revealed a STIC lesion. While a residual risk of primary peritoneal cancer of up to 4.3% has been reported in BRCA carriers following RRSO [5], there is as yet insufficient evidence to indicate whether this risk is higher in women with *STIC* lesions and positive cytology and possibly even in those with *STIC* alone. This has implications for counselling and follow up of this sub-group of patients.

Limitations to our findings include a lack of central pathology review, incomplete data on staging in some series, absence of well-defined pathology protocols in some initial series and evolving terminology over a period of time. It is possible that the number of occult in situ / invasive lesions may be an underestimate of the true prevalence.

Conclusion

Available data suggest that the majority of occult invasive/ in situ cancers reported in women undergoing RRSO are early stage invasive/ in situ lesions. In the former situation, peritoneal cytology is mandatory for staging and subsequent decision regarding chemotherapy. It would be helpful if publications on RRSO specifically reported peritoneal cytology findings. Based on the available literature, we advocate that peritoneal washings should be part of the routine RRSO surgical protocol for high-risk women. The management of women with *STIC* remains a clinical dilemma. It is unknown whether these women (particularly with positive cytology) would represent a sub-group at higher risk who may need adjuvant therapy and closer follow up. Given the low incidence of such cases at risk-reducing surgery, there is a need for an international register to collect long term data on these patients and develop an evidence base to inform clinical practice/future research. The Pelvic-Ovarian Cancer Interception (POINT) Project [25] is an effort aimed at furthering the understanding of the frequency and outcome of these lesions.

Acknowledgments

We are particularly grateful to all our patients. A portion of this work was done at UCLH/UCL within the “women's health theme” of the NIHR UCLH/UCL CBRC supported by the Department of Health.

Submission declaration and verification

The work described in this manuscript has not been published previously. This work is not under consideration for publication elsewhere, and its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. If accepted, this work will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Conflict of interest statement

IJ has consultancy arrangements with Becton Dickinson, who have an interest in tumour markers and ovarian cancer. IJ and UM have a financial interest through UCL Business and Abcodia Ltd in the third party exploitation of clinical trials biobanks which have been developed through the research at UCL. IJ is a member of the board of Abcodia Ltd and Women's Health Specialists Ltd. The other authors declare no conflict of interest.

Contribution to authorship

RM, was involved in initial data collection. RM, UM were involved in analysis, and writing initial draft and of the manuscript. RD and IJJ reviewed and contributed to writing the manuscript. The final draft was prepared by RM, UM and approved by the others.

Details of ethics approval

As this is a clinical commentary, hence, no separate ethical approval was deemed necessary. The part of the work reported from UCLH was referred to the Chair of the Research Ethics committee (National Hospital for Neurology and Neurosurgery & institute of Neurology

Joint REC, reference number 07L 173). Under the Research Governance Framework this project was deemed to be a clinical audit, and permission for data analysis and submission for publication was given.

Funding

This work has not been directly funded by any commercial organisation, charity, or other sources. A portion of this work was done at UCLH/UCL within the "women's health theme" of the NIHR UCLH/UCL comprehensive biomedical research centre (CBRC) supported by the Department of Health.

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29 June 2011