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

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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/ preinvasive disease are summarised in tables 1-3.

1) 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 stage 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 stage1 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 stage1a and Stage1b 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) stage1a and stage1b 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 stage1 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).

2) 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 insitu 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 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 microinvasive 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 insitu / invasive lesions may be an underestimate of the true prevalence.

Conclusion

Available data suggest that the majority of occult invasive/ insitu cancers reported in women undergoing RRSO are early stage invasive/ insitu 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.

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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.

Disclosure of interests

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.

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TABLE LEGENDS

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

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

*Follow up data previously unpublished (personal communication)

BSO- bilateral salpingo-oophorectomy, C- Carboplatin, ca- cancer, CIS- carcinoma insitu, 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 insitu, TAH- total abdominal hysterectomy, TLH- total laparoscopic hysterectomy, T- Taxotere

Table 2: Occult carcinoma insitu (CIS) / Serous tubal insitu carcinoma (STIC) lesions[#] (without concomitant invasion) detected at RRSO

[#]includes cases where the final histological diagnosis is STIC without concomitant invasive cancer

*Follow up data previously unpublished (personal communication)

BSO- bilateral salpingo-oophorectomy, bx- biopsy, C- Carboplatin, ca- cancer, CIS- carcinoma insitu, 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 insitu, TAH- total abdominal hysterectomy, T- Taxotere.

Table 3: Cases of Normal histology and positive cytology detected at RRSO

BSO- bilateral salpingo-oophorectomy, C- Carboplatin, dis- disease, mth- months, NA- not available, Pos- positive, P- Paclitaxel, TAH- total abdominal hysterectomy