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**Diathermy induced injury may affect detection of occult tubal lesions at risk reducing salpingo-oophorectomy (RRSO)**

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**ABSTRACT**

**Diathermy induced injury may affect detection of occult tubal lesions at risk reducing salpingo-oophorectomy (RRSO).**

**Background**

Electro-surgery induced tubal thermal injury obscures cellular detail and hampers histo-morphological assessment for occult pathology.

**Objective**

To report on diathermy related thermal injuries to the fallopian tube observed at RRSO and explore its potential impact on the detection of occult tubal epithelial lesions.

**Design**

High-risk women from breast and/or ovarian cancer families attending a tertiary high-risk familial gynaecological cancer clinic. Retrospective case control analysis of high-risk women who underwent RRSO. Cases: All women detected to have occult lesions (tubal atypia/carcinoma in situ/cancer) between January-2005 and December-2010. Controls: All women with normal tubal/ovarian histology between August-2006 and December-2007

**Methods**

Two pathologists performed histopathological assessment for grade of thermal injury. Tubal diathermy injury rates were compared between cases and controls. Statistical analysis was undertaken using SPSS-18. The Mann-Whitney test compared age distributions, Chi-Square / Fisher's tests the difference between proportions and Gamma test the difference in ordinal variables between the groups.

**Results**

A novel tubal thermal index to describe the severity of injury is reported. Lack of fimbrial thermal injury is twice as likely (odds ratio 2.04, 95%CI 1.06,3.92) to be associated with detection of occult tubal pathology, whereas isthmic injury does not affect detection rate (p=0.744). The groups were comparable with respect to age at RRSO (p=0.531) and the presence of BRCA mutations (p=0.192).

**Conclusions**

This report highlights the potential impact of electrosurgical thermal injury on detection of occult tubal pathology following RRSO. It is important for surgeons to avoid thermal injury to the distal end of the tube.

**Background**

Familial cancers are responsible for 5-10% of gynaecological cancers and mutations
in the BRCA1 and BRCA2 genes account for most of the known hereditary risk for
ovarian cancer (OC). These mutations have a low prevalence (1 in 300 to 1 in 800)[1-4]
in the general population, but are associated with high penetrance. Meta-analyses
report cumulative OC risks (till age 70 years) to be up to 40% for BRCA1 carriers,
and up to 18% for BRCA2 carriers,[5, 6] with even higher penetrances documented in
carriers ascertained from high-risk families.[7-10] The most effective management
option for these women is risk reducing salpingo-oophorectomy (RRSO) (HR 0.21;
CI 0.12, 0.39).[11]

Occult invasive/*in situ* cancer has been documented in 4.7%[12] (range 0 to 10%)[13] of
BRCA carriers and up to 3.1% of high-risk women with unknown mutation status
(UMS) undergoing RRSO.[14] Around two-thirds of these lesions occur in the distal
tube.[15] Given the high incidence of occult cancer and potential implications for
subsequent care, it is necessary to accurately identify these lesions. Use of a strict
pathological protocol with 2-3 mm serial sectioning of the tube and ovary has been
shown to increase the detection rate of occult cancers.[12, 13, 16] Use of a SEEFIM
(Sectioning and Extensively Examining the FIMbria) protocol has been reported to
further improve detection of these lesions.[17]

These efforts have led to the distal end of the tube, particularly the fimbriae, emerging
as the site of origin of an increasing proportion of tubal/ovarian/ pelvic serous
cancers.[18-22] A putative precursor lesion (p53 signature) has been described in the
fallopian tube and it is proposed that genotoxic injury is more likely to lead to

progression of these lesions to cancer in women at high risk for disease.[23-25] There have also been reports of molecular and histological changes in tubal epithelium (particularly at the fimbrial end) which do not amount to carcinoma *in situ* (CIS),[18, 20] the clinical significance of which is yet to be established.

RRSO is undertaken using a variety of different laparoscopic techniques with diathermy being one of the most commonly used techniques to secure pedicles and obtain surgical haemostasis. Electro-surgical diathermy induced thermal injury can obscure cellular detail and prevent complete morphological assessment. We report on the results of a pathological review of RRSO specimens undertaken to assess the frequency of diathermy associated thermal injury to the fallopian tube and explore its potential impact on the detection of occult tubal/ovarian pathology. In addition we propose a novel classification for grading severity of electrosurgical thermal injury in the fallopian tubes.

**Methods**

The primary recommendation for women at 'high-risk' for OC attending the multidisciplinary tertiary level UCLH familial gynaecological cancer clinic is RRSO once they have completed their family. Comprehensive advice on the advantages and disadvantages and the timing of RRSO is provided.[26] Demographic, clinical and histopathological data are collected using a standardised proforma and stored in a bespoke familial clinic database.

Surgery involves removal of both tubes and ovaries (or all remaining adnexae in women who have undergone previous partial removal), peritoneal washings for cytological examination and endometrial sampling. All surgical procedures are undertaken or directly supervised by a consultant (attending surgeon) experienced in laparoscopic surgery. Bipolar thermocoagulation is used to achieve haemostasis in the ovarian and infundibular-pelvic pedicles, prior to excision with the use of laparoscopic scissors. Bipolar is set to 30-40 Watts. Specimens are processed by a dedicated senior pathologist (EB) with a special interest in familial gynaecological cancer. From 2005 onwards, a strict surgico-pathological protocol has been adopted. Serial transverse sectioning of the ovaries and the proximal, mid and distal fallopian tubes at 2mm intervals is undertaken, followed by perpendicular sectioning of the fimbrial end to maximise the surface area of the fimbrial plicae visualised. The entire specimen is embedded and microscopically examined.

Histological assessment of dysplasia/atypia was based on epithelial and architectural changes, including degree of stratification, mitotic index, nuclear:cytoplasmic ratio, prominent nucleoli, hyperchromasia, chromatin clumping and loss of ciliated cells. Histological abnormalities not amounting to carcinoma *insitu* (CIS), but showing, some nuclear enlargement, hyperchromatic nuclei, incomplete replacement of the adjacent normal ciliated cells, and less than full thickness epithelial involvement with some preservation of epithelial polarity, were graded as mild- moderate epithelial atypia depending on the degree of abnormality. Occult lesion was defined as any case of tubal/ovarian cancer, carcinoma *in situ* or mild-moderate tubal atypia .

The familial clinic as well as the 'CoPath' pathology databases were searched for (a) all patients from breast and/or ovarian cancer families with occult lesions who underwent RRSO between Jan 2005 and December 2010 ('cases') and (b) all patients from breast and/or ovarian cancer families who underwent RRSO between August 2006 and December 2007 ('controls'). Cytology and histopathology reports and the slides were retrieved for all 'cases' and 'controls'. A histological review of all the slides was undertaken by two pathologists (EB and AS) and consensus on findings achieved.

All sections from the fallopian tubes were assessed for the presence/absence of heat artefact in the isthmic, ampullary and fimbrial regions of the tube. Electro-surgery/diathermy induced thermal injury to the tube obscures cellular detail by blurring cellular outlines, causing elongation, hyperchromasia and smearing of nuclear DNA. Dependent on the extent of affected epithelial surface area of the section, the degree of tubal thermal injury was graded using a novel index, as follows– (a) Grade 0: No thermal artefact; (b) Grade 1 (mild): thermal artefact involving <20% epithelial surface area (Figure-1); (c) Grade 2 (moderate): thermal artefact involving 20-50% epithelial surface area (Figure-2); and (d) Grade 3 (severe): thermal artefact involving >50% epithelial surface area (Figure-3). When diathermy artefact was present in multiple sections the most severe grade of artefact identified was taken for the purpose of the analysis.

Statistical analysis was undertaken using SPSS 18. The potential impact of diathermy induced thermal artefact on occult lesions was explored by undertaking a case-control analysis for frequency and grade of thermal artefact between these two groups. The

null hypothesis was defined as no difference in thermal injury between these two groups. For the purpose of this analysis the right and left adnexae were considered independent of each other. A per-tube analysis was undertaken to enable analysis of thermal injury data for each tube separately. Chi-Square test (n>30) and Fisher's test (n<30) were used to calculate the difference between proportions. Odds Ratio was used to quantify the association of any differences in thermal injury between cases and controls. Gamma test was used to evaluate the difference in ordinal variables between the two groups. The Mann-Whitney non-parametric test was used to compare age distributions between groups after reviewing histograms. Two sided p values are reported for all statistical tests.

**Results**

A search of the familial clinic and CoPath databases for breast and/or OC families revealed (a) 37 cases and (b) 85 consecutive RRSO controls. Histological specimens were accessible for 34 'cases' and 78 'controls'. Findings in the 34 cases were as follows: tubal/ovarian cancer in 7 patients, tubal CIS in 11 patients, and mild-moderate tubal atypia in 16 patients.

Characteristics of the 'cases' and 'control' groups are compared in Table-1. The two groups did not differ significantly with respect to age at surgery (p=0.531) or presence of BRCA1/2 mutations (p=0.192). Bilateral salpingo-oophorectomy was undertaken in 33 of 34 cases and in 75 of the 78 controls (Table-1). There were 67 tubes and 68 ovaries in cases, and 154 tubes and 153 ovaries in the control groups respectively. The

different grades of tubal thermal injury found in the 'cases' and 'control' groups are given in Table-2.

In both cases and controls, the highest rate of diathermy injury was in the isthmic region (Table 2) and in this region, there was no significant difference in the diathermy injury rates whether high-grade (p=0.546) or overall (p=0.744) between cases and controls (Table-2).

However, comparing diathermy induced thermal artefact in the fimbrial region of the tube between cases and controls, there was a significant difference in the grades of injury (p=0.017) with 37% of controls having some degree of diathermy induced thermal artefact present in the fimbrial region, compared to 22.4% of cases (odds ratio 2.04, 95% CI 1.06, 3.92) (Table-2). Higher grades (Grade 2/Grade 3) of thermal injury were found to occur more commonly in the distal (ampullo-fimbrial) region of the tube in controls (29.2%) compared to cases (16.4%) (p= 0.044) (odds ratio 2.1 95% CI 1.02, 4.32) (Table-1).

**Discussion**

To the best of our knowledge this is the first report high-lighting the potential impact of electrosurgical thermal injury on detection of occult tubal pathology following RRSO. Lack of fimbrial or Grade 2-3 distal tubal thermal injury is twice as likely to be associated with detection of occult tubal pathology. It is important for surgeons to avoid thermal injury to the distal end of the tube.

The two groups did not significantly differ with respect to age at surgery and presence of BRCA mutations (Table-1). Of note, most of the tubal pathology was in the fimbrio-ampullary region, which is in keeping with reported literature and the fimbrial portion of the tube being the commonest site for occurrence of occult lesions in high-risk women,[23]

Use of our novel tubal thermal injury index that takes into account the extent of affected tubal surface area /severity and may serve as a useful histological reporting tool in women undergoing RRSO. Temperatures >42°C can cause cell membrane damage and protein denaturation leading to microscopic appearances of disruption of cellular outlines, detachment of epithelium, elongation, hyperchromasia, pseudostratification or loss of nuclei and homogenisation of connective tissue.[27] This obscures cellular detail and hampers morphological assessment of the tubal epithelium. Given the potential impact on detection of small (few mm in size) intraepithelial/invasive carcinomas in RRSO specimens, quantification of thermal injury in histopathological reports seems warranted.

It is possible that potentially missed occult invasive/*in situ* lesions may contribute to the residual risk of primary peritoneal cancer in these women.[28] Long term follow up studies of women undergoing RRSO are ongoing to assess this risk. Routine reporting of grade of thermal injury in these women may provide information which can help shed further light on this issue.

The similar high rates of isthmic tubal thermal injury observed in both groups are consistent with the surgical technique using diathermy. Most gynaecologists use

diathermy/ electrosurgery for haemostasis and securing pedicles at RRSO (including those at our institution). However, this can cause thermal damage beyond the point grossly visible to the naked eye, with the degree of lateral thermal spread dependent on the type of instrument used, the application time and power setting. Newer electrosurgical instruments: Harmonic Scalpel[TM] (Harmonic ACE[TM] Ehthicon, USA) and LigaSure[TM] (Valleylab, Boulder, CO, USA) cause less collateral damage. but are only effective for securing vessels up to 5mm,[29] and 7mm in size respectively. Amongst electrosurgical instruments, monopolar diathermy causes maximum lateral tissue damage (>1cm from point of application)[30] with an area of coagulation necrosis twice as large as bipolar electrosurgery.[31] It takes up to a minute for temperature at the tip of the instrument to reduce below 42°C.[30] Bipolar, Harmonic Scalpel[TM] and LigaSure[TM] cause similar levels of thermal damage, with the latter producing the smallest rise in temperature.[30] Thermal damage may be reduced by using shorter application times or midpoint interruptions with the same total duration of application,[32] and use of non-electrosurgical techniques: intra/extra corporeal suturing or use of endoloops. However, suturing requires more advanced laparoscopic skills, and has cost and time implications. Cost is also a consideration with the use of advanced laparoscopic instruments such as Harmonic Scalpel[TM] and LigaSure[TM]. Additional artefacts which may obscure histological appearances include crush injury to the tube and in particular to the fimbrial end. It is important for all gynaecologists performing these procedures to be aware of these issues.

The presence of occult invasive/*in situ* cancer at pathology has implications for future care and follow-up. These women may need referral to a gynaecological oncologist for assessment and further management. Routine peritoneal cytology is essential in

this population, as positive cytology in many situations determines the need for surgical staging and possible chemotherapy.[33] As the UK national health service (NHS) provides restricted access to genetic testing for BRCA1/2 mutations, identifying occult lesions also means that individuals who have no live affected relatives with a relevant cancer diagnosis, are able to access genetic testing for themselves.[26] A positive test permits predictive testing of other family members and may have implications for their own treatment (e.g. access to PARP inhibitors if chemotherapy is warranted).

The limitations of our study include retrospective design and the lack of detailed data on co-morbidity such as endometriosis/adhesions that may have contributed to greater need for use of diathermy.

Performing RRSO without subjecting the crucial fimbrial and ampullary regions of the fallopian tube to thermal damage or crush injury should be possible in the majority of cases. However, some degree of focal diathermy in the proximal isthmic portion of the fallopian tube may be unavoidable if electrosurgery is used to secure this pedicle. This should be acceptable as occult lesions are unlikely to occur in the proximal isthmic part of the tube. Inadvertent injury should be minimised by avoiding monopolar diathermy, use of low power settings and short application times . Our experience and the literature indicate the need for an evidence based surgical protocol alongside a histopathological protocol in order to optimise both detection of occult pathology as wells as maximise benefit of ovarian cancer risk reduction. The surgico-pathological protocol currently followed at our institution is provided in Table-3.

**Conclusion**

Our findings for the first time high-light the potential impact of diathermy related thermal injury on detection of occult tubal pathology in women undergoing RRSO. We also propose a novel tubal thermal index for grading such injuries. Our data suggest that lack of fimbrial or Grade 2-3 distal tubal (fimbrio/ampullary) thermal injury is twice as likely to be associated with detection of occult tubal pathology. It is important that gynaecologists undertaking these procedures be made aware of these issues. A strict surgico-pathological protocol for RRSO should include both histopathological aspects (such as serial sectioning and peritoneal cytology), as well as appropriate surgical technique to optimise detection of occult pathology and maximise the benefits that identification of such lesions may confer on patients and their relatives.

**Short Title**

Diathermy related tubal injury may affect detection of occult lesions at RRSO

**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 in Abcodia, Ltd., a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. IJ is a member of the board of Abcodia Ltd and Women's Health Specialists Ltd. ANR has received honoraria from Fujirebio Diagnostics for giving lectures and attending meetings on the use of biomarkers in ovarian cancer management, but none were directly related to this work. ES received honoraria from Ethicon for provision of training to healthcare professionals; this was not related to this work. The other authors declare no conflict of interest.

**Contribution to authorship**

RM, AS and AA were involved in initial data collection. RM, UM were involved in analysis, drafting and writing of the paper. AS and EB reviewed the histological specimens and contributed to the histopathological sections of the manuscript. RM and MB performed the statistical analysis and contributed to writing the statistical sections of the manuscript. IJ, ANR, ES, AA, MJ, CB, GP, NA, AV contributed to writing of the manuscript. UM, IJ, ANR, RM, CB, ES, GP, NA, AV were responsible for the clinical care of the patients. The final draft was prepared by RM, UM and approved by the others.

**Details of ethics approval**

The project 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 the project was deemed to be a clinical audit, and permission for data analysis and submission for publication was given.

**Copyright Statement**

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**TABLE AND FIGURE LEGENDS**

**Table-1**

**Characteristic of the two groups: 34 'occult cases' and 78 'controls'**

BSO- bilateral salpingo-oophorectomy, B/L- bilateral, C/L- contra-lateral, HBC – high-risk breast cancer only family, HBOC- high-risk breast and ovarian cancer family, HOC- high-risk ovarian cancer only family, IQR- inter quartile range, UMS- unknown mutation status, USO – unilateral salpingo-oophorectomy

**Table-2**

**Grades of diathermy induced thermal injury in both groups**

Gr- grade, Mod- moderate, Sev- severe

**Table-3: UCLH Familial Cancer Clinic Surgico-histopathological Protocol**

**Figure-1**

**Histopathological section of the tube showing mild thermal injury changes**

The epithelium shows focal areas of disruption and detachment of tubal epithelium (arrows) with blurring of cell boundaries compared to normal epithelium (N) (x100)

**Figure-2**

**Histopathological section of the tube showing moderate thermal injury changes**

The changes of thermal injury are more extensive, encompassing 20-50% of the epithelial surface area. There is epithelial distortion with elongated hyperchromatic nuclei and indistinct cytoplasmic membranes. (x200)


**Figure-3**

**Histopathological section of the tube showing severe thermal injury changes**

Widespread thermal injury entirely obscuring cellular detail, hampering histopathological assessment. Elongated and stratified appearance of nuclei with loss of cellular detail. The changes affect both the epithelium and subepithelial connective tissue and there is tissue disruption. (x200)