Appendectomy with cytoreductive surgery for ovarian and type 2 endometrial carcinoma

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Summary

There is considerable variation within and between cancer centers in the practice of appendectomy as part of cytoreductive surgery for ovarian carcinoma and in the surgical staging of endometrial carcinoma. The purpose of this study was to determine the prevalence and the type of appendiceal pathology, the morbidity associated with appendectomy in gynaecologic cancer surgery. *Materials and Methods:* This is a retrospective review of all cytoreductive surgery for ovarian carcinoma and surgical staging for endometrial carcinoma with appendectomy over a four year period. *Results:* Two hundred and fifty-one patients (38 patients for endometrial carcinoma surgery and 213 patients for ovarian cytoreduction) had an appendectomy performed. Metastases to the appendix was present in 46 (23.2%) of primary ovarian carcinoma and one (2.6%) primary endometrial carcinosarcoma. The appendix was more likely to be involved in advanced stage ovarian cancer with positive peritoneal washings, omental deposits, grade 3 differentiation, and papillary serous histology. Sixteen (6.4%) co-incidental primary appendiceal tumours were detected. No postoperative morbidity specific to appendectomy was identified. One case of ovarian carcinoma was upstaged from IC to IIIA by the appendiceal metastases. There was no upstaging of disease in the endometrial carcinoma group. *Discussion:* Appendectomy is an integral part of ovarian cytoreductive surgery but the authors found it did not upstage the disease in a clinically significant manner. The incidence of co-incidental appendiceal primary tumours was high in this series and may add value to the procedure in preventing further surgeries. The absence of procedure related morbidity is reassuring. The authors recommend appendectomy for all ovarian staging surgery and its consideration in type 2 endometrial cancer.

Key words: Cytoreductive surgery; Ovarian cancer; Endometrial cancer; Appendectomy; Gynaecological malignancy; Staging; Appendiceal tumours.

Introduction

Appendectomy is a common procedure in cytoreduction of ovarian epithelial cancers. Papillary serous and clear cell cancers originating in the endometrium (type 2 cancers) also have a propensity to spread in the peritoneal cavity. Surgical practices in cytoreduction of ovarian cancer vary from universal appendectomy to selective removal as part of the gross cytoreductive effort in Stage IIIC disease or only in apparent Stage I disease. [1-3] There is no defined standard of practice in intraperitoneal extirpation for staging of endometrial cancer. Occult intraperitoneal metastasis has been reported in patients with endometrial cancer grossly confined to the uterus. [4] Dilek *et al.* [5] reported 3.9% incidence of appendiceal metastasis with endometrioid carcinoma.

The geographical proximity of appendix to the right adnexa and shared coelomic epithelial covering may enhance the likelihood of its involvement by metastasis from ovarian or endometrial cancers. Synchronous primary malignant and benign tumours of appendix can be detected. The authors' practice has been to excise the appendix and infracolic-omentum in all ovarian epithelial cancers and less consistently endometrial cancers other than grade 1 or 2 endometrioid adenocarcinoma that appear to be confined to the uterus. They undertook this review of appendectomy to evaluate their practice by measuring the prevalence of appendiceal pathology and the morbidity associated with the procedure in the surgical management of ovarian and endometrial cancers.

Materials and Methods

This retrospective review of all appendectomies performed at surgical staging laparotomy for endometrial type 2 and ovarian carcinoma was conducted in a tertiary gynaecology oncology centre over a four year period (2008-2011). This centre receives an average 87 new referrals for ovarian cancer and 80 new referrals for endometrial cancer annually. All surgical procedures were performed by three experienced gynaecologic oncologists.

The authors identified all cases of appendectomy with confirmed ovarian or uterine malignancy from the gynaecology cancer database. Information on histopathology was obtained from the tumour board multidisciplinary outcomes and laboratory database. Supplementary information was extracted from the patients' medical records.

This study has been approved by the Division of Gynaecologic Oncology, St James's Hospital, St James's Hospital Ethics Committee, prior to commencement of the project.

A positive histology of the appendix was defined as histology other than normal and included malignant primary and metastatic cancer and benign appendiceal tumours. Primary appendiceal tumours were classified using the WHO histological classification of tumour of the appendix. Appendiceal metastases included tumours at all locations.

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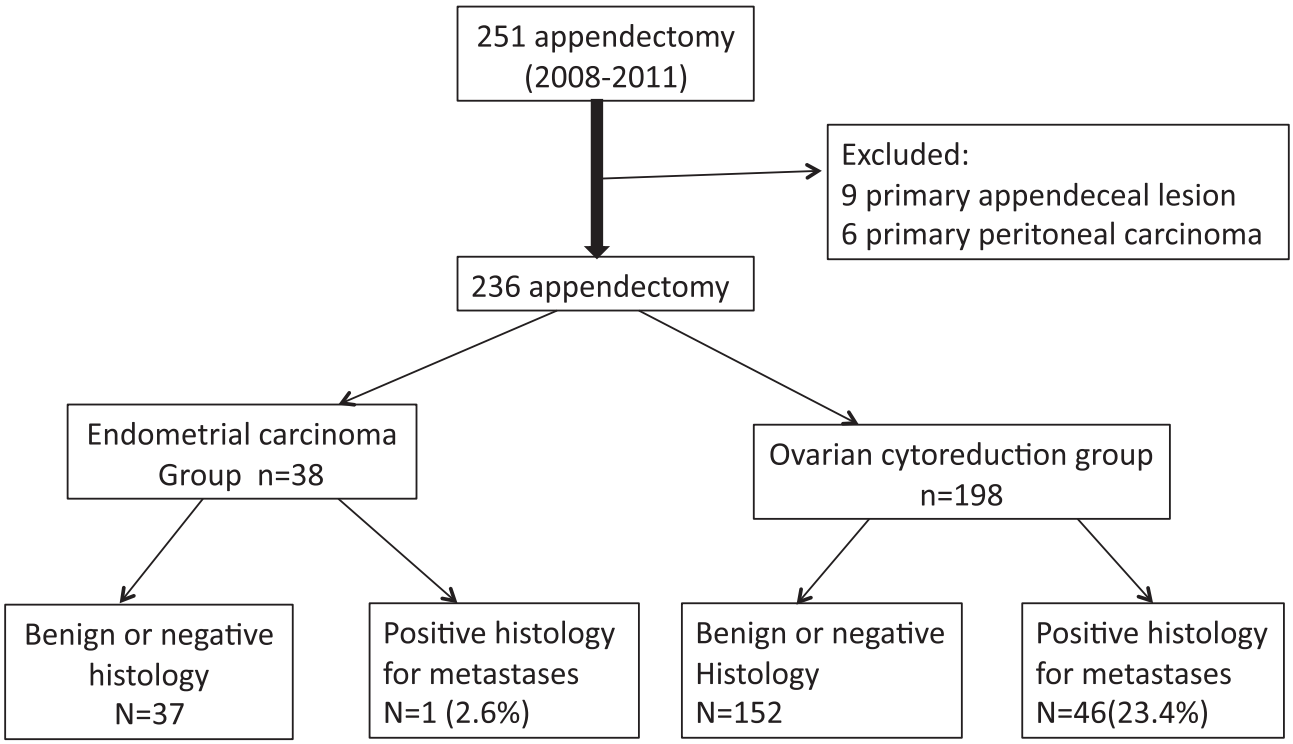

Figure 1. — Study population.

Statistical analysis

All data was processed using Microsoft Excel 2010, SPSS 18 (PASW Statistics 18). Significance values were calculated using Pearsons Chi Square Test or x^2 test.

Results

Two hundred and fifty-one patients had an appendectomy performed at ovarian or endometrial cancer surgery over the four year period (January 1st 2008 to December 31st 2011). During this time, there were a total of 242 ovarian debulking and 233 endometrial staging surgeries. Two hundred and thirteen patients (84.9%) initially presented with a pelvic mass suggestive of ovarian carcinoma. Thirty-one of these had radiologically guided cytology or histological diagnosis and had chemotherapy prior to surgery. Six patients who had surgery for ovarian cancer were deemed at final histopathological diagnosis to have primary peritoneal cancer and four of these had metastasis to appendix. Five patients had primary appendiceal carcinoma with large volume metastasis to pelvis. Four patients with primary endometrial/ovarian cancer had occult primary malignant appendiceal tumours. All other malignant appendiceal lesions were considered to be metastatic. Seven patients had benign primary appendiceal tumours. Thirty-eight patients had surgery for a preoperative histological diagnosis of endometrial malignancy. Figure 1 shows the groupings.

The patients' median age was 65.0 (45-83) years for endometrial cancer and 58.0 (22-87) years for ovarian cancer. Nulliparity was 11(28.9%) for the endometrial and 38 (17.8%) in the ovarian cancer group. Body-mass index was 27.8 (20-34) for endometrial and 27.3 (20.4-44.9) for ovarian cancer group. Median Karnofsky score at diagnosis was 80% (range 60-100%) in the endometrial group and 70% (range 50-100%) in the ovarian cancer group.

Figure 2 compares the outcomes of those with and without appendiceal metastases in the ovarian cancer group of 198 patients. Forty-six (23%) had appendiceal metastases. Twenty (43.4%) had obvious tumour deposits in the appendix on gross pathological examination. One patient with disease apparently confined to ovary at laparotomy had appendix as the sole site of histopathological extra ovarian disease but her peritoneal cytology was positive. Her cancer was papillary serous grade 2 within a cyst in her left ovary. Her pelvic and para-aortic lymph nodes were negative. Her disease was upstaged on the basis of appendiceal metastasis from Stage IC to IIIA. She received adjuvant chemotherapy. A comparison of ovarian cancer patients with and without appendiceal metastases showed those with appendiceal metastases were more likely to have apparent advanced Stage III/IV disease (97.7% vs 28.9%, $p < 0.001$), omental disease (91.8% vs 15.7%, $p < 0.001$), papillary serous histology (76% vs 46.1%, $p < 0.001$), grade 3 differentiation (84.7% vs 36.1%, $p < 0.000$) and positive peritoneal cytol-

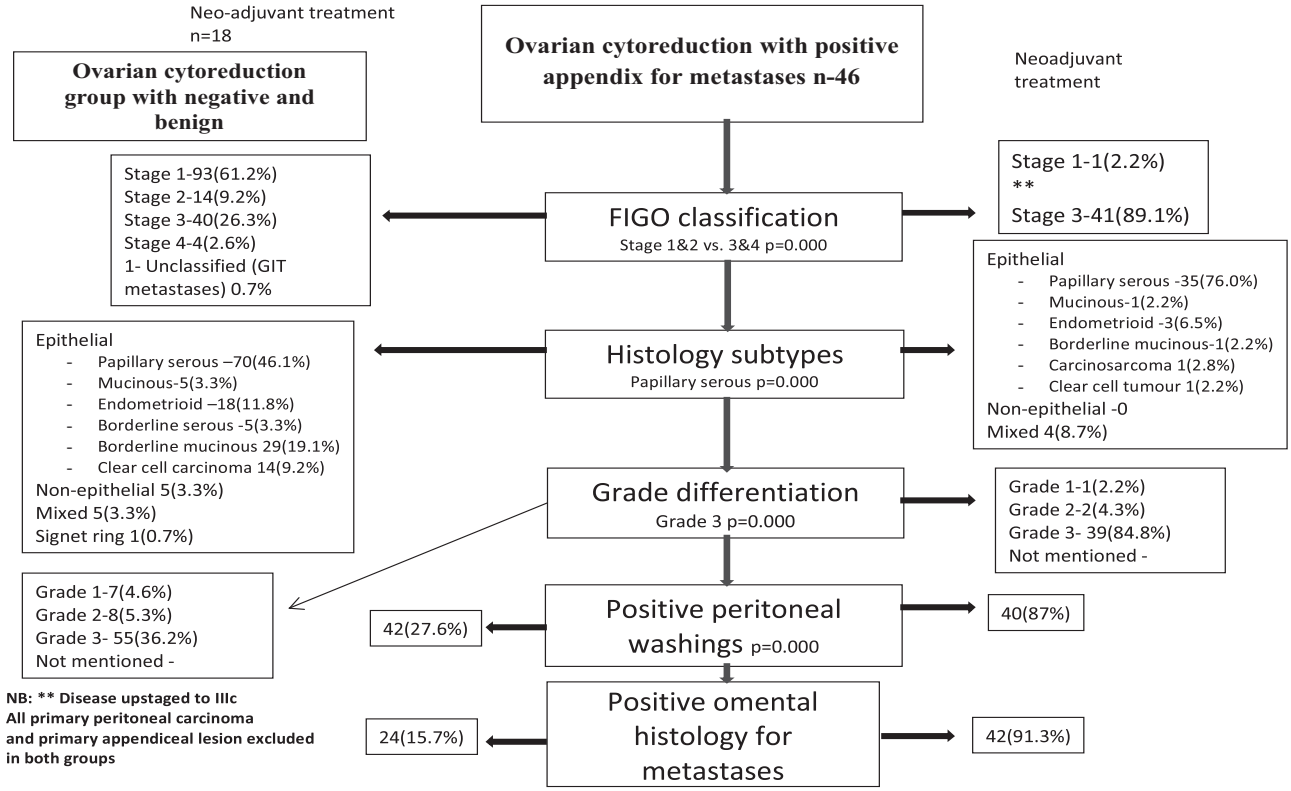

Figure 2. — Histological characteristics of the ovarian cytoreduction group; those with positive appendiceal metastases compared with the group with negative or benign appendix histology.

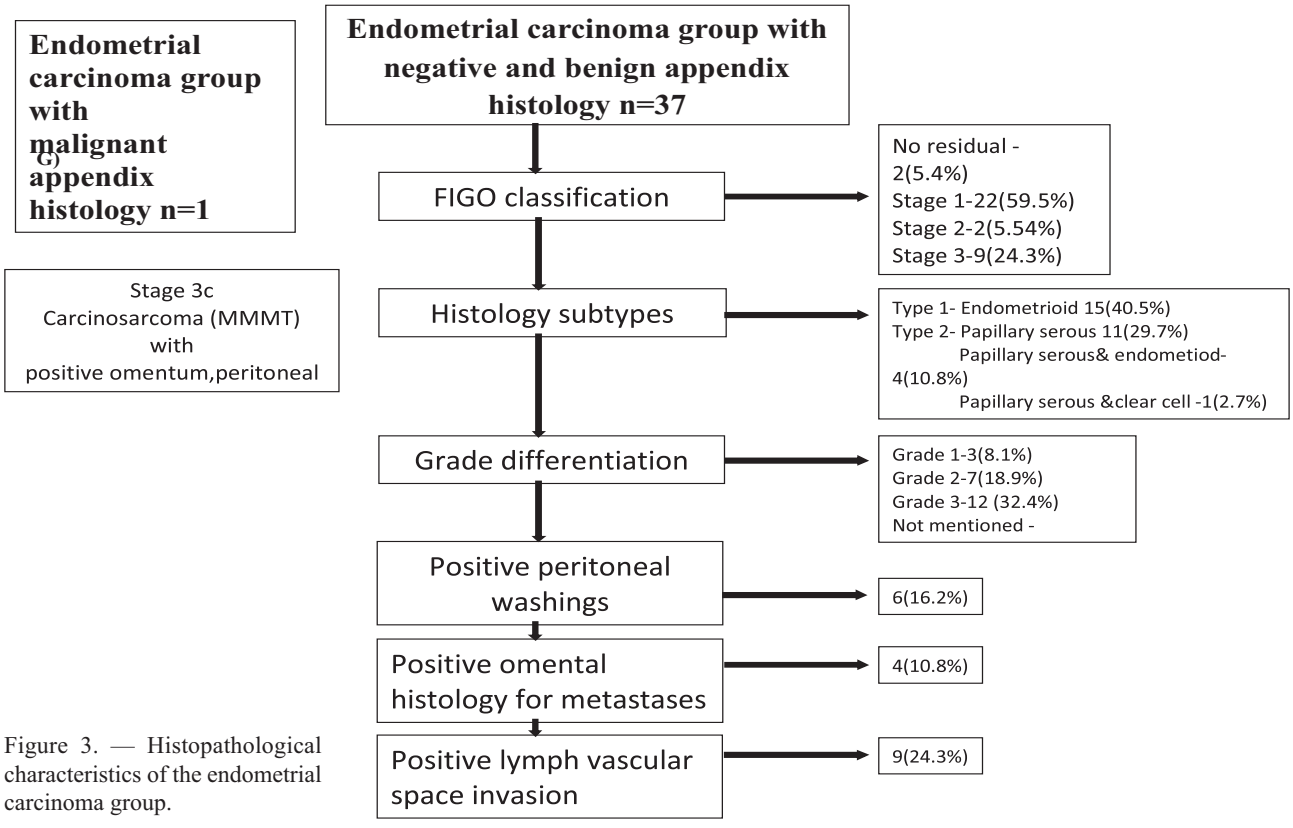

Figure 3. — Histopathological characteristics of the endometrial carcinoma group.

Table 1. — *Malignant primary appendiceal tumour in association with ovarian cytoreductive surgery and surgical staging for endometrial cancer. There are no endometrial cancers in this group.*

No	Appendix tumour type	Appendix lesion overt or occult at laparotomy	Histology of ovarian pathology	FIGO staging of ovarian disease
1	Small cell carcinoid tumour	Occult	Borderline endometrioid, carcinoma	IC
2	Goblet cell carcinoid tumour	Overt – fusiform expansion of distal appendix	Carcinoid	N/A
3	Goblet cell carcinoid	Occult	Papillary serous	IIIC
4	Myxoma	Occult	Mucinous cystadenocarcinoma with Pseudomyxomaperitonii originating from appendix.	IC
5	Signet ring cell	Overt – fibrosed shrunken appendix	Signet ring	N/A
6	Borderline Mucinous cystadenoma	Occult	Borderline mucinous cysadenoma (primary in appendix, metastasising to ovary)	N/A
7	Carcinoid	Occult	Borderline mucinous tumour	IA
8	Myxoma	Occult	Pseudomyxomaperitonii originating from appendix	N/A
9	Carcinoid	Occult	Benign serous cysadenofibroma	N/A

ogy (87% vs 27.6%, $p < 0.001$). Out of the 31 patients who received neo-adjuvant chemotherapy, appendiceal metastases were present in eight (25.8%).

Figure 3 shows the histolopathological characteristics for the endometrial carcinoma group. One patient had metastasis to appendix that was grossly visible at surgery. Her final histology was carcinosarcoma of uterus. A further eleven patients with advanced Stage III/IV disease had no involvement of appendix.

Table 1 shows the individual cases of primary malignancy of appendix. All cases arose in patients presenting with complex pelvic mass deemed likely to be primary ovarian preoperatively. The appendix appeared macroscopically abnormal in only two cases. One, a goblet cell carcinoid had a fusiform expansion of the distal appendix. Another, a signet ring cancer had a shrunken fibrosed appearance. Frozen section was not performed.

The benign tumours of the appendix were hyperplastic polyp (3), mucinous cystadenoma (2), and benign mucocele (2). Other benign appendiceal lesions were acute appendicitis (6), necrotizing granulomata (1), endometriosis (3), intussusception (1), lymphoid hyperplasia (1), and focal dysplasia (1).

There were no perioperative / postoperative adverse events attributed to the appendectomy in all 251 patients.

Discussion

A questionnaire based European review of clinical practice of cytoreductive surgery for ovarian carcinoma by Cibula *et al.* [1] revealed substantial differences in the spectrum and complexity of procedures performed for advanced ovarian cancer. Half of the centres reviewed would conduct an appendectomy in advanced ovarian cancer. A third would remove the appendix only if it was macroscopically involved. As appendectomy is not routinely performed in most gynaecology oncology centers in Europe, the present authors undertook this review to evaluate their own practice of appendectomy in the surgical staging of all ovarian neoplasms and type 2 endometrial cancer. Overall 32.7 % (82) of 251 patients undergoing surgical staging for ovarian and endometrial cancer in this series had some appendiceal pathology. Forty-seven patients had metastases to the appendix and 20 patients with benign appendiceal pathology. Nine patients had malignant primary appendiceal tumours.

Our ovarian cancer patients had metastasis to appendix in 23% which is lower the 37% to 43% reported by other authors Ayhan *et al.* [6], Fontanelli *et al.* [2], Rose *et al.* [3]. All but one of the patients in this series had gross metastases within the peritoneum and/or omentum. Appendiceal metastases were more likely with grossly evident Stage III/IV disease, positive peritoneal cytology, and with the papillary serous (PSC) type histology. This association confirms the authors' impression that PSC is more likely to involve the peritoneal cavity more extensively than the clear cell, mucinous or endometrioid sub-types. PSC is also the sub-type that arises de novo in the fallopian tubes and peritoneum and metastases may represent transcoelomic spread or synchronous malignant evolution of other parts of the coelomic epithelium [7]. The close proximity of the appendix to the adnexa makes it a likely repository for transcoelomic spread. The authors consider removal of the appendix is an integral part of the cytoreductive effort. Usually a simple surgical procedure, extreme fibrosis or large volume metastasis can make appendectomy challenging and caecotomy can result but repair of this is well within the remit of Gynaecological Oncologists.

Only one patient out of 108 with apparent Stage I/II ovarian disease had occult appendiceal metastasis that upstaged her. The low rates of sole occult appendiceal metastases is confirmed by other authors. Fontanelli *et al.* [2], Ramirez *et al.* [8], and Bese *et al.* [9] reported none in their series of 57, 160, and 90 patients respectively. Ayhan *et al.* [6] reported a rate of 4.9% in 106 patients. Only Ayhan *et al.* [6] has previously reported upstaging of the disease based on appendiceal metastases alone and our case adds a second to this category. That upstaging may not have been clinically relevant in our case because her positive peritoneal cytology would have raised her to Stage IC and chemotherapy would have been administered in any case. However, complete excision of microscopic disease may be beneficial. The absence of complications related to the appendectomy in this and all other series (Ayhan *et al.* [6]; Fontanelli *et al.* [2]; Rose *et al.* [3], Raminez *et al.* [8]) is particularly reassuring when the appendiceal pathology per se did not dictate additional treatments.

One of 35 borderline ovarian tumours involved the appendix. As expected the borderline tumours in our series were predominantly mucinous (85.7%) and the single case with appendiceal metastasis was mucinous. A further three cases had mucinous cystadenoma or myxoma of appendix with secondary involvement of ovary and the appendiceal primaries were occult in all these cases. The appendix and ovarian surface share a propensity for mucinous neoplasia. [10]. Failure to identify and remove the appendiceal mucinous tumour might put the patient at risk of tumour recurrence or subsequent pseudomyxoma peritoneii. Timofeev *et al.* [11] found a low prevalence of appendiceal pathology with cystadenoma of ovary and recommended appendectomy for borderline or invasive mucinous tumours of ovary. However, exclusion of borderline change in a large mucinous cystadenoma of ovary is not easy on frozen section sampling. The occult nature of the appendiceal lesions is concerning. The authors concur with Dietrich *et al.* [12] that routine appendectomy is reasonable when a mucinous ovarian tumour is suspected. When there is a suspicion of primary appendiceal cancer frozen section should be undertaken so that appropriate colonic staging with right hemicolectomy can be progressed if needed.

The authors' policy of routine appendectomy identified 16 (6.4%) coincidental primary appendiceal tumours, both benign (2.7%) and malignant (3.6%). All were occult and the rate of detection may reflect the thoroughness of their histopathologists. Tumours of the appendix are infrequent and are usually found during a "routine" appendectomy. In a study of 71,000 specimens taken at appendectomy, Collins *et al.* [13] found 958 malignant and 3,271 benign tumours, giving an overall incidence of 4.6% for benign tumours and 1.35% for the malignant tumours. The significance of small carcinoid tumours is unknown. Lesions less than one centimetre and possibly up to two centimetres are unlikely to metastasize from the appendix. Metastasis from small bowel carcinoid may occur earlier. Primary appendiceal cancer often presents as pelvic adnexal masses. A review of goblet cell carcinoid like and signet ring tumours by Hristov *et al.* [14] revealed a majority presenting as ovarian lesions and appendix thickened but fibrosed and not expanded. Goblet cell carcinoid (adenocarinoid) tumour of the appendix is rare and carries a risk of concomitant and metachronous colorectal cancer [15], so follow-up with endoscopy is recommended. The authors' general surgery colleagues did not undertake further staging surgery in any of these cases. The only case of signet ring cell carcinoma of the appendix with metastases to the pelvis was deemed unfit for further surgery. The diagnosis of benign appendiceal lesions ranged from acute and chronic inflammation, lymphoid hyperplasia in a cohort of patients with adnexal or uterine pathology is interesting. The inflammation may be a response to the neoplastic process in the pelvis or truly co-incidental but giving rise to symptoms that lead to diagnosis of the pelvic neoplasm.

Current gynaecologic oncology guidelines make no clear recommendations on appendectomy and omentectomy in type 2 endometrial cancers. In this group, intraperitoneal staging yielded positive omental metastases in 10.8% and positive peritoneal washings in 16.2%, and appendiceal metastases in 2.6% of 38 patients. The single patient with appendiceal metastasis had omental disease as well. Dilek *et al.* [5] reviewed appendectomy and omentectomy in 51 patients with clinical Stage I endometrioid adenocarcinoma and found that 3.9% metastases to appendix and six percent metastasis to the omentum. Saygili *et al.* [16] also found a similar rate with six percent omental metastasis and two percent appendiceal metastasis in apparent early Stage I endometrial adenocarcinoma. To the authors' knowledge, this is the first review on appendectomy with type 2 endometrial carcinoma. It is known that type 2 endometrial histology has a propensity for earlier extra uterine spread. Adjuvant chemotherapy is of limited value in such cases and disease remission may rely most on optimal surgical debulking. As such, the present authors would recommend that an appendectomy should be included in the primary surgery effort for patients with type 2 endometrial cancers. Appendectomy does not add to the morbidity of the surgery and can be safely undertaken with minimal access surgery as well.

The continued practice of appendectomy in all ovarian neoplasms and type 2 endometrial cancers is reasonable and safe.

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