Inadequately Staged Endometrial Cancer: a Clinical Dilemma

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Abstract Incidental diagnosis of carcinoma endometrium following hysterectomy requires clinical expertise from a gynecologic oncologist, with regard to subsequent management. We report our experience with completion staging in endometrial cancer, to determine the benefits and risks of completion staging in women with posthysterectomy diagnosis of endometrial cancer. Design: A retrospective case series of 20 women with postoperative diagnosis of endometrial cancer, who had undergone completion staging. Setting: A gynaecologic oncology unit in a tertiary level hospital in Tamil Nadu, India. Patients: Electronic medical records of patients who underwent completion staging between January 2011 and December 2014 for endometrial cancer were reviewed. Two hundred and sixty four women with endometrial cancer were evaluated during this period. Twenty women with carcinoma endometrium, with a mean age of 53 (range 31–67) who were previously inadequately staged, were found to be at risk of extrauterine disease, following histopathological review, consented to undergo completion staging over an average of

57 days (range 30–91) following the initial surgery. Forty-five percent (9/20) had a BMI of more than 30, and 40% (8/20) had metabolic syndrome. The most common indications for the initial surgery were perimenopausal abnormal uterine bleeding and postmenopausal bleeding. Only eight patients had a pre-hysterectomy endometrial sampling/biopsy (40%) of whom, one had a pre-operative diagnosis of carcinoma endometrium. Sixteen (80%) had pathological risk factors for lymph nodal involvement and in the others, besides histological grading, surgicopathological details for risk assessment were unavailable. Adnexae were retained in 11, and uterus was bisected/cored during surgery in three women. Following completion staging, 5/20 (25%) patients were upstaged, 9 (45%) required no adjuvant treatment, 5 required vaginal brachytherapy therapy alone and 5 were advised chemotherapy and radiation. Two patients during the study period of 48 months had disease recurrence, and two women died of disease progression. Complications of surgery included the following: iliac vein injury (1) and bladder injury (1). Patients with incidental diagnosis of endometrial cancer following hysterectomy after clinical and radiological assessment and histopathological review, should be offered completion staging, if at risk for extrauterine disease. Completion staging permits appropriate prognostication of disease and thereby allows tailoring of adjuvant treatment, avoiding risks of overtreatment and undertreatment.

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Introduction

The GLOBOCAN 2012 statistics report an incidence rate of 2.3% of endometrial cancer in India, and it is the ninth most

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common cancer among Indian women. However, these rates will change in the years to come as the population ages along with altered food habits and the growing epidemic of obesity and diabetes [1].

Women can be diagnosed to have endometrial cancer following hysterectomy for apparent benign conditions in 0.3–3% of cases [2], in the absence of pre-operative endometrial biopsy or blind endometrial biopsy techniques in case of focal endometrial lesions. Most of these incompletely staged endometrial cancers are in women with poor access to surgical or gynaecological oncologists and are initially managed in small hospitals.

Though 75% of women with endometrial cancer are diagnosed with stage I disease [3], lymph node involvement is the most important prognostic factor in endometrial cancer. There are several approaches to addressing the lymph nodes at initial management: universal pelvic and para-aortic lymphadenectomy, selective lymphadenectomy or sentinel node biopsy. However, when dealing with women who have had incomplete surgery elsewhere, the dilemma is whether to complete the surgery or to give adjuvant treatment. There is a need for reviewing surgical notes, pathology reports and slides for risk stratification of these understaged women who have had inadequate surgery and individualize further management. The SGO and NCCN guidelines recommend comprehensive surgical staging in women who have been diagnosed to have endometrial cancer incidentally after hysterectomy but are at risk of extrauterine disease.

Using models for risk of lymph nodal involvement may help, but in India, operative and histological details are often not available. Tumour size cannot be ascertained from tissue block, and poor preservation techniques may make assessment of depth of myometrial invasion difficult. Completion staging will help individualize treatment for these inadequately staged women to avoid undertreating or overtreating them.

This study was undertaken to retrospectively review women who were referred to our hospital with postoperative diagnosis of endometrial cancer and to identify benefits and risks of completion surgery in these women.

Patients and Methods

Between January 2011 and December 2014, 28 women were identified from the endometrial cancer database, who were referred to the gynaecologic oncology division of a tertiary hospital in Tamil Nadu, India, with a postoperative diagnosis of endometrial cancer. Twenty-seven had undergone hysterectomy, and one had had a myomectomy. The electronic records of these women were retrospectively reviewed. Following histopathological review, five patients were advised follow-up in view of low-risk pathological features. Among the 23 women who were thought to benefit from surgical

exploration, 20 women underwent completion surgery and three women refused surgery and did not return to the hospital for further follow-up. During this time period of 48 months, a total number of 264 women with endometrial cancer were seen in this hospital of whom, 257 underwent surgery. Twenty women with high-risk features (large tumour size, grade 3, non-endometrioid histology, deep myometrial invasion, lymphovascular invasion, cervical involvement and extrauterine disease) on review of the operative notes, slides, blocks or hysterectomy specimen or with inadequate histopathological details for risk stratification, consented to undergo completion staging for endometrial cancer. We have been following a protocol of omitting lymphadenectomy in low-risk patients and performing pelvic lymphadenectomy in intermediate risk patients and pelvic and para-aortic lymphadenectomy in high-risk patients with carcinoma endometrium.

Results

The mean age was 53 years (range 31–67) (Table 1), and 8 (40%) women were premenopausal. The median BMI and median parity were 29 and 2, respectively. Three women had family history of ovary/colon cancer.

All the premenopausal group of women had undergone primary surgery for abnormal uterine bleeding (AUB) (Table 2). The most common indication in postmenopausal women was postmenopausal bleeding (10/12: 83%). Only eight patients had a pre-hysterectomy endometrial sampling/biopsy (40%). Four women with postmenopausal bleeding did not have a pre-surgery endometrial biopsy. Only one patient had a pre-hysterectomy diagnosis of endometrial cancer which showed high-grade histology following hysterectomy. The primary surgery done is as described in (Table 2). Adnexae were not removed in 11 (55%) patients, and there was documentation of bisection or coring of the uterus in 3 (15%) patients.

On histopathological review of the primary specimen, 14 women had low-grade histology (grade 1 and 2 endometrioid adenocarcinoma); however, ten of these had risk factors for nodal involvement such as large tumour size, deep myometrial

Table 1 Demographics

Demographic characteristics	Results (n = 20)
Age (mean and range)	53 (31–67)
BMI (median and range)	29 (16–40)
Parity (median and range)	2 (0–4)
Associated risk factors	
Metabolic syndrome	8 (40%)
Family history of ovary/colon cancer	3 (15%)

BMI body mass index

Table 2 Details of primary surgery

Details of primary surgery	Results (<i>n</i> = 20)
Indication	
AUB	8 (40%)
Postmenopausal bleeding	10 (50%)
Postmenopausal discharge	1 (5%)
Uterine prolapse	1 (5%)
Presurgery endometrial biopsy	8 (40%)
Endometrial hyperplasia	5
Benign endometrial polyp	2
Endometrial cancer	1
Primary surgery performed	
Laparoscopic hysterectomy	1
Abdominal hysterectomy	3
Abdominal hysterectomy with adnexectomy	8
Subtotal hysterectomy	1
Myomectomy	1
Vaginal hysterectomy	6
Histology	
Grade 1 or 2 endometrioid	14 (70%)
Grade 3 or nonendometrioid	6 (30%)
Mean duration from primary surgery to completion surgery	57 days (30–91)

AUB abnormal uterine bleeding

invasion or lymphovascular involvement. In the other four patients, risk factors for lymph node involvement could not be assessed as information was not available. Six women had high-grade histology (30%).

Details of completion surgery are in Table 3. Two patients underwent laparoscopic completion surgery. Based on risk assessment of extrauterine disease following histopathological review of the hysterectomy specimen, 18 patients underwent lymphadenectomy and nine patients each underwent pelvic lymphadenectomy alone and pelvic combined with paraaortic lymphadenectomy. Five patients were upstaged following completion surgery and received adjuvant chemotherapy besides radiation. Five required vaginal brachytherapy alone but nine patients required no adjuvant treatment, following completion staging. There were two intraoperative complications: one bladder injury and one iliac vein injury that were dealt with appropriately during the operation.

Discussion

Incidental diagnosis of endometrial cancer following hysterectomy poses a clinical dilemma to the gynaecologic oncologist. Supracervical hysterectomies or preservation of adnexa in these women are major issues as endometrial cancer can involve the cervix or has metastatic or synchronous

involvement of the ovaries. Though lymphadenectomy in endometrial cancer has been a contentious issue, lymph nodal involvement is the most important prognostic factor in cases of endometrial cancer at high risk of lymph nodal involvement. When women with endometrial cancer are evaluated and treated by a specialist, selective or super-selective (sentinel lymph node biopsy) lymphadenectomy can be planned. Patients with advanced stage endometrial cancer benefit from adjuvant radiation therapy as well as chemotherapy. However, incompletely staged women cannot have sentinel node biopsy and may need to have their ovaries or cervix removed in addition to their lymph nodes. Some can be treated with adjuvant therapy but face risk of overtreatment or undertreatment. Completion staging tries to avoid pelvic radiation but exposes these women to risks of surgical morbidity. It thus allows tailoring of optimal adjuvant therapy including chemotherapy. Treatment decisions have to be made after scrutiny of surgical notes, pathological review, detailed counselling and informed consent.

Mahnert et al. reported an incidence of unexpected endometrial cancer of 1.02% following hysterectomies for benign

Table 3 Details of completion surgery

Details of completion surgery	Results (<i>n</i> = 20)
Laparoscopic adnexectomy and pelvic lymphadenectomy	2
Laparotomy and adnexectomy	1
Excision of vaginal tumour, bowel and peritoneal nodule	1
Abdominal hysterectomy, bilateral adnexectomy and pelvic lymphadenectomy (previous myomectomy)	1
Laparotomy, cervical stump excision, adnexectomy	1
pelvic lymphadenectomy	
Laparotomy and pelvic lymphadenectomy	5
Pelvic and paraaortic lymphadenectomy	9
Complications	
Iliac vein injury	1
Bladder injury	1
Final stage	
Stage I a	11
Stage I b	3
Stage II	1
Stage III c1	1
Stage III c2	1
Stage IV	3
Need for adjuvant treatment	11 (55%)
Vaginal brachytherapy alone	5
Vaginal brachytherapy and external pelvic radiation	1
Chemotherapy and radiation	5

Eighteen of the 20 patients followed up after surgery with a median follow-up period of 10 months (range 3–29 months). Two women died of progressive disease, and two presented with disease recurrence, one of whom with stage IV a, who had refused adjuvant treatment

conditions [4]. The incidence varied depending on the preoperative indication: an incidence of 20.88% and 6.88% in cases of endometrial hyperplasia with atypia and endometrial hyperplasia without atypia, respectively. Independent histopathological review of the hysterectomy specimen will help identify women who will benefit from completion staging.

Besides removal of adnexa and cervix in these cases, identification of women who will benefit from lymphadenectomy would be essential. Though two major randomized controlled trials have not shown survival benefit following systematic lymphadenectomy in early endometrial cancer [5, 6], the revised 2009 staging continues to recommend it. CT scan and MRI scans have limited ability in identifying lymph nodal micrometastasis. Imaging following incomplete staging may reveal postoperative artefacts which interfere with interpretation. Completion staging would be the most precise method in identifying lymph nodal metastasis which is the most common site of extrauterine disease in endometrial cancer. Identification of lymph nodal disease, besides providing prognostic information, will help modulate or eliminate adjuvant treatment. Completion staging would also be mandatory in women who have had bisection/coring/morcellation of the uterus.

Completion staging may not be feasible in all women following incomplete surgery, considering their comorbidities and body habitus. These women could be referred for radiation therapy. A second surgery can be difficult due to bowel adhesions and obliteration of surgical planes and is best done within 10 days or after 6 weeks of the initial surgery. Completion staging is associated with risk of surgical morbidity, including intraoperative blood loss secondary to adhesions, wound infection, lymphocyst formation and lymphedema secondary to lymphadenectomy. Hence, it is recommended that these women who had incomplete surgery and who are high risk for lymph nodal involvement be identified from various risk assessment models and be offered completion staging before deciding adjuvant therapy [7].

Though pelvic lymphadenectomy has not shown any survival benefit in early endometrial cancer in the ASTEC and CONSORT trial [5, 6], a comparison of outcomes in 39,396 women from the SEER database, revealed improved survival in women with stage I grade 3 and more advanced endometrial cancer who underwent lymphadenectomy [8]. Todo et al., in a retrospective study, concluded that pelvic and paraaortic lymphadenectomy had a survival benefit in patients with intermediate to high risk of recurrence [9].

Researchers have proposed various models to identify patients at low risk and high risk for lymph nodal metastasis [10–12]. These models have been designed based on surgicopathological characteristics such as histology, grade of tumour, depth of myometrial invasion and presence of macroscopic peritoneal disease which can be obtained from the

available hysterectomy specimen, provided preservation techniques are adequate.

As per the GOG pilot study by Boronow et al. [10], surgicopathological features indicative of low risk for nodal metastasis were as follows: cancer confined to endometrium regardless of grade or grade 1 or 2 histology with superficial one-third myoinvasion or middle-third involvement by grade 1 tumour, in the absence of cervical or adnexal involvement and lymphovascular space involvement. Contrarily, identification of superficial myometrial invasion by grade 3 cancer, intermediate myometrial invasion by grade 2 or 3 cancer, deep myometrial invasion by cancer of any grade, vascular space involvement, and cervical and or adnexal involvement, was suggestive of increased risk of lymph nodal involvement. LVSI has been considered as a high-risk factor which has been validated as an important prognostic risk factor for lymph nodal involvement and relapse, by several other researchers [13, 14].

GOG 33 [11] confirmed the findings of the above study and considered grade 1, endometrial involvement only and no peritoneal disease as surgicopathological characteristics at low risk for nodal involvement. An intermediate risk group was also considered, a grey zone for surgeons, to decide on lymphadenectomy, depending on the presence of one or more risk factors. These factors were inner-mid myometrial invasion, histology grade 2 or 3 with no intraperitoneal disease.

Mariani et al. [12] demonstrated primary tumour diameter, as an independent predictor of lymph nodal involvement. As per this model, grade 1 or 2 endometrioid histology, less than 2 cm in size, myometrial invasion $\leq 50\%$, with no intraoperative evidence of macroscopic disease would not require lymphadenectomy.

In the above low-risk groups, the risk of lymph nodal involvement ranged from 0 to 5%. Evaluation of these three models showed similar negative predictive values (97.1 to 97.4%) and negative likelihood ratios in identifying low-risk groups with a false-negative rate of 2% when the prevalence of lymph nodal metastases was 10% [15]. However, Boronow et al.'s model and Mariani et al.'s model identified the largest and smallest proportion of low-risk patients, respectively, with similar negative predictive values. Any of these models can be used to identify patients who might benefit from completion surgery. However, till date, no data is available on the therapeutic benefit of completion staging, except for the retrospective SEPAL study [9].

In the current study, Mariani et al.'s model was used to identify patients who required completion staging. Consideration was given to presence of LVSI also, in the hysterectomy specimen. Eight had upstaging of histology and grade following hysterectomy when compared to the preoperative endometrial biopsy. Following completion staging, 5/20 (25%) patients were upstaged and required

chemotherapy and radiation; 5/20 (25%) required vaginal brachytherapy alone, but 9 /20 (45%) required no adjuvant treatment.

Conclusion

Patients with postoperative diagnosis of carcinoma endometrium indeed pose a clinical dilemma to the gynecologic oncologist. Adequate preoperative evaluation, good clinical judgement and availability of reliable frozen section facilities can prevent such dilemmas. In patients with postoperative incidental diagnosis of carcinoma endometrium, histopathological review, good clinical and radiological assessment can identify patients who will benefit from completion staging. Based on the surgeon's discretion, usage of various risk models can be used to decide on requirement of pelvic and paraaortic lymphadenectomy during completion staging. Completion staging allows removal of adnexa or cervix if left behind, proper staging of the disease, prognostication and helps tailoring adjuvant treatment. Larger trials are required to assess its therapeutic benefit.

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Compliance with Ethical Standards

Ethical Approval For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Conflict of Interest The authors declare that they have no conflict of interest.

The results of this retrospective case series have not been published before and are not under consideration for publication anywhere else. Its publication has been approved by all the authors.

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