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The utility of sentinel lymph node mapping in the management of endometrial atypical hyperplasia

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HIGHLIGHTS

- Risk of endometrial cancer is higher with preop diagnosis of "AH-cannot rule out cancer".
- Lymph node metastasis, deep myometrial invasion and grade 2–3 disease are also higher.
- SLN mapping may a be good compromise for lymph node staging in these cases.

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ABSTRACT

Objectives. To determine the risk of endometrial cancer (EC) and lymph node involvement in patients with a preoperative diagnosis of "AH-only" versus "AH - cannot rule out carcinoma" and to study the value of SLN mapping.

Methods. We reviewed all patients with a preoperative diagnosis of atypical hyperplasia, who underwent primary surgery with SLN mapping followed by pelvic lymphadenectomy. Sensitivity and negative predictive value (NPV) of SLN and rates of endometrial cancer were calculated.

Results. Overall, 64/120 (53.3%) patients were found to have EC on final pathology: 58 stage IA, 3 IB, and 3 IIIC1. In patients with preoperative diagnosis of "AH", 44.3% (31/70) had EC on final pathology compared to 66% (33/50) in patients with "AH - cannot rule out cancer" ($p = 0.02$). Overall, 3.3% of the patients (4/120) had lymph node involvement. In patients with EC with a pre-operative diagnosis of "AH", none had lymph node metastasis (0/31), compared to 12.1% (4/33) in patients with "AH - cannot rule out cancer" ($p = 0.06$). Elevated preoperative CA125 levels (>25 U/mL) were statistically associated with the risk of lymph node metastasis on final pathology ($p = 0.024$). Unilateral and bilateral SLN detection occurred in 93.7% and 78.1% respectively. In patients with EC and bilateral SLN mapping, sensitivity and NPV were respectively 66.6% and 97.9%. There was one false negative (ITCs in non-SLN).

Conclusion. Our data indicate that the risk of lymph node involvement in patients with a preoperative diagnosis of "AH-only" is null. Lymph node assessment could be omitted in those patients. Conversely this risk is significant in patients with "AH - cannot rule out cancer". SLN mapping could be a valuable staging procedure in these patients.

1. Introduction

Up to 50% of patients with atypical hyperplasia (AH) diagnosed on preoperative endometrial biopsy are found to have endometrial carcinoma on final pathology [1], and thus, the American College of Obstetricians and Gynecologists (ACOG) recommends that patients with a preoperative diagnosis of AH be referred to a gynecologic oncologist [2].

However, even in the "gynecologic-oncology community", the optimal surgical management of these patients is unclear as to the needs for lymph node staging at the time of surgery. Some argue that it is reasonable to perform a lymph node dissection in all patients with AH undergoing definitive surgery as the lymph node staging may provide treatment-influencing information in up to 10% of AH patients

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undergoing lymph node dissection [3]. Costales et al. support routine intra-operative frozen section evaluation of the uterine specimen in women with a preoperative diagnosis of AH to tailor the needs for lymph node staging [4]. Finally, others are not in favor of lymph node dissection in patients with pre-operative diagnosis of AH, as even if an endometrial carcinoma is found on final pathology, two large randomized trials suggested that pelvic lymphadenectomy had no clear impact on survival outcomes but increased morbidity [5,6].

A major concern with regards to the management of AH, is that the distinction between AH and well-differentiated endometrioid carcinoma on preoperative endometrial biopsy can be very challenging for pathologists [7]. A Gynecologic Oncology Group (GOG) study reported on the poor reproducibility in the diagnosis of atypical endometrial hyperplasia among contributing institutions and a panel of experts, with both underestimations and overestimations leading to misclassification of hyperplasia and carcinoma [8].

Hence, Longacre et al. introduced the concept of a "borderline lesion" termed "atypical hyperplasia, **cannot exclude** well-differentiated carcinoma" as an intermediate category between AH and well-differentiated carcinoma [9]. The authors divided the spectrum of architectural complexity on endometrial biopsy specimen into 3 groups based on the associated risk of myoinvasion on final pathology: complex atypical hyperplasia, complex atypical hyperplasia, cannot exclude well-differentiated adenocarcinoma (borderline) and well differentiated adenocarcinoma [10]. The majority of studies found a strong correlation between myometrial invasion and lymph node involvement in endometrial cancer on final pathology [11]. However, none of these studies looked at the risk of lymph node involvement based on the results of **preoperative** endometrial biopsy, information which could be helpful to plan the management of patients with preoperative diagnosis of AH-only.

Thus, the aim of the present study was to determine if there is a difference in the risk of finding endometrial cancer on final pathology as well as the risk of lymphatic spread between patients with a preoperative diagnosis of "AH-only" compared to patients with a preoperative diagnosis of "atypical hyperplasia cannot exclude well-differentiated carcinoma" (AH-C"). We also aimed to evaluate the accuracy (detection rate, sensitivity, negative predictive value) of the sentinel lymph node (SLN) mapping as a staging procedure in these patients.

2. Methods

2.1. Patients

From November 2010 to December 2016, all patients referred to L'Hôtel-Dieu de Québec Hospital with a preoperative diagnosis of atypical hyperplasia (AH) were prospectively included in the study. The data was analyzed retrospectively. Inclusion criteria were as follows: patients with "AH-only" or "AH-C" diagnosed by office endometrial biopsy or operative curettage, older than 18 years of age and with no desire of fertility preservation. Patients with a preoperative diagnosis of endometrial carcinoma, simple hyperplasia and hyperplasia without atypia, were excluded. Information regarding the diagnostic method used to investigate the uterine bleeding (i.e. endometrial biopsy, dilatation and curetage or hysteroscopic curetage) was not available. Patients were counseled about their risk of concurrent endometrial cancer and offered, in most cases, to undergo surgical staging, including hysterectomy, bilateral salpingo-oophorectomy (BSO), sentinel lymph node mapping and pelvic lymph node dissection. All enrolled patients gave written informed consent. The study was approved by our institutional ethics committee.

2.2. Histopathology

The diagnosis of atypical hyperplasia was based on standard WHO 2014 criteria [12]. The term 'cannot exclude endometrioid carcinoma' was used when there was uncertainty about the presence of endometrioid carcinoma in addition to atypical hyperplasia. Cases of uncertainty fell into two categories: i) when there was concern over the degree of glandular complexity but the volume of tissue present in the specimen was too low to allow confident identification of endometrioid carcinoma; and ii) when areas of unequivocal atypical hyperplasia were accompanied by foci of increased gland complexity that raised suspicion, but were not fully diagnostic, of endometrioid carcinoma. Cases in which there were high grade cytologic features, and hence may represent serous endometrial intraepithelial carcinoma, were not included. Pathology review of the diagnostic endometrial biopsy/curettage was not performed. Reproducibility of the criteria used to establish the diagnosis among our pathologists was not specifically assessed.

SLNs and non-SLNs were analyzed by pathologists experienced in SLN ultrastaging and who had previously validated the quality control of the technique in previous studies of SLN biopsy in cervical cancer and endometrial cancer [13]. "Ultra-staging" of the SLNs was performed on permanent sections. Intra-operative frozen section of the uterus was not performed.

2.3. Statistical analysis

The first objective of our study was to determine the risk of endometrial carcinoma as well as the risk of lymph node spread in women with a preoperative diagnosis of AH-only and "AH-C". The second objective was to evaluate the performance of SLN mapping as a staging procedure in these patients, i.e. sensitivity and negative predictive value. If an endometrial carcinoma was diagnosed on final pathology, the primary tumor was analyzed with respect to histological type, histological grade, depth of myometrial invasion, lympho-vascular space invasion (LVSI) and cervical stromal invasion. Descriptive statistics were used to summarize the demographic and clinic-pathological data. Statistical analysis included Chi-square, Fisher's exact test, was performed using the STATA version 13.1 software (Stata Corp, College Station, TX). Significance was determined at $p < 0.05$.

3. Results

A total of 120 patients were included in the study: 70 patients had a pre-operative diagnosis of "AH-only" and 50 had a pre-operative diagnosis of "AH-C". The median age of the entire cohort was 57 years (range, 40–82). The majority of the patients (60%) were postmenopausal. The mean BMI was 29 (range, 17–47). All patients underwent a total hysterectomy, bilateral salpingo-oophorectomy, SLN mapping and bilateral pelvic lymph node dissection. The surgery was performed by laparotomy in 39 patients (32.5%), laparoscopy in 51 (42.5%) and by robotic-assisted surgery in 30 (25%).

Overall, 64 patients (53.3%) were found to have an endometrial carcinoma (EC) on final pathology. In the group of patients with a preoperative diagnosis of "AH-only", 44.3% (31/70) [(CI 95% (32,4–56,1)] had a diagnosis of EC on final pathology, compared to 66% (33/50) [(CI 95% (52,5–79,3)] in patients with preoperative diagnosis of "AH-C" ($p = 0.02$) (Fig. 1). FIGO stage distribution for the 64 patients with EC was as follows: 58 (90.6%) were stage IA, 3 (4.7%) were stage IB, 3 (4.7%) were stage IIIC1 (one patient had ITCs but is not considered a stage 3C1).

Histopathological characteristics of EC found on final pathology in the 2 groups are summarized in Table 1. All the 64 patients with EC had endometrioid histology. None of the patient with pre-operative diagnosis of "AH-only" had deep myometrial invasion when an EC was found on final pathology (0/31) compared to 4/33 patients (12.1%) with a pre-operative diagnosis of "AH-C" ($p = 0.06$). There was also a statistically significant difference between the histologic grades on final pathology in patients with a preoperative diagnosis of "AH-only" versus "AH-C". Indeed, only 1/31 patient (3.2%) in the former group had a grade 2–3 EC on final pathology compared to 9/33 (27.2%) in

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