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Impact of sentinel lymph node mapping on recurrence patterns in endometrial cancer

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HIGHLIGHTS

- Sentinel lymph node (SLN) mapping improves the recurrence free interval at the pelvic sidewall.
- Post lymphadenectomy 71,4% of recurrences were along the pelvic sidewall versus 30.8% post SLN.
- Ultrastaging found metastases in 2 out of 3 cases with unexplained pelvic sidewall recurrences.

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ABSTRACT

Background. Sentinel lymph node (SLN) mapping has emerged as a promising solution to the ongoing debate regarding lymphadenectomy in the initial surgical management of endometrial cancer. Currently, little is known about its possible impact on location of disease recurrence compared to systematic lymphadenectomy.

Methods. In this retrospective study, 472 consecutive patients with endometrial cancer who underwent either SLN mapping (SLN cohort, $n = 275$) or systematic lymphadenectomy (LND cohort, $n = 197$) from sequential, non-overlapping historical time points were compared. Clinical characteristics were extracted from a prospectively gathered electronic database. Both overall and pelvic sidewall recurrence free survival (RFS) were evaluated at 48-month post-operative follow-up.

Results. No significant difference in overall RFS could be identified between the cohorts at 48 months (HR 0.74, 95% CI 0.43–1.28, $p = 0.29$). However, the SLN cohort had improved pelvic sidewall RFS compared to the LND cohort (HR 0.32, 95% CI 0.14–0.74, $p = 0.007$). The pelvic sidewall recurrences accounted for 30% of recurrences in the SLN cohort (8 out of 26 recurrences) compared to 71.4% in the LND cohort (20 out of 28 recurrences).

Conclusions. SLN mapping may enable more efficient detection of the LNs at greatest risk of metastasis and help to guide adjuvant therapy, which in turn seems to decrease the risk of pelvic sidewall recurrences.

1. Introduction

In recent years, the role of systematic lymphadenectomy for clinical early stage endometrial cancer has been debated [1], with recommendations ranging from no lymph node dissection to full lymphadenectomy. Although the latter was previously seen as the gold standard, two large randomized-control trials did not show an improvement in overall survival in the routine lymphadenectomy (LND) group compared to the control group [2,3]. Despite the lack of apparent survival benefit seen in these two trials, gynecologic oncologists performing lymphadenectomies use lymph node (LN) status to guide adjuvant therapy, whereas others who omit LND utilize proxies such as patient age and uterine risk factors to tailor post-operative adjuvant therapy [4,5]. Both approaches can be associated with over- or under-treatment of disease [1].

More recently, sentinel lymph node (SLN) mapping has emerged as a possible alternative technique used to determine LN status [6–8]. SLN mapping seeks to identify the presence or absence of LN involvement while avoiding potential surgical complications such as blood vessel and nerve injury, lymphedema, and lymphocyst formation. The role of SLN is already well-established in the management of melanoma [9]

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and breast cancer [10], and appears promising in gynecologic cancers such as vulvar [11] and cervical cancer [12]. A number of techniques have been reported for SLN mapping in endometrial cancer [13–17], but there has been little data regarding the influence of SLN mapping on survival outcomes. In the present study we evaluated the impact of SLN mapping compared to standard lymphadenectomy on recurrence patterns and recurrence free survival (RFS) in patients with endometrial cancer.

2. Methods

2.1. Procedure

In this retrospective, single institution cohort study design, all consecutive patients with clinical stage I endometrial cancer undergoing robotic-assisted (using the da Vinci® surgical system) or traditional laparoscopic surgery from December 2007 to June 2014 were included into the study, and all underwent surgical staging with complete pelvic lymphadenectomy. At our institution all consecutive patients undergoing surgical staging from December 2007 until December 2010 received complete pelvic lymphadenectomy whereas all consecutive patients from December 2010 until June 2014 underwent SLN mapping followed by complete pelvic lymphadenectomy. All patients were grouped into one of two cohorts based on whether SLN dissection was performed. Any patients with metastatic disease prior to surgical staging were excluded from the study. The study was approved by the Jewish General Hospital Institutional Research Board. The robotic surgical procedures were performed by one of three fellowship trained gynecologic oncologists. Prior to the introduction of SLN mapping for endometrial cancer at our institution in 2010, the team had performed close to 400 robotic surgeries and had performed sentinel lymph node sampling for vulvar and cervical cancers since 2003. Feasibility of this approach in patients with endometrial cancer was prospectively analyzed and previously reported by our group [14,15].

2.2. SLN cohort

In the cohort undergoing SLN mapping (SLN cohort), all patients received an intra-operative injection of blue dye (methylene or patent blue), indocyanine green (ICG), and/or technetium-99 m micro-sulfur-colloid (99mTc-SC) in the 3 and 9 o'clock position of the cervix, as previously described [7,14,15]. Detection of SLNs was accomplished via direct visualization of either blue colored lymphatics/nodes, immunofluorescent green lymphatics/nodes (using the infrared imaging mode on the da Vinci ® surgical system only on robotic surgical cases) and/or detection of radioactive nodes by a handheld gamma probe (Daniel Probe, RMD Instruments Corp, Watertown, MA, USA). Detected SLNs were removed and sent for intra-operative frozen section. Subsequently, patients underwent bilateral complete pelvic lymphadenectomy (with or without para-aortic lymphadenectomy), total hysterectomy, and bilateral salpingo-oophorectomy. Defined according to the Gynecologic Oncology Group Surgical Procedures Manual, a complete pelvic lymphadenectomy constituted bilateral removal of nodal tissue from the distal one-half of each common iliac artery, anterior and medial aspect of the external iliac artery and vein, and the obturator fat pad anterior to the obturator nerve [18]. A para-aortic lymphadenectomy was performed if the patient had one or more of the following characteristics: pre-operative type II endometrial cancers (clear cell, serous, or carcinosarcoma), grade 3 endometrioid carcinomas, positive SLN on intra-operative frozen section, or grossly enlarged para-aortic LNs suspicious for malignancy.

2.3. LND cohort

In the cohort not undergoing SLN mapping (LND cohort), patients underwent bilateral pelvic lymphadenectomy (with or without para-aortic lymphadenectomy), total hysterectomy, and bilateral salpingo-oophorectomy. A para-aortic lymphadenectomy was performed for similar criteria as stated above for the SLN cohort.

2.4. Histopathology

Intra-operative frozen section analysis of the SLNs was performed in all cases in the SLN cohort and suspiciously enlarged LNs were sent for intra-operative frozen section analysis in both cohorts. In the SLN cohort, the SLNs were first bisected and stained with hematoxylin & eosin (H&E) and some unselected cases underwent pathologic ultrastaging, with serial sectioning of the entire SLN at 200 to 300 μm, with three consecutive H&E levels with one slide for immunostaining per level. Immunostaining for cytokeratin (clone AE1/AE3, Millipore Inc., dilution 1:150) was performed in SLNs after H&E routine histological examination. In both cohorts, all non-SLNs were processed using entire node examination with H&E staining.

2.5. Adjuvant therapy

Both cohorts followed the institutional protocol for adjuvant therapy shown in fig. 1 and were in accordance with NCCN clinical practice guidelines [19] and the GOG 99 study [20].

2.6. Follow-up

All follow-up information was obtained from electronic medical charts, and included routine follow up visits at 3 weeks post-surgery, followed by every 4 months for the first two years, every 6 months till year 5 post-surgery, then annually.

2.7. Statistics

SLN detection rates were calculated. For continuous, parametric variables, the Student's *t*-test was used. For categorical variables, the Chi-square test or Fisher's exact test was used as appropriate.

Survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test. Recurrence-free survival (RFS) was defined as time from surgery to the time of recurrence. Patients who did not have a recurrence at their 48-month visit were censored at the time of that visit. Patients who were lost to follow-up or died from any cause were censored at the time of their last visit or death, respectively.

We calculated and compared RFS between the SLN and LND cohorts. Cox proportional hazards model was performed to calculate hazard ratios with 95% confidence intervals. Multiple analyses were performed including an unadjusted analysis followed by a multivariate-adjusted cox-proportional regression utilizing the following variables associated with recurrence: final histology (endometrioid vs non-endometrioid), final grade (grade I/II vs grade III), myometrial invasion (<50% vs >50%), lymphovascular space invasion (LVSI) (absence vs presence), or LN metastases (absence vs presence). Furthermore, to reduce the error of finding a false positive significant result a cox proportional regression was performed utilizing propensity scores.

To analyze pelvic sidewall recurrence-free survival, we performed a similar analysis as above but defined time to recurrence beginning from surgery until pelvic sidewall recurrence. Patients who developed a first non-pelvic sidewall recurrence were censored at the time of their recurrence for this sub-analysis. Pelvic sidewall recurrence was defined as a recurrence in the pelvic or para-aortic lymph node area with at least one of the following: radiologic evidence of enlarging nodes/nodal areas (at least 10 mm) on CT scan, increasing metabolic activity on PET-CT scan, or a positive biopsy for endometrial cancer.

Sensitivity analyses were performed for the univariate, multivariate-adjusted, and propensity score-adjusted models for overall and pelvic sidewall RFS. First, stage 3C patients were excluded in order to examine

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