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Can sentinel lymph node biopsy replace pelvic lymphadenectomy for early cervical cancer?

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HIGHLIGHTS

- Large cohort study of sentinel node biopsy alone for stage I cervical cancer
- No difference in RFS between sentinel node biopsy and pelvic lymphadenectomy
- Lower morbidity in the sentinel lymph node biopsy group

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ABSTRACT

Objective. Evaluate recurrence-free survival (RFS) and short-term morbidity in patients with early cervical cancer who undergo bilateral pelvic lymphadenectomy (BPLND) versus bilateral sentinel lymph node biopsy only (BSLNB) at primary surgery.

Methods. All patients with pathologically confirmed node negative stage IA/IB cervical cancer managed with BPLND or BSLNB were identified in the University of Toronto's prospective cervical cancer database from May 1984–June 2015. Groups were compared with Wilcoxon rank-sum, Chi-square, and Fisher's exact tests. Predictors of RFS were identified with Cox proportional hazard models. Kaplan-Meier survival curves were compared. Statistical significance was $p < 0.05$.

Results. 1188 node negative patients were identified, BPLND-1078; BSLNB-110. There was no difference between BPLND and BSLNB in 2 and 5 year RFS (95% vs 97% and 92% vs 93% respectively), tumor size, histology, invasion depth, intra-operative complications or short-term morbidity. BPLND was associated with increased surgical time (2.8 vs 2.0 h, $p < 0.001$), blood loss (500 mL vs 100 mL, $p < 0.001$), transfusion (23% vs 0%, $p < 0.001$) and post-operative infection (11% vs 0%, $p = 0.001$). Age, surgery date, stage, LVSI, and radicality of surgery differed between groups. Controlling for age, stage, LVSI, invasion depth and histology, there was no significant difference in RFS between groups. Only invasion depth, LVSI and histology were predictors of RFS.

Conclusion. A negative BSLNB is not associated with a difference in RFS compared to a negative BPLND. Short-term morbidity may be reduced, however due to the long study period, changes in demographics and surgery may contribute to differences noted.

1. Background

Lymph node status is one of the most important prognostic indicators in early cervical cancer [1,2]. Traditionally, lymph node assessment is conducted via bilateral pelvic lymph node dissection (BPLND). In attempt to reduce morbidity, many have investigated the accuracy of bilateral sentinel lymph node biopsy (BSLNB) which is associated with a decreased risk of surgical complications and lower leg lymphedema than BPLND [3,4]. A meta-analysis in 2015 of 67 studies comparing BSLNB with blue dye, radiotracer, or both to BPLND demonstrated a pooled sensitivity of sentinel lymph node mapping of 94.7% for cervical tumors <2 cm with a side-specific sensitivity of 96.9%. The pooled detection rate was 93.4%, but higher using the combined radiotracer and blue dye technique [5]. Another meta-analysis in 2016 found that the detection and false negative rates with indocyanine green (ICG) were equivalent to the combination of blue dye and radiotracer [6].

Despite ample evidence for the accuracy of the sentinel lymph node procedure in early cervical cancer, there is a paucity of data on the long-

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term outcomes for patients who undergo sentinel lymph node biopsy (alone) without pelvic lymphadenectomy. This is mainly due to the concerns of false negatives. A study of 86 patients by Devaja et al. on sentinel lymph node detection in cervical carcinoma included 18 patients who underwent BSLNB alone. After a median follow-up time of 28 months, there were 4 recurrences, all in patients who underwent both SLNB and PLND [7]. In another cohort of 23 node-negative patients who underwent BSLNB alone, after a median follow-up time of 49 months, there were no pelvic recurrences, but 1 lung and 2 vaginal metastases [3].

At the Sunnybrook Health Sciences Center, bilateral sentinel lymph node biopsy has been the standard mode of lymph node assessment for small volume tumors since 2008 after evaluations at our center showed no false negatives using BSLNB compared to BPLND [8], and later demonstrated a 2.4-fold higher detection rate of metastatic lymph nodes using BSLNB compared to BPLND in controls matched on tumor size, histology, depth of invasion and presence of LVSI [9].

The objective of this study was to compare the recurrence-free survival and morbidity among node-negative patients with early cervical cancer who underwent BSLNB alone vs. those who underwent BPLND.

2. Methods

2.1. Study design and patients

All patient data was prospectively recorded in the cervical cancer database at the University of Toronto which has ongoing approval of the Institutional Review Board at Sunnybrook Health Sciences Center. This cohort study was from May 1984 to June 2015. Patients were included if they had International Federation of Gynecology and Obstetrics (FIGO) stage IA2 to IB2 cervical cancer and underwent primary surgery including either BSLNB alone or BPLND. For inclusion, all lymph nodes had to be negative on final pathology and the BSLNB group had to have bilateral sentinel lymph nodes identified. In general, at our center, patients were selected for BSLNB if they had stage IA1 (with LVSI), IA2, and IB1. Patents with tumors >4 cm (IB2) were included only if the tumor was exophytic with minimal stromal involvement. Patients were excluded if the surgical procedure was abandoned for any reason, neoadjuvant chemotherapy was administered, intracavitary radiation therapy was administered as primary definitive therapy, or the primary surgical procedure was not recorded in the database. Patients who had positive sentinel lymph nodes for metastatic cancer underwent BPLND and were not included in this study. The primary outcome was recurrence-free survival. Secondary outcomes included intra-operative complications, blood loss, blood transfusion, length of stay, time to normal residual urine, short-term morbidity and post-operative infection.

2.2. Lymph node assessment

The SLN procedure used has been previously published [8,9]. The initial sentinel LN technique included an intra/submucosal cervical injection at 3 and 9 o'clock of technetium sulphur colloid 4 h preoperatively. If bilateral SLNs were identified on a pre-operative scintogram 20 min later, no blue dye was used. If bilateral sentinel LNs were not detected, then 1 mL of patent blue was injected in the same locations of the cervix (on the side(s) that was not identified) at the beginning of the surgery. As of January 2015 indocyanine green (ICG) was used instead of technetium and blue dye. ICG powder was diluted with sterile water to a concentration of 2.5 mg/mL. One mL of this ICG solution was injected as above at the beginning of the surgery.

Intraoperatively, SLN detection was performed with a laparoscopic gamma probe (Navigator GPS, Tyco Healthcare). The pelvic sidewalls, presacral and paraaortic areas were scanned. Lymph nodes were considered sentinel if the radioactive count was 5 times the background or by visualization of blue lymph channels and blue nodes. When ICG was used, a near infrared/ICG endoscopic camera [Pinpoint, Novadaq] was used to identify sentinel nodes. Sentinel nodes were removed and sent to pathology for intraoperative review.

Patients undergoing bilateral pelvic lymphadenectomy had removal of all fatty lymph node bearing tissue within the borders of the lower portion of the common iliac artery, deep circumflex iliac vein, psoas muscle, ureter and obturator nerve. These nodes were sent for non-sentinel node processing without intra-operative pathology assessment. Sentinel node pathological ultrastaging and non-sentinel lymph node processing was as previously described [9].

2.3. Statistical analysis

Descriptive statistics were calculated for all variables of interest. Continuous measures were summarized using means and standard deviations and were compared using the Wilcoxon rank-sum test. Categorical variables were summarized as proportions and compared using Chi-square and Fisher's exact tests. A crude cox proportional hazards model was applied to quantify the association between mode of lymph node assessment and recurrence-free survival as well as the association between specific risk factors and RFS. A multivariable cox proportional hazards model was used to assess the association between mode of lymph node assessment and recurrence-free survival after adjusting for confounders. Kaplan-Meier survival analysis was used to create recurrence-free survival curves, which were compared using the log-rank test. Statistical significance was defined as $p < 0.05$. All analyses were conducted with STATA version 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

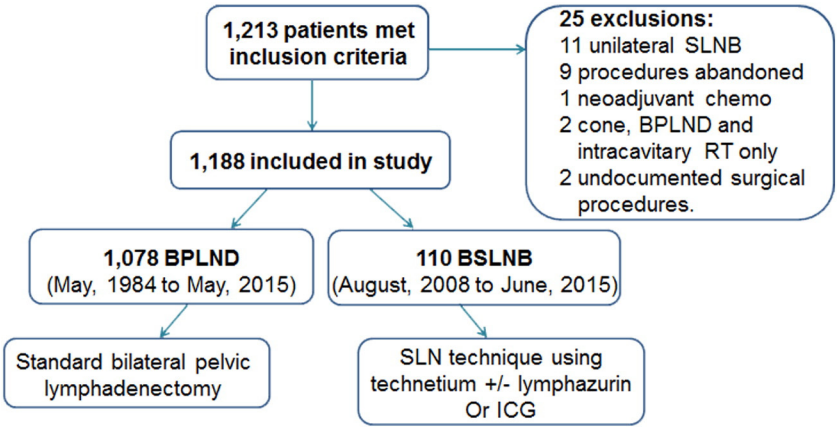

Fig. 1. Study design, inclusions and exclusions. SLNB, sentinel lymph node biopsy; BSLNB, bilateral sentinel lymph node biopsy; BPLND, bilateral pelvic lymph node dissection; chemo, chemotherapy; ICG, indocyanine green; RT, radiation therapy; cone, cervical conisation.

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