

Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial

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ABSTRACT

Background: Accurate identification of sentinel lymph nodes in patients with cancer improves detection of metastatic disease and decreases surgical morbidity. We sought to establish whether indocyanine green fluorescent dye is non-inferior to isosulfan blue dye in detecting sentinel lymph nodes in women with cervical and uterine cancers.

Methods: In this non-inferiority, within-patient comparison study, patients aged 18 years or older with clinical stage I endometrial or cervical cancer undergoing curative surgery were randomly assigned 1:1 to lymphatic mapping with isosulfan blue dye (visualised by white light) followed by indocyanine green (visualised by near-infrared imaging), or indocyanine green followed by isosulfan blue dye. Laparoscopic surgery with the PINPOINT near-infrared fluorescence imaging system (Stryker, Kalamazoo, MI, USA) was used in all cases. The primary outcome was defined as the number of lymph nodes identified by indocyanine green and isosulfan blue dye, respectively (and confirmed as lymphoid tissue by histology), divided by the number of lymph nodes identified intraoperatively and excised. The trial was registered with ClinicalTrials.gov, number NCT02209532, and is completed and closed.

Findings: Between Dec 21, 2015, and June 19, 2017, 180 patients were enrolled and randomly assigned to the two groups (90 to each group); 176 patients received the intervention and were evaluable (modified intention-to-treat population). 13 patients with major protocol violations were subsequently excluded from the per-protocol population. 517 sentinel nodes were identified in the per-protocol population (n=163), of which 478 (92%) were confirmed to be lymph nodes on pathological processing: 219 (92%) of 238 nodes that were both blue and green, all seven nodes that were blue only, and 252 (95%) of 265 nodes that were green only (p=0.33). Seven sentinel lymph nodes were neither blue nor green but were removed for appearing suspicious or enlarged on visual examination. In total, 471 (97%) of 485 lymph nodes were identified with the green dye and 226 (47%) with the blue dye (difference 50%, 95% CI 39–62; p<0.0001). In the modified intention-to-treat population (n=176), 545 nodes were identified, of which 513 (94%) were confirmed to be lymph nodes on pathological processing: 229 (92%) of 248 nodes that were both blue and green, all nine nodes that were blue only, and 266 (95%) of 279 nodes that were green only (p=0.30). Nine sentinel lymph nodes were neither blue nor green but were removed for appearing suspicious or enlarged on visual examination. 495 (96%) of 513 nodes were identified with the green dye and 238 (46%) with the blue dye (50%, 39–61; p<0.0001).

Interpretation: Indocyanine green dye with near-infrared fluorescence imaging identified more sentinel nodes than isosulfan blue dye in women with cervical and uterine cancers, with no difference in the pathological confirmation of nodal tissue between the two mapping substances.

KEY POINTS:

1. FILM was an international, multicenter, RCT designed to assess the safety and efficacy of ICG and PINPOINT in identification of lymph nodes (LN) in women with cervical and uterine malignancies undergoing lymphatic mapping following interstitial cervical injection of ICG.
2. 180 participants were prospectively enrolled and randomized
 - a. The dye was injected in the cervix deeply and superficially at both 0300h and 0900h, followed by the second dye deeply and superficially at both 0300 h and 0900 h, for a total of eight injections.
 - i. Each ICG injection consisted of 1 mL of a 1.25 mg/mL ICG solution for a total dose of 5 mg. (4mL total)”) Each dose was blue dye injection consisted of 1 ml of a 10 mg/mL solution (1% isosulfan blue) for a total dose of 40 mg
 - b. The surgeon identified ICG, LNs and lymphatic vessels with near-infrared imaging using PINPOINT with white light and isosulfan blue.

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3. 163 in the per-protocol population were analyzed and 517 nodes were identified and excised.
4. In total, 471 (97%) of 485 lymph nodes were identified with ICG and 226 (47%) with the blue dye. 7 lymph nodes were neither blue or green but identified as suspicious or visibly enlarged.
5. The mean number of nodes per patient was 3.2 (SD 1.6). In the per-protocol population, at least one node was identified in 159 (98%) of 163 patients with ICG and in 124 (76%) with isosulfan blue dye ($p < 0.0001$). In the per-protocol population, at least one node was identified in 168 (95%) of 176 patients with indocyanine green and 131 (74%) patients with isosulfan blue dye (difference 21%, 95% CI 14–28; $p < 0.0001$).
6. Bilateral sentinel nodes were identified in 141 (80%) of 176 patients in the mITT population. Bilateral sentinel nodes were identified in 54 (31%) of 176 patients with isosulfan blue dye and 138 (78%) of 176 patients with indocyanine green ($p < 0.0001$).
7. There were no allergic reactions or adverse events related to ICG or isosulfan blue.
8. Authors suggest:
 - a. ICG “was superior to isosulfan blue dye in identifying sentinel lymph nodes in women with cervical and uterine cancer because indocyanine green identified sentinel lymph nodes in a much larger proportion of patients than isosulfan blue dye did.”
 - b. ICG “was also significantly superior to isosulfan blue dye in detecting at least one sentinel node and in detecting bilateral sentinel nodes.”
 - c. “The use of indocyanine green and isosulfan blue dye together does not seem to be necessary, because the addition of isosulfan blue dye to indocyanine green identified few sentinel nodes beyond those identified with indocyanine green alone.”
 - d. “All metastatic sentinel nodes were detected with indocyanine green, but more than a third would have been missed had isosulfan blue dye alone been used.”
 - e. “Interstitial injection of indocyanine green seem to be safe, as we recorded no adverse events related to the compound.”

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