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Short Communication
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Pelvic Lymphadenectomy in Advanced Stage Ovarian Cancer: Is the Controversy Over?

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Short Communication

The LION (Lymphadenectomy in Ovarian Neoplasm) trial is a prospective, randomized, adequately powered, international multicenter trial [1]. It demonstrated that a systematic pelvic and para-aortic lymphadenectomy in patients with advanced ovarian cancer with complete intra-abdominal macroscopic resection and normal lymph nodes before and during surgery was not associated with improvement in overall or progression-free survival as compared to no lymphadenectomy. Postoperative complications were significantly more common in lymphadenectomy group. This trial amounts to a level I evidence in favor of no lymphadenectomy in advanced ovarian cancer, an answer to a long standing debate on this issue.

Some prior retrospective studies have reported survival benefits from systematic pelvic and para-aortic lymphadenectomy in patients with macroscopically completely resected advanced ovarian cancer [2-6]. As a consequence, this procedure has been performed in this group of patients over decades. However, there are significant biases in retrospective analysis. There is an inclination towards performing lymphadenectomy in healthy and fit patients as compared to patients with poor performance status, for whom lymphadenectomy is usually not performed. A major prospective randomized trial was reported by Panici et al. [7], which did not show an overall survival benefit. However, there were many limitations in this trial and the rectification of these formed the basis of planning the LION trial. Even after inclusion in the trial, some had to be eliminated in the final analysis due to reasons like surgical protocol violations, non-randomization of treatment, residual tumor after surgery, early stage, borderline or other cancers etc.

The eligibility criteria for inclusion in the LION trial were: A primary diagnosis of epithelial ovarian cancer which was histologically proven, advanced cancer with stages IIB through IV (FIGO), feasible macroscopically complete resection, age between 18 to 75 years, Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1 and those who have provided an informed consent. FIGO Stage IV patients with metastasis outside the peritoneal cavity were only included in the trial, if it was a completely respectable metastatic lesion. Evaluation of the lymph node status comprised of evaluating the retroperitoneal space from the inguinal ligament to the renal vein by opening it. This improved the chances of finding any bulky lymph node, which formed exclusion criteria.

Three hundred and twenty three (323) patients were recruited in the lymphadenectomy group and 324 patients in the no lymphadenectomy group. The baseline patients' characteristics were similar in both the study arms. The primary outcome measure was overall survival and secondary outcome comprised of progression-free survival. The median overall survival in lymphadenectomy and no lymphadenectomy arm was 65.5 months *vs.* 69.2 months, respectively, with the hazard ratio of 1.06 (95% CI, 0.83 to 1.34; p=0.65). Likewise, the analysis of progression-free survival did not show a significant difference. The median progression-free survival was 25.5 months in both arms, with the hazard ratio of progression in the lymphadenectomy group being 1.11 (95% CI, 0.92 to 1.34; P=0.29). The reason for better outcomes in both the groups as compared to previous reports may be due to the exclusion of patients with macroscopic residual disease after surgery.

Prior studies have demonstrated that patients with clinically negative nodes may often have occult metastases [8]. The histopathological evaluation of lymph nodes revealed microscopic metastases in 55.7% of the patients in the lymphadenectomy group in the LION trial. This finding may not be acceptable to many surgeons, who would argue against leaving this tumor burden inside. The authors of LION trial assumed that this macroscopically complete yet microscopically incomplete resection is the surgery deemed necessary. Lymphadenectomy in this group of patients did not provide any added benefit. The refinement in adjuvant chemotherapy over last decades could

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also potentially account for the futility of extensive nodal resection.

The duration of surgery (p-0.001), blood loss (p-0.001), requirement of blood transfusions (p-0.005), and requirement of postoperative intensive care unit admissions (p-0.01) were significantly more in the lymphadenectomy group. Post-operative complications like incidence of infections (p-0.03), formation of lymphatic cysts (p-0.001), requirement of re-laparotomies (p-0.01) and mortality within 60 days (p-0.049) were also higher in lymphadenectomy arm. The differences in quality of life measures and patient reported outcomes were not reported to be relevant and significant. Post-operative treatment with platinum and taxane with or without bevacizumab was almost similar in both the groups.

Another randomized trial on this issue reported no improvement in overall survival after lymphadenectomy [7]. There were many criticisms to this trial. It analyzed systematic removal of lymph nodes *vs.* removal of enlarged lymph nodes, hence, lymphadenectomy was allowed in both groups; also, it included patients with macroscopic total resection as well as those with residual disease of 1 cm. This drawback was addressed in the LION trial, by excluding patients with bulky nodes and including patients who have had completely resection macroscopically. Another issue of the trial by Pacini et al. [7] was that the centers participating in the trial were not assessed for quality of surgery. A prospective evaluation of all centers for quality of surgical procedure in the LION trial, to remove surgical heterogeneity. This led to improved surgical outcomes in terms of resected lymph nodes as compared to prior clinical trials analyzing this issue.

The morbidity and mortality reported in the lymphadenectomy arm of this trial is higher as compared to previously reported trials in early stage ovarian cancer [9]. The reason might be that lymphadenectomy in advanced disease adds up to an already existing longer and more complex surgery, along with it being performed on a less healthy individual as compared to early stage cancer patient.

The biases in the study are that the recurrence patterns and treatments given were missing. Also, despite quality check by the investigators, biases are bound to occur due to different surgeons performing lymphadenectomy with different level of expertise.

Lymphadenectomy is a procedure with a considerable treatment burden. In India, with massive load of cancer and prolonged surgical wait time, omission of this procedure may have evident benefits, more so, if the procedure in deemed unnecessary. The surgical time, requirement of analgesia, the post-operative hospital and ICU stay, incidence of post-operative infections are more in lymphadenectomy group. This may have huge implications in Indian scenario, where public hospitals are over-burdened with post-operative management. This trial may change the clinical practice of performing lymphadenectomy in advanced ovarian cancer.

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