

Editorial



Comprehensive pelvic and paraaortic lymphadenectomy in patients with apparently early stage uterine serous carcinoma – an anachronism?

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Many patients with endometrial cancer (EC) which is apparently limited to the uterus have extrauterine disease [1]. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) therefore introduced the concept of surgical staging for EC, including hysterectomy, bilateral salpingo-oophorectomy, pelvic washing, and pelvic plus paraaortic lymphadenectomy (LNE) [2]. Systematic retroperitoneal LNE was considered to be an essential staging tool to indicate adjuvant radio- and/or chemotherapy in case of nodal involvement [3,4]. In addition, comprehensive lymphadenectomy was regarded to be therapeutic by removing nodal micrometastases, which were not sterilized by radio- and/or chemotherapy [3,4]. A number of retrospective analyses found a significantly improved overall survival after multisite pelvic lymph node sampling, which even remained after postoperative radiation therapy [5]. A review of the Surveillance, Epidemiology, and End Results (SEER) data of 4,178 women with serous endometrial cancer found that any LNE, as well as more extensive LNE were associated with improved 5-year overall survival (OS), even in patients with negative lymph nodes [6]. Consequently, comprehensive LNE was recommended for all patients with EC, even for those with well-differentiated endometrial cancers [3,4,7]. By the end of the first decade of the new century, 2 European randomized controlled trials were published that found no survival benefit by performing pelvic LNE in patients with early stage endometrial cancer [8,9], but a relevant increase in side effects, including lymphedema and lymphocysts [10].

An analysis of data from 27,000 EC patients (SEER) showed that disease specific 5-year survival of women with endometrioid EC, stage 1 was >98% (G1) or >96% (G2) respectively, no matter whether or not LNE had been performed [11]. In a retrospective analysis, the Mayo-Group observed that tumors with grade 1 or 2 histology ≤ 2 cm in diameter and $\leq 50\%$ myometrial invasion had a lymph node metastasis rate of virtually zero [12]. These new data [8-12] and others led to the stepwise weakening of the recommendation of systematic LNE in patients with endometrioid EC, grade 1 or 2 and $\leq 50\%$ myometrial invasion. It is either not recommended [13] or considered only as an option [14-16].

The analysis of Chan et al suggested that LNE was associated with an improved survival in stage 1 grade 3 and more advanced endometrioid EC [11]. Another land mark study retrospectively compared two cohorts of EC patients treated either with exclusive pelvic LNE

or pelvic plus para-aortic complete systematic lymph node dissection [17]. They found a clear survival benefit of the extended surgical procedure for patients with EC of intermediate or high risk of recurrence [17]. Both, the analysis of Chan et al. [11] as well as the SEPAL-study [17] have been questioned due to high risks of potential bias, e.g. due to their retrospective design and imbalances, e. g. in the adjuvant therapies [17]. Recent retrospective analyses of the data from large population-based registries failed to demonstrate a survival benefit of systematic LNE in early stage EC even in high risk cases [18,19].

With the development of sentinel lymph node (SLN) mapping in EC, it has been proposed that the evaluation of retroperitoneal lymph nodes in EC is merely diagnostic and not therapeutic [20,21], though no data from randomized controlled trials are available to support this conclusion.

In the very interesting paper “Survival implication of lymphadenectomy in patients surgically treated for apparent early-stage uterine serous carcinoma” Casarin and colleagues [22] have compiled the data from 140 consecutive patients with apparent early stage serous EC treated at 6 Italian referral centers. One hundred six patients had at least pelvic LNE and 34 had no lymph node dissection. The patients in the LNE group were significantly younger and had fewer comorbidities. Positive nodes were independently associated with worse disease-free survival (DFS) and disease-specific survival (DSS), while adjuvant chemotherapy significantly improved DFS. However, at Cox regression analysis, lymphadenectomy did not significantly influence DFS ($p=0.09$) and DSS (hazard ratio=0.14; 95% confidence interval=0.02–1.21; $p=0.07$) [22]. Only 25 patients (24%) had complete retroperitoneal staging including the removal of both pelvic and para-aortic lymph nodes, while 76% underwent only systematic pelvic LNE [22]. Though prognostic factors were significantly worse in the non LNE-group and significantly less adjuvant therapy was used in these patients, no significant survival differences were observed between groups [22].

If we have learned anything from the LACC trial in cervical cancer [23] it is that retrospective surgical cohort studies should be validated in randomized controlled trials. At first, we should have reliable data answering the question, whether or not a systematic pelvic and para-aortic LNE performed by dedicated surgeons in respective centers has a survival benefit in EC patients with stage I or II EC and high risk of recurrence. The German Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) has started the Endometrial Cancer Lymphadenectomy Trial (ECLAT) (ClinicalTrials.gov Identifier: [NCT03438474](https://clinicaltrials.gov/ct2/show/study/NCT03438474)) in 2018 randomizing 640 patients to obtain a systematic pelvic and para-aortic LNE up to the renal veins or no LNE [24]. As adjuvant therapy for all patients (LNE or no LNE) chemotherapy with carboplatin and paclitaxel plus vaginal brachytherapy is recommended. Eligible patients have stage pT1b–pT2, all histological subtypes; pT1a G3 endometrioid or serous or clear cell EC or carcinosarcomas. All participating surgeons have to show their qualification and to document the correct extent of systematic LNE [24,25]. Primary endpoint will be overall survival. Approximately one third of the required patients have been recruited in Germany. ECLAT-trial will now be supported by investigators from the Republic of Korea. Another prospective randomized controlled trial was designed to address the use of systematic LNE to restrict adjuvant therapy (other than vaginal brachytherapy) to node positive women. Selective Targeting of Adjuvant Therapy for Endometrial Cancer (STATEC) (ClinicalTrials.gov Identifier: [NCT02566811](https://clinicaltrials.gov/ct2/show/study/NCT02566811)) was started in 2015 and terminated due to poor recruitment in 2019 [26]. The ECLAT trial will show, whether or not comprehensive retroperitoneal LNE can be safely abandoned in patients with high risk EC. Other RCTs

should address the role of sentinel node biopsy in high and low risk EC, especially in combination with the new molecular markers [27]. In the ECLAT-trial (funded by the German Cancer Aid) these new markers (ProMisE) [27] will be prospectively assessed and correlated with nodal status and survival.

High quality surgical trials are difficult to perform, as funding is not easily available. But as shown in ovarian [25] and cervical cancer [23] our treatment strategies should be based on prospective evidence.

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