Lymph node status (Core and Non-core)

Lymph node status is an important prognostic factor for endometrial carcinoma and its assessment is crucial for determining both stage and appropriate adjuvant therapy. According to the International Federation of Gynaecology and Obstetrics (FIGO) Staging System, metastatic involvement of lymph nodes increases tumour stage (IIIC1 and IIIC2 for pelvic and para-aortic nodes, respectively).[1] In contrast, a therapeutic benefit from lymph node resection has not been shown yet in randomised trials,[2-4] although a large retrospective study has shown benefit from extensive nodal dissection especially in serous tumours.[4]

Intraoperative frozen section analysis can be useful to assess lymph node metastases.[5] The technique has its limitations for the detection of micrometastasis and isolated tumour cells.[6] Notably, intraoperative frozen section is only justified if the results have immediate therapeutic consequences. Serial sections from different levels are not recommended to avoid tissue depletion. The tissue block used for frozen section needs to be fixed in formalin and embedded in paraffin and, if negative for metastasis, submitted for ultrastaging.

Resected lymph nodes are categorised as regional (paracervical, parametrial, various pelvic lymph node groups, including obturator, internal, common or external iliac, presacral and lateral sacral, and para-aortic) or non-regional nodes (inguinal and other nodes). It should be noted that non-regional lymph nodes (including inguinal nodes) are considered to be distant metastases.

Core data regarding lymph node status includes the number of lymph nodes identified from the various sites, the number of lymph nodes involved by metastatic tumour and the size of largest metastasis (maximum diameter in millimetres (mm)). Some other parameters which may be useful for future research may be recorded, such as extranodal spread. Extranodal spread is a non-core element. Occasionally, metastatic tumour is present in the specimen removed, but no lymph node tissue is identified.

The FIGO Staging System includes lymph node status, and its structure is similar to that of the TNM system.[1,7,8] Pelvic lymph node involvement is Stage IIIC1 and para-aortic nodal involvement Stage IIIC2. For TNM stage, regional lymph node metastases contribute to the N category, whereas metastases in non-regional nodes are regarded as distant metastasis and belong to the M category.[7,8] According to TNM8,[8] macrometastases are >2 mm, micrometastases are >0.2 to 2 mm and/or >200 cells, and isolated tumour cells are up to 0.2 mm and ≤200 cells. Macrometastases are regarded as pN1 or pN2 depending on location (pelvic for pN1, para-aortic for pN2), micrometastases as pN1mi or pN2mi (depending again on location of the involved lymph nodes) and isolated tumour cells are pN0(i+); isolated tumour cells do not upstage a carcinoma.[7-10]

Grossing of the lymph nodes is an important step for a thorough histologic evaluation. Lymph nodes up to 2 mm are embedded whole. If lymph nodes are larger than 2 mm, they should be sliced perpendicular to the long axis at 2 to 3 mm intervals and entirely submitted.

Traditionally, lymph node status has been assessed either by removal of enlarged and grossly suspicious lymph nodes or systematic lymphadenectomy. More recently, the technique of sentinel node biopsy has been developed and established for endometrial carcinoma as an alternative to systematic and selective lymphadenectomy. Multiple studies confirm the high sensitivity of the sentinel lymph node approach for determining the lymph node status in early-stage endometrial carcinoma and underscore the value of sentinel node biopsy in selecting therapeutic approaches.[11-14] Currently, indocyanine green is considered the most reliable tracer and the highest detection rate can be achieved when the substance is injected into the cervix.[15,16]

One of the strengths of sentinel lymph node biopsy is the detection of a high percentage of lymph node positive cases by accurate analysis of one or a few lymph nodes. Isolated tumour cells, micrometastases, and small macrometastases are detected by ultra-staging of the lymph nodes in combination with immunohistochemistry (IHC). In addition, sentinel lymph node biopsy is associated with a substantially lower risk of post-operative morbidity, especially lower leg lymphoedema when the dissection of other pelvic lymph nodes is avoided.[17,18]

A study by Kim et al (2013) on low risk endometrial carcinoma patients (myometrial invasion <50%, low histologic grade) has shown involvement of sentinel lymph nodes in 6% of patients, of which half were identified by pathological ultra-staging.[19] Patients with carcinomas limited to the endometrium were not identified with positive sentinel lymph nodes and, therefore, sentinel node biopsy could be omitted in this patient population.[20] However, this usually is confirmed after hysterectomy only.

The presence of nodal micrometastases is associated with worse prognosis, particularly in patients not receiving adjuvant treatment.[21] There is no evidence that the presence of isolated tumour cells which would be classified as pN0(i+) has prognostic ramifications. Based on large randomised trials,[2-4] lymph node staging does not show any impact on survival but provides information on extent of the disease and decisions about adjuvant treatment. According to recent European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Pathology (ESP) 2020 guidelines,[22] sentinel lymph node biopsy can be considered for staging purposes in patients with low/intermediate risk disease and can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended for these carcinomas due to the morbidity associated with the procedure and low incidence of positive nodes. For high-intermediate/high-risk carcinomas in Stages I/II, surgical lymph node staging should be performed and sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy.[23]

Ultrastaging is recommended for the analysis of sentinel nodes negative for metastasis by routine histopathologic analysis since it provides valuable clinical information.[24,25] Notably, if sentinel nodes are negative by ultrastaging the occurrence of isolated nodal paraaortic metastasis is less likely.[22,25] Several ultrastaging protocols have been published, however there is no preferred standardised technique. Ultrastaging consists of additional sections cut at defined intervals and stained by haematoxylin and eosin (H&E) and pankeratin for improved detection of micrometastases and isolated tumour cells. There is some evidence that the results between different protocols do not reveal significant differences.[24-27] Two different methods were compared without significant differences: five H&E levels at 250 micrometres (µm) intervals with two unstained slides at each level; pankeratin IHC performed on level 1 in cases with negative H&E levels; or one H&E level plus two unstained slides cut 250 µm into the tissue block and pankeratin IHC performed in cases with negative H&E.[24] Another protocol uses H&E and pankeratin IHC at 50 µm into the tissue block with a total of five sections per block.

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