Lymph node status (Core and Non-core)

Lymph node status is one of the most important prognostic factors for survival in patients with cervical cancer.[1] The 5 year survival rate decreases from 85% to 50% when lymph node metastases are identified.[2]

Radical hysterectomy or trachelectomy and pelvic lymphadenectomy are the standard of treatment in most centres for International Federation of Gynaecology and Obstetrics (FIGO) Stage IB1, IB2 and IIA1 cervical carcinomas and, in some centres, for Stage IA2 carcinomas. There is an increasing trend for a more conservative approach, such as loop/cone excision, in the treatment of FIGO Stage IA2 and small Stage IB1 carcinomas, particularly if additional risk factors such as lymphovascular invasion (LVI) are absent.[3] In such cases, lymphadenectomy is often performed. Lymphadenectomy may also occasionally be performed for bulky nodal metastases (>20 mm) which are resistant to radiotherapy and/or chemotherapy; debulking of enlarged pelvic nodes has been shown to reduce the risk of pelvic recurrence but does not benefit survival.[4,5]

Core data items regarding lymph node status are restricted to the number of lymph nodes identified from the various sites and the number involved by tumour. The size of the tumour deposit is included as a non-core item. Some of the other parameters discussed below (extracapsular spread and lymph node ratio) may be recorded if locally agreed. Recording these parameters may be useful for future research.

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).[6] The FIGO 2018 Staging System,[7,8] unlike previous systems, includes lymph node status and is thus now closely aligned with the structure of the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) 8th edition TNM Classifications (see **PROVISIONAL PATHOLOGICAL STAGING**).[6,9] In the FIGO 2018 Staging System, pelvic lymph node involvement is Stage IIIC1 and para-aortic nodal involvement Stage IIIC2.[7,8] In applying a TNM stage, regional lymph node metastases contribute to the N category, but non-regional node involvement is regarded as distant metastasis. One point to emphasise is that the TNM8 Classification takes into account the size of the nodal metastasis in assigning the N category.[6,9] According to TNM8,[6] macrometastases (MAC) are >2 mm, micrometastases (MIC) are >0.2-2 mm and isolated tumour cells (ITCs) are up to 0.2 mm. MAC are regarded as pN1, MIC as pN1 (mi) and ITCs are pN0 (i+); ITCs do not upstage a carcinoma. The 2018 FIGO Staging System originally stated that MIC and ITCs can be recorded but this does not alter the tumour stage.[7,8] However, a corrigendum was later issued stating that MIC should be counted as nodal involvement and FIGO Stage IIIC.[10]

According to the UICC, a pelvic lymphadenectomy specimen should normally include six or more lymph nodes, but if this node count is not met and the resected lymph nodes are negative, the carcinoma should still be classified as pN0.[6] The mean or median number of lymph nodes removed during pelvic lymphadenectomy varies widely in different studies and ranges from 13 to 56 nodes. Apart from the arbitrary minimum number of nodes proposed by the UICC, there is no internationally accepted minimum for the number of resected lymph nodes required as part of a lymphadenectomy for cervical cancer. A study by Inoue et al (1990) reported that the number of positive nodes was of greater prognostic significance than the presence of nodal metastasis per se.[11] While a more recent study by Park and Bae (2016), showed that the number of lymph nodes with metastases is an independent risk factor for reduced survival in patients with cervical cancer.[12]

In many centres, sentinel lymph node (SLN) biopsy is now being undertaken in patients with presumed low-stage cervical carcinoma.[13-15] Overall, in FIGO Stage I cervical cancer the incidence of pelvic lymph node metastasis is approximately 10%.[16] If the SLN is negative, this avoids the morbidity associated with full pelvic lymphadenectomy in the remaining 90% of patients, i.e., SLN biopsy is of value in reducing the requirement for a complete lymphadenectomy with its attendant morbidity in a patient population at low risk for lymph node metastases. With regard to the issue of MIC (which, as discussed, should be staged as pN1 (mi)) and the use of immunohistochemistry (usually cytokeratin AE1/AE3), a study by Juretzka et al (2004) found immunohistochemically-detected MIC in 8.1% of patients with initially

reported 'negative' nodes (comprising 4 of 976 or 0.41% of pelvic lymph nodes examined).[17] The immunohistochemically-detected MIC were more frequent in tumours with LVI; another study showed that immunohistochemically-detected MIC were a risk factor for tumour recurrence.[18] Other studies have shown higher rates of lymph node MIC in early stage cervical carcinomas for example, 10.1% of cases in a study by Cibula et al (2012)[19] and 15% in a study by Lentz et al (2004).[20] The latter study also showed that MIC were more likely in patients in whom larger numbers of lymph nodes were removed. A study by Horn et al (2008) revealed that lymph node MIC were prognostically significant; patients with MIC had a reduced 5 year survival rate compared with node-negative patients, but fared better than those patients with MAC.[21] In the study by Cibula et al (2012)[19] ITCs were detected in 4.5% of cases and were found to be of no prognostic significance. If SLN biopsy is carried out, the number of nodes examined, the number of positive nodes and the size of the tumour deposit should be recorded. It is acknowledged that there are few published data regarding MIC and ITCs in cervical cancer and until further data emerge it is recommended that these should be reported in the same way as ITCs at other sites.

Frozen section of SLNs is also performed routinely in some institutions, while others may take a more selective approach in choosing SLNs to send for frozen. If positive lymph nodes are detected at the time of surgery, the procedure is abandoned, and the patient receives adjuvant chemoradiation therapy and is spared also undergoing a radical surgical procedure. The sensitivity for detecting metastases at frozen section varies depending on the method of sectioning the lymph nodes and appears to be better in high volume centres. In general, frozen section has low sensitivity (47%-56%)[22,23] for detecting clinically relevant metastases.[22-24] In addition, performing frozen section on all SLNs is resource heavy and may not be feasible in under resourced areas. It may be more efficient to only send clinically or radiologically suspicious lymph nodes for frozen section evaluation.

The size of lymph nodes with metastatic carcinoma has been reported to be a prognostic factor in one study; patients with lymph nodes >15 mm in short-axis diameter had significantly lower survival rates than nodes of smaller size.[25]

Lymph node ratio (LNR), the ratio of positive to negative lymph nodes, has been assessed in a wide range of different cancers. The significance of LNR in cervical carcinoma has only recently been evaluated and there is insufficient evidence to include this as a data item in the current dataset. However, in early stage cervical cancer, the LNR identifies node-positive patients with a worse prognosis[26] and has been found to be an independent prognostic indicator of overall survival and disease-free survival in patients with SCC.[27]

There are very few studies that assess the significance of extracapsular/extranodal spread of metastatic cervical carcinoma, and the item has not been included in this dataset. One study showed extracapsular spread to correlate with advanced stage disease, the number of involved nodes and the size of metastatic deposits.[28] In another study, patients with extracapsular lymph node spread had a significantly lower 5 year recurrence-free survival rate compared to patients whose nodes showed no extracapsular spread.[29]

The lymph node parameters, LNR and extracapsular spread have not been included as specific data items due to a lack of supporting evidence. However, as indicated above, individual pathologists or institutions may choose to include some or all these items in their own protocols. This may be useful for prospective data collection.

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