

Lymph node count in colorectal cancer - do we have the final answer?

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Lymph node count in colorectal cancer patients has been the subject of long ongoing debate. The most important aspect and the single most significant prognostic factor involving the lymph nodes is their number - the more node is retrieved, the more precise is the staging and consequently - the prognostication. The lymphatics provide a convenient spreading for the cancer cells and the first stops for those cells are the regional lymph nodes. In their review article entitled "The complexity of the count: considerations regarding lymph node evaluation in colorectal carcinoma" Laura Denham and her colleagues highlight the different aspects (1).

The initial attempts to get the optimal (and even minimal) node count were fraught with many difficulties (2). Surgical technique and pathology retrieval has developed steadily, and by the end of the nineties, the optimal number of 12 lymph node per specimen has been reached (3).

The surgical technologies were getting refined and the therapeutic options were stratified by the staging data, therefore the importance of good node staging has increased (2,4).

Why the lymph node count is so important?

Several studies found that the increased node count are correlated with increased disease free interval and overall survival (5). This most likely based on the more accurate staging information, which enabled more tailored treatment. However, the effect is most likely multi factorial and there are other factors which are also important, but the exact role and individual effect of the components is difficult to measure.

There are many factors influencing the final node count. Most often quoted is the patient's age (6), also the experience of the surgeon and the pathologist (7); but there is also important to consider the anatomical location and previous treatment modalities.

The anatomical distribution and the extent of the excision will limit the number of potentially recoverable lymph nodes; in theory and with diligent practice, up to 87 lymph nodes achievable (4) from a total colectomy specimen. However, we need to note that most of these nodes are in the sub-2 mm category. This degree of dissection and retrieval is usually beyond the possibilities and resources of a busy pathology department.

The most important factors in the lymph node count equation are: the patient (age, BMI, individual differences), the surgeon (the experience seems to be the one which counts most), the specimen type (total colectomies yield significantly more nodes than segmental colectomy), the pathologist (diligence and experience).

There are factors which are difficult to influence, but there are some which are possible to do so - that's where our assessment comes in.

But how precise should we be - i.e. how much is enough?

When we look at the optimal lymph node count to get accurate stage information for all stages, it seems that 15 lymph nodes seem to be safest option to cover all angles and include all stages. At our department (University Hospital with approximately 400 colorectal cancer resections/ year) we found in an audit of one year whole section caseload that if we had at least 16 lymph nodes found, no staging information needed changing - and we were able to reliably differentiate between N1 and N2 stages - any additional node harvested did not improve accuracy.

In the days of hard economic driving forces, an optimal number of lymph nodes need to be found. However, as a pathologist I will always look for the maximum number of recoverable nodes in any specimen - it is important not to stop at 16.

When we look for the lymph nodes - it is quite

straightforward that one seeks the lymph nodes between the tumour and the feeding vessels (please note: lymph node collecting areas follow the ways of arterial distribution, not the veins - venous system confluences in the portal vein/liver). It is important that we need to look around the tumour, and make sure we looked this area carefully - nodes collected around splenic flexure in an extended right hemicolectomy for a caecal cancer are not likely to contain metastatic disease and will not going to influence the treatment.

Several major series suggest that we need at least 12-14 nodes to get sufficient prognostic information. Obviously - cannot be emphasised enough - one needs to find all the nodes, however it is generally sufficient to stick to the minimum of 12. It is important to collect all nodes though in the collecting basin.

Size of the nodes does matter, but what will be the accepted lower end of the size for a node to be counted? It is easy, when we establish that metastatic deposits more than 4 mm need to be counted as mets, but when can accept one a negative, but very small node?

The minimum seems to be around 1 mm - which may not be visible macroscopically, but there is one important criterion on which most agree: the node should have marginal sinus (i.e. lymph node architectural feature) to be counted. For the rest, the name of lymphoid aggregate is probably more appropriate.

The different types of colonic cancer may have impact on the prognosis of the tumour and this effect is also seen with the lymph nodes - mucinous cancers generally have a lesser metastatic rate - conversely finding many nodes might be more important. Molecular genetic subtyping will become more and more important - the review highlights the important issues here as well.

When one looks into the matter of who is most influential on the lymph node count: the surgeon or the pathologist, the picture is far from clear. It seems the experience of the surgeon does matter, those with more than 15 years of experience collected significantly more nodes than those less than 15 years. The effect of the pathologist is a bit less clear - it seems the diligence of the dissecting pathologist is the most important factor - no correlation with experience can be confirmed.

It is accepted that different fat-clearing methods increase lymph node yield, up to 50 percent higher lymph node count can be achieved. The disadvantages of the more complicated and usually longer dissection and cutup process are offset by the increased accuracy of the nodal staging.

A better alternative to conventional fat-clearing is the use of a modified fixation method, usually applied as post-fixative agent. The method is more extensively used in upper gastrointestinal (oesophageal and gastric) resection

specimens. It involves using a mixture of glacial acetic acid, ethanol, water and formaldehyde (GEWF) (8). Following 24 hours of initial fixation in buffered formal-saline, the tissue is transferred into this medium, and a further 24 hour fixation follows. After this period the lymph nodes are standing out more from the fatty background, and easier to recognise - this is a clear advantage with smaller lymphoid aggregates.

There is still the question of N1 vs. N2 - how many nodes we need to reliably distinguish between nodal stages?

This question is not extensively addressed in the literature.

Our own experience showed that when we had at least 16 nodes harvested at the first instance, none of the tumours needed upstaging, when additional nodes were harvested for the purpose of increasing node yield. Others experience may not be so clear, but I feel that when this number is achieved, the staging information is most likely to be correct.

What is the magic number then?

It seems that we have a reasonable consensus - the 12 nodes are the accepted minimum worldwide. Our task is though to try achieve this number in all of the cancer resection cases in every hospital. The data of compliance with this from the earlier literature seems rather bleak (9), but improvements have been made. The review article of Denham *et al.* concludes that 12-15 lymph nodes, as currently suggested by CAP is appropriate.

The question might arise - what is the significance of this all? Why are we chasing numbers? The ultimate aim is to achieve the best available treatment for everyone. This is only possible though, if we pay attention to all the details, collect and evaluate the evidence, then apply it carefully in practice. In addition, proper statistics need to be applied in order to draw the right conclusion.

If we all provide more accurate staging information, our conclusions and follow-ups of the different stages will be more clear, and this will benefit all, and the review article has examined all of the relevant aspects in detail.

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