

COMMENTARY

Suboptimal Sensitivity and Specificity of PET and Other Gross Imaging Techniques in Assessing Lymph Node Metastasis

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In recent years, we have emphasized the limitations of positron emission tomography (PET) in imaging disorders that are beyond the capability of current instruments and available radiotracers [1–6]. These include imaging islets, bacteria, plaques and tangles, and atherosclerotic plaques. The spatial resolution of PET has substantially improved over the past decade, and therefore, high-quality images can be generated, particularly with specialized instruments for brain and animal studies. However, when the spatial resolution of PET instruments that are designed to image the entire body compared to that of dedicated brain scanners, it becomes quite evident that image quality deteriorates substantially due to large field of view and volume of the structures assessed. In other words, specially designed PET scanners for the brain (and possibly other small organs such as the breast) can provide images with spatial resolutions at around 4–5 mm that are similar to that of phantom studies (3–5 mm) [7, 8]. Therefore, such instruments are capable of generating images with great details of regional function in various structures in the brain. Unfortunately, conventional body scanners suffer from significant deterioration of signals emitted and this adversely affects the spatial resolution of objects examined. In particular, this becomes a major source of error in obese patients where significant scattering of the gamma rays further degrades the image quality. Since most metastatic lymph nodes reside in the trunk in most common cancers, detection of spread in such structures is a major challenge and therefore unreliable for accurate staging. Recent advances in PET instrumentation including the introduction of time-of-flight PET machines have overcome this issue to some extent [9]. We should also mention that metastatic lymph nodes are at times visualized on uncorrected images when the nodes are superficial

in certain locations such as the groin and neck regions [10]. Additionally, small field of view PET imaging in the head and neck region can be employed to detect metastatic lymph nodes with higher sensitivity than that of the deeply seeded lymph nodes in the trunk.

Overall, the spatial resolution of conventional PET body scanners is approximately 8–10 mm. Based on the assumption that the diameter of malignant cells averages around 15 μm , in order to detect metastasis with a diameter of 8–10 mm by PET, at least 150–300 million cells should be aggregated at the site. This calculation was based on dividing the volume of the lesion by the volume of an average cell, where all volumes were assumed to be spheres. For instance, in a lesion with a diameter of 8 mm (radius of 4 mm) and a malignant cell with a diameter of 15 μm (radius of 7.5 μm), the following formula was used to estimate the number of cells:

$$N = \frac{V(\text{lesion})}{V(\text{cell})} = \frac{\frac{4}{3}\pi r^3}{\frac{4}{3}\pi r^3} = \frac{\frac{4}{3}\pi(4\text{ mm})^3}{\frac{4}{3}\pi(7.5\text{ }\mu\text{m})^3} = \frac{268.1\text{ mm}^3}{1,767.2\text{ }\mu\text{m}^3}$$

$$= \frac{2.681 \times 10^{11}\text{ }\mu\text{m}^3}{1,767.2\text{ }\mu\text{m}^3} \approx 152\text{ million}$$

The same calculation was then repeated for a lesion with a diameter of 10 mm to estimate that it would take 300 million cells to form such a volume. Therefore, we believe detection of early spread of cancer cells to the lymph nodes is not achievable with current imaging techniques. This limitation can be overcome to some extent by enhancing the degree of tracer uptake at the targeted sites but is unachievable with the existing positron-emitting radiopharmaceuticals. It is possible that lesions with substantially higher uptake than the background will be visualized with

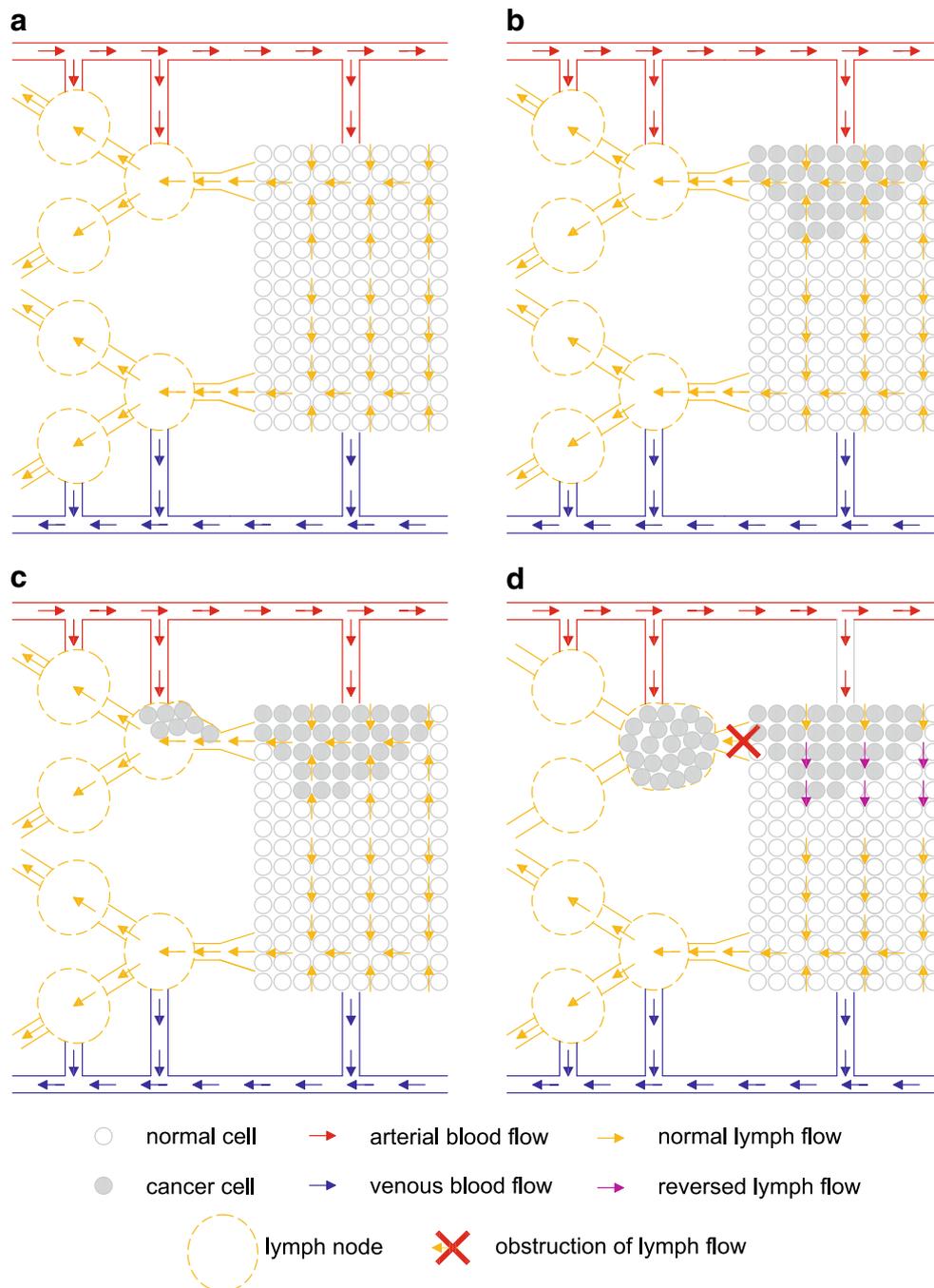


Fig. 1. Schematic drawings showing blood supply and lymphatics of lymph nodes in normal (healthy) and different pathological situations, and problems that may arise when using radiotracers/contrast agents that reach the lymph nodes through the interstitium. **a** An example of a normal (healthy) situation with two sentinel lymph nodes, second echelon nodes, arterial and venous blood flow to and from the lymph nodes and interstitium (for the sake of clarity, only one main arterial branch and one main venous branch are shown), formation of lymph from the interstitial fluid, and flow of lymph from the interstitium to the sentinel lymph nodes and second echelon nodes. **b** The same situation as in **a**, but with cancer cells in the tissue. There are no lymph node metastases, and flow of blood and lymph to the lymph nodes is not impeded. **c** The same situation as in **b**, but with metastatic cancer cells in the corresponding sentinel lymph node. Although the metastatic cancer cells occupy a part of this sentinel lymph node, flow lymph to this node is not impeded. In addition, blood flow to this node is not impaired either. **d** The same situation as in **c**, but with progressive sentinel lymph node metastasis. The sentinel lymph node is entirely replaced by tumor cells, as a result of which flow of lymph to this node is obstructed and reversed to the next (sentinel) lymph node. Radiotracers and contrast agents which reach the lymph nodes through the interstitium will fail to depict this metastatic sentinel lymph node. On the other hand, vascular supply of this metastatic sentinel lymph node is not impeded, as a result of which systemically administered compounds can still reach and depict this involved node (reprinted with permission from Kwee et al. [13]).

fewer cell counts and the reverse will be true for metastases from low-grade tumors with subtle uptake. The estimates noted above about the detectable lesion size are based on the average degree of uptake of tracers in the cells and may differ among lesions examined by PET. Also, over the years, it has been shown that delayed 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F FDG) imaging allows better contrast between the involved sites and the background. In other words, there is clear evidence that ^{18}F FDG uptake in malignant lesions increases over time (for up to 3–4 h following tracer administration), while background activity surrounding the lesion decreases with time. As a result, the contrast between the target tissue and the surrounding areas improves and this translates to a higher sensitivity for delayed imaging with ^{18}F FDG and possibly other tracers.

Over the past few decades, sentinel lymph node imaging has been routinely employed to visualize the draining nodes where metastases are likely to occur from the primary tumors [11]. This approach has been primarily utilized to detect probable metastatic nodes in patients with breast cancer and melanomas [12]. The methodology involves administering radiolabeled particles that are very small in size (less than 500 nm), and as such, are transported by the lymphatics to the draining nodes from the primary tumor site where radiolabeled particles are administered. This technique is still routinely employed for microscopic detection of probable metastatic nodes. The intended nodes are visualized by conventional nuclear medicine instruments by marking the skin for surgical excision by the attending surgeon. Soon thereafter, these nodes are submitted for pathological examination. Unfortunately, detection of evidence for metastasis is not guaranteed by this approach and many nodes with cancer spread may be overlooked. The basis for effectiveness of this approach is that the entire volume of the dissected nodes will be thoroughly examined by the pathologist for the presence of cancer cells. Obviously, this is impractical since comprehensive examination of nodes by microscopic examination would require generating numerous slices of the excised node. Because this is an impractical task, most laboratories opt for selecting a few slices for each node as representing evidence for metastasis for the entire specimen. This practice results in overlooking metastasis in the remaining tissue (among the selected slices) that may bear cancer cells. This is obviously a major source of error, and therefore, sentinel node imaging for detection of metastasis cannot be considered the gold standard for assessing the extent and staging of various malignancies. With this in mind, there is no reliable technique that will allow accurate staging of cancer in the lymph nodes at this time. Therefore, currently, there is no gold standard available for validating newer methodologies for this purpose.

We have previously described the sequence of movement of malignant cells from the primary sites to the draining lymph nodes (Fig. 1) [13]. Initially, metastatic malignant cells are located at the periphery of the lymph node and will be receiving their nutrients from the lymphatics draining the peripheral tissues. It is conceivable that by time the cells proliferate

substantially, tracer concentration in the remaining lymphatics becomes substantially lower than that of plasma, and this may result in sub-optimal uptake by the cancer cell. This results in minimal contrast between the lymph node uptake and the surrounding background. However, as the malignant cells replicate, they stop lymphatic drainage, and as a consequence, the arteries from the lymph node capsule start to invade the inner lymph node structures to provide nutrients from the systemic circulation. Overall, this prolonged sequence of events results in low sensitivity of radiotracer-based imaging for detecting cancer cells in the lymph nodes compared to the other organs such as the lung and the liver. We realize that this is a somewhat speculative hypothesis and its accuracy has to be proven by well-designed experiments in animal models in the future. Such research studies will further clarify the potential sources of error in this setting.

Also, we should point out that in certain locations in the body imaged for metastasis with specific tracers, we may encounter non-specific uptake in the adjacent structures that may be interpreted as metastatic nodes as recently reported [14]. This report described the non-specificity of ^{68}Ga PSMA uptake in the ganglia that could be mistaken for metastatic lymph nodes. Additionally, inflamed lymph nodes due to systemic disorders or infection can mimic lymph node metastasis when ^{18}F FDG is employed for detection of malignant cells. We should also express our concerns about the limited role of structural imaging techniques such as CT and MR in these settings [15]. The sensitivity and specificity of these imaging modalities are substantially lower than those provided by modern PET techniques [15].

Therefore, relying on PET for detecting early metastasis to the lymph node is unrealistic, and thus, a negative scan for metastasis cannot rule out microscopic lesions for an extended period of time. Delayed ^{18}F FDG-PET imaging may improve the sensitivity and specificity of this modality in assessing lymph node metastasis [16]. Based on multiple reports in the literature, the uptake of ^{18}F FDG increases over time, while that of inflammatory or most normal cells decreases as noted on dynamic scans. This leads to a higher contrast between the lesions and the surrounding background.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

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