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Research review paper

Clinical relevance of novel imaging technologies for sentinel lymph node identification and staging

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ABSTRACT

The sentinel lymph node (SLN) concept has become a standard of care for patients with breast cancer and melanoma, yet its clinical application to other cancer types has been somewhat limited. This is mainly due to the reduced accuracy of conventional SLN mapping techniques (using blue dye and/or radiocolloids as lymphatic tracers) in cancer types where lymphatic drainage is more complex, and SLNs are within close proximity to other nodes or the tumour site. In recent years, many novel techniques for SLN mapping have been developed including fluorescence, x-ray, and magnetic resonant detection. Whilst each technique has its own advantages/disadvantages, the role of targeted contrast agents (for enhanced retention in the SLN, or for immunostaging) is increasing, and may represent the new standard for mapping the SLN in many solid organ tumours. This review article discusses current limitations of conventional techniques, limiting factors of nanoparticulate based contrast agents, and efforts to circumvent these limitations with modern tracer architecture.

Contents

1. Introduction

The metastatic status of regional lymph nodes is the most significant prognostic factor in breast cancer, melanoma and other solid organ tumours with lymphatic spread (Gershenwald and Ross, 2011; Krag

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et al., 2010; Salhab et al., 2011). Since the initial demonstration of the sentinel lymph node concept by Morton et al. (Morton et al., 1992), there has been much focus in clinical oncology around the role the lymphatic system plays in cancer prognosis and treatment. More specifically, the sentinel lymph node (SLN) concept describes the preferential lymphatic drainage of a primary tumour to a regional lymph node(s). Studies have shown that the status of the SLN is an accurate indicator of the status of the second and subsequent tier nodes (Ball et al., 2010; Hayashi et al., 2006; Mansel et al., 2000). The SLN concept has become the standard of care for melanoma and breast cancer patients with non-clinically detectable metastases and has improved patient management, morbidity, and – although this has yet to be confirmed – mortality (Leong et al., 2011a).

Current identification of the SLNs is typically performed using lymphoscintigraphy; where, after peritumoral injection of radiolabelled nanoparticulate agents, lymphatic drainage from the primary tumour is imaged preoperatively using nuclear imaging, and/or detected intraoperatively with a gamma probe. This technique can also be performed intraoperatively with blue dyes, which enable direct visual identification of the SLNs at the time of the surgery. The uptake of these lymphotropic contrast agents by the lymphatic system is monitored intraoperatively by surgeons, until the first nodes along the drainage pathway have been identified (Fig. 1A). These nodes are then surgically extracted, and the presence of cancer cells is determined through pathological examination. The presence of metastases within SLNs has been correlated with poor prognostic outcomes for a range of diseases (Carter et al., 1989; Ferrone et al., 2002; Muller et al., 2001) and accurate staging of the SLNs is therefore of high clinical importance.

The prognostic significance of the detection of small metastatic deposits however remains controversial. In addition, aside from being the current standard of care for breast cancer and melanoma, the clinical application of the SLN concept to other type of cancers, for instance gastrointestinal ones, remains limited and its clinical relevance controversial. One of the main factors preventing its application to other cancer types are the technological challenges yet to be solved in correctly identifying the SLNs. Imaging modalities currently used for the detection of radiolabeled agents are indeed limited by their poor spatial resolution in solid tumour types in which the SLNs are in close proximity to the primary tumour. In addition, gamma probe based detection of the SLN can be compromised when the SLN is close to the injection site because of shine-through radioactivity (Fig. 1B). Further, when blue dyes are used visualisation is not always possible – as is the case for some cancer types located in internal organs (e.g. lung and oesophageal) where tissue penetration is poor and lymph nodes often anthracotic.

There is therefore, much need for improvement in the ability to detect the SLNs using lymphotropic contrast agents. An 'ideal' contrast agent would be one that imposes little risk to patients' health; has good specificity to the SLN; lymphatic uptake and migration speed is optimised; creates a high signal to noise ratio (e.g. good retention and distinguishable from background signals); can be detected with high resolution, and in low quantities (sensitivity); and is relatively easy and economical to use. Although no such contrast agent currently exists, the quest to find

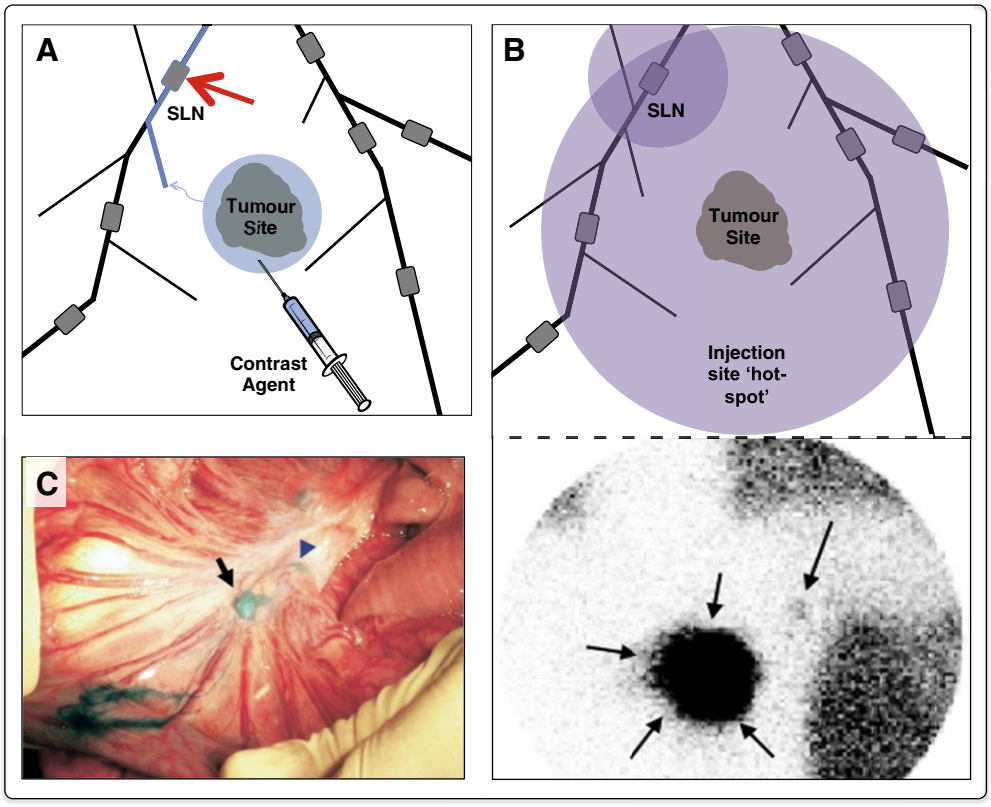

Fig. 1. Sentinel node detection: (A) Demonstration of the SLN concept: a tracer is injected at the tumour site, accumulating in the interstitial tissue. It is not until the complicated network of lymphatic vessels drains the tracer and highlights the first lymph node that the SLN can be identified (arrow), and uptake from the tumour site can be mapped in vivo. (B) In some instances proximity of the SLN to the tumour site is such that the hot spot from the injection site can mask the hot spot of the SLN (represented as shaded circles, top panel). In such instances, the sensitivity of the technique is overshadowed by its poor spatial resolution, and it may be difficult to visualise all nodes of interest (bottom panel). *Reprinted from Aarsvold and Alazraki (2005) with permission from Elsevier.* (C) Use of blue dyes to intraoperatively highlight the SLN. After injection, the surgical team may have less than 10 min to locate the stained sentinel node (arrow) before efferent flow stains subsequent, lower tier nodes too. *Reprinted from* Kitayama et al. (2007), *with permission from Elsevier.*