The Sentinel Lymph Node Concept

6

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Contents

Learning Objectives

- To become familiar with how lymphatic mapping evolved into current practice
- To comprehend the physiologic principle on which lymphatic mapping is based
- To become familiar with the concept of lymphatic mapping
- To appreciate the technical challenges of the sentinel lymph node biopsy (SLNB)
- To learn and understand the definition of a sentinel lymph node (SLN)
- To realize that there is no consensus on the definition of a SLN
- To beware of other definitions
- To appreciate why some alternative definitions are associated with an increased risk of false-negative SLNB
- To understand how some definitions are associated with unnecessary removal of innocent lymph nodes

6.1 History

For many years, regional lymph node dissection was a routine component of the surgical treatment of various solid cancers, even if the nodes appeared clinically normal. Common examples include head and neck cancer, breast cancer, melanoma, and tumors of the gastrointestinal tract. This practice was rooted in the observations by the German pathologist Rudolf L. K. Virchow (1821–1902) that lymph nodes filter particulate matter from lymph fluid and that cancer metastasizes via lymph ducts to such nodes [1]. These fundamental findings inspired the American surgeon William S. Halsted to develop the mastectomy with *en bloc* axillary lymph node dissection for breast cancer at the end of the nineteenth century [2]. Halsted's concept was based on the notion that cancer generally metastasizes first to regional lymph nodes. These nodes act as filters that temporarily prevent further spread of cancer cells. This barrier

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creates a window of opportunity for radical local-regional surgery to cure the patient.

These general concepts eventually led to the current concept of SLNB. The term "sentinel" lymph node was first mentioned in 1923 by the British surgeon Braithwaite, who studied lymph drainage. He dripped a blue dye onto the omentum and removed the lymph node to which the blue-stained lymphatic drained and called this the "gland sentinel" [3]. In 1960, Gould et al. used the term SLN to describe a lymph node at the junction of the anterior and posterior facial veins [4]. In a study of parotid cancer, they found that this node was the first one to be involved when a parotid tumor spread, and they designated this node the SLN [1]. A radical lymph node neck dissection was performed if frozen section examination revealed metastatic disease in this node.

In the 1980s, work of Dr. Bernard Fisher and others appeared to refute Halsted's postulation [5, 6]. They advocated that cancer does not spread in an orderly fashion. The Fisher hypothesis indicates rather that lymph nodes and distant sites tend to become involved simultaneously and that lymph nodes are ineffective as barriers to further dissemination. As a result, lymph node metastasis was presumed to indicate that the disease had spread to various sites and that curative surgery was no longer an option.

Against the common opinion at that time, some surgeons held on to the Halstedian view. A few developed his concept further in attempts to avoid the—in hindsight—often unnecessary, elective regional lymph node dissections that were routinely performed for various cancer types. The purpose was to identify and remove the lymph nodes that were the first to be involved, so that regional node dissection could be reserved for patients who really had metastases. This way, patients without lymph node metastases could be spared a full dissection. One of these surgeons was Ramon Cabañas from Paraguay, who had a special interest in penile cancer, a common tumor in his country. Squamous cell carcinoma of the penis tends to metastasize to lymph nodes but not to distant sites until at a late stage. In 1977, Cabañas found that penile cancer initially drains to a particular lymph node that is always at the same location in the groin and termed this node the SLN [7]. So, the node was defined by its constant anatomic position, which appears plausible for penile cancer, because the primary cancer is always situated in the exact same location, on the glans. However, the hypothesis that lymph drainage rigorously follows a pattern to a lymph node that is always in the exact same location did not hold. False-negative procedures occurred and urologists found that results with biopsy of this SLN were not reliable enough to make the technique routine clinical practice [8, 9].

In the late 1980s, the surgeon Donald L. Morton at the John Wayne Cancer Center in Santa Monica and his pathologist Alistair J. Cochran from the University of California, Los Angeles, took the SLN procedure a major step forward when they proposed the innovative concept of "lymphatic mapping with SLNB" for melanoma [10]. They suggested that a melanoma could drain to any lymph node in a particular lymph node field or even outside a nodal field, depending on the location of the primary lesion and with a certain individual variability. They developed a technique to identify and remove this lymph node after administration of patent blue dye at the tumor site. The dye is taken up by the lymphatic system. Delicate dissection of the afferent blue lymph duct guided Morton to the SLN (Fig. 6.1). Subsequently, lymphoscintigraphy was added to reliably identify the field to which the tumor drained and to indicate the number of SLNs actually present. The radiopharmaceutical enabled an alternative technique to retrieve the SLN. Intraoperatively, the radioactivity was gauged with a gamma ray detection probe and guided the surgeon to it. The pathologist obtained multiple sections from the lymph node and used sensitive immunohistochemistry staining techniques to detect even minute deposits of malignant cells.

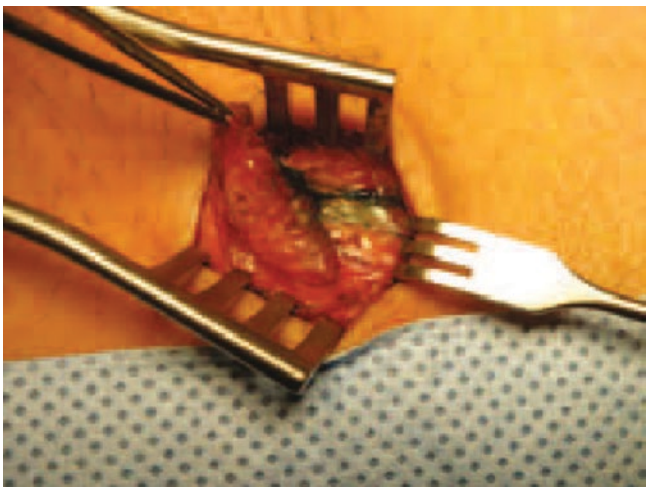

Fig. 6.1 Blue afferent lymph channel with SLN

It has been demonstrated that the hypothesis of Morton and Cochran is correct and that lymphatic dissemination generally occurs in a sequential fashion [11, 12]. The SLN is indeed the first node to be involved and its tumor status reflects the status of the entire lymph node field.

Key Learning Points

- Lymphatic mapping is based on the Halstedian principle, which entails that cancer generally metastasizes first to regional lymph nodes. In the absence of metastases elsewhere, removal of affected lymph nodes cures the patient.
- Modern-day SLNB is based on the physiology of lymphatic drainage.

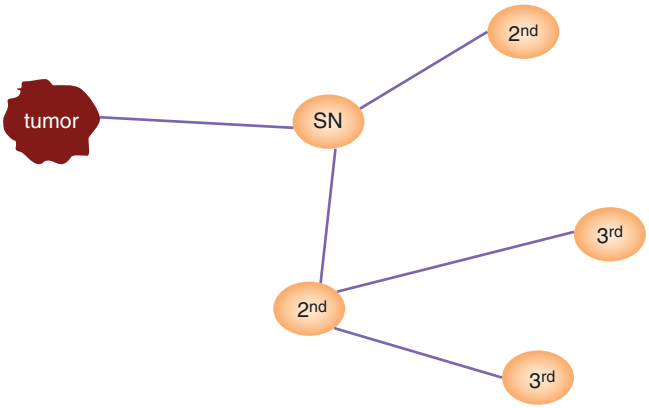

Fig. 6.2 The concept of lymphatic mapping is based on the notion that lymph fluid from a primary cancer drains to a particular regional lymph node. *SN* SLN, *2nd* second-tier lymph node, *3rd* third-tier lymph node

6.2 Concept

Cancer cells that are shed from the primary tumor enter the lymphatic system with the excess of interstitial fluid. The fluid in the lymph vessels passes through a number of lymph nodes on the way to the upper chest, where the fluid is returned to the bloodstream. Lymph nodes act as filters that temporarily prevent further spread of cancer cells. As lymph node metastases commonly precede blood-borne metastases, this barrier creates a window of opportunity for radical local-regional surgery to cure the patient. In order to fully utilize this opportunity, lymph node involvement must be detected at the earliest possible stage.

The concept of lymphatic mapping is based on the notion that lymph fluid from a primary cancer drains through an afferent lymph vessel to at least one particular regional lymph node (Fig. 6.2). This is the SLN, also known as first-tier node or first-echelon node. From this lymph node, lymph fluid passes through efferent lymph vessels to other lymph nodes in the nodal field. When tumor cells spread, they will first lodge in the SLN. So, this is the node at greatest risk of harboring tumor cells. Other nodes downstream may subsequently become involved in a stepwise fashion.

Lymphatic mapping identifies and removes this SLN, and determines whether it contains metastatic disease. Knowledge of the tumor status of the lymph nodes facilitates informed decisions on completion of regional lymph node dissection to remove other potentially involved lymph nodes and on adjuvant systemic therapy.

Key Learning Points

- Many cancers spread in a stepwise fashion through the lymphatic system.
- The SLN is the first lymph node to be involved with metastasis.
- The purpose of SLNB is to detect lymph node metastases at an early stage.
- SLNB is used to select patients who may benefit from completion lymph node dissection.
- SLNB is used to select patients who may benefit from adjuvant systemic therapy.

6.3 Definition of a SLN

Morton et al. used the definition "a SLN is the initial lymph node upon which the primary tumor drains" [10]. The word "initial" was prone to misinterpretation. For instance, multiple lymph vessels may link the tumor to multiple nodes that may not necessarily light up simultaneously on the lymphoscintigrams, yet they all are directly at risk of receiving tumor cells. To avoid confusion, the definition was slightly modified to the following: "a SLN is any lymph node on the direct drainage pathway from the primary tumor." This definition reflects the physiology of lymphatic drainage and the stepwise dissemination of cancer through the lymphatic system. This is the definition most experts adhere to.

6.4 Other Definitions

Later, the definition of a SLN being any lymph node on the direct drainage pathway was challenged [13–17]. Some investigators have come up with their own definitions (see Table 6.1) [18–21]. This development is understandable, since specialists from different fields are involved and each is addressing the concept from their own background and perspective. Also, lymphoscintigrams may be difficult to interpret, as they tend to depict multiple lymph nodes and do not always clearly indicate the order of lymph drainage. Moreover, the surgical procedure can be challenging. SLNB requires a considerable ability to think in a three-dimensional fashion. The surgeon needs to translate the one-dimensional probe readings and the two-dimensional scintigrams into a three-dimensional image in his/her mind. Furthermore, when using the blue dye the stained lymphatic vessel that visually

Table 6.1 Less appropriate definitions of a SLN

Lymph node closest to the primary lesion
First lymph node depicted on the lymphoscintigrams
Lymph node with the highest count rate
Any radioactive lymph node
Lymph node with a count rate that is a certain factor higher than the background or compared to non-SLNs
Lymph node with a count rate that exceeds a certain fraction of the hottest node
Any blue-stained lymph node

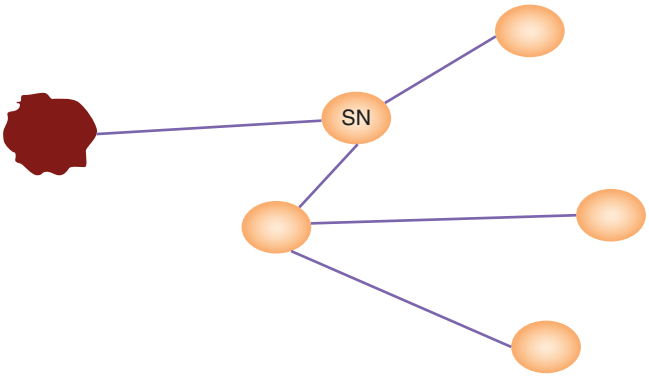

Fig. 6.3 Alternative definition. The lymph node closest to the cancer is not necessarily directly at risk of receiving tumor cells

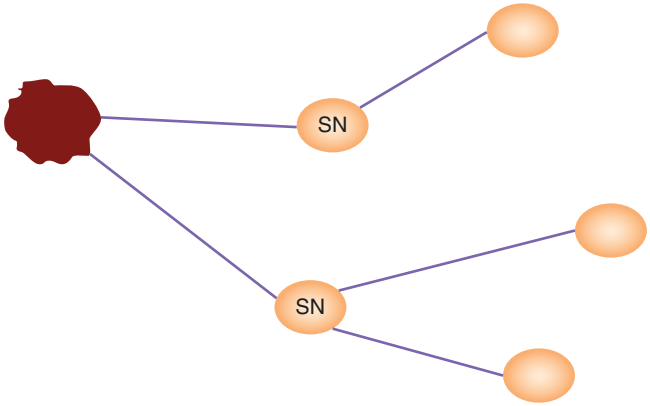

Fig. 6.4 Two lymph vessels originating in the tumor draining upon separate lymph nodes

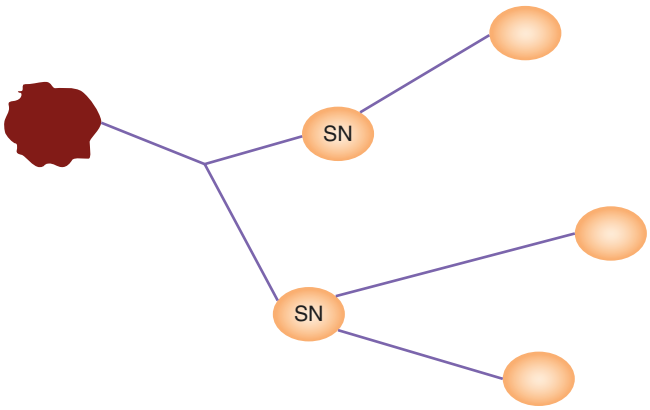

Fig. 6.5 Lymph duct dividing into two channels leading to separate lymph nodes

guides the surgeon to the SLN is very fragile. It requires considerable experience and finesse to dissect this delicate structure in a small, confined space, through a small incision, in a sometimes-deep lymph node field. For these reasons, some surgeons sought easier criteria to determine which lymph node(s) to remove in the situation that lymphoscintigraphy depicts multiple nodes.

Developing a more practical procedure using the definition that is based on the concept was problematic. Instead, the color of the node and its radioactivity were used as criteria. In the process, some investigators changed the definition. Some defined the SLN as the lymph node closest to the primary lesion [22]. Oftentimes, the node closest to the tumor is indeed (the) one into which the lymph vessel from the tumor drains, but this is not always the case (Fig. 6.3). So, this anatomy-based definition does not take into account the physiology of lymph drainage and the wrong lymph node could be removed.

Other investigators defined the SLN as the first lymph node that becomes visible on the lymphoscintigraphic images. It is inevitable that the first node that is depicted lies on a direct drainage pathway from the cancer and must be classified as SLN. However, this definition does not acknowledge the facts that more lymph nodes than a single one can be on a direct drainage pathway and that there may be reasons that prevent them from becoming visible simultaneously. For instance, there may be two lymph vessels originating in the tumor that drain upon different lymph nodes (Fig. 6.4). Sometimes, a single lymph duct divides into two channels going to separate lymph nodes (Fig. 6.5). Tumor cells may follow either route and both lymph nodes are at direct risk of being involved. Because the lymph flow speed may be quite different in the two channels, lymphoscintigraphy may visualize one lymph node before the other, but this does not imply that the other node need not be removed. All lymph nodes in direct drainage contact with the primary tumor are directly at risk of harboring tumor cells. All these first-tier lymph nodes should be harvested and examined by the pathologist. Therefore, the definition of the SLN being the first node to be visualized is too narrow; too few nodes are designated as SLN and metastases may be left unnoticed.

When lymphoscintigraphy shows multiple lymph nodes, some people considered only the brightest on the scintigrams or the one that yields the highest probe reading as SLN [21]. This definition of the "hottest" lymph node being the SLN has several drawbacks. Again, lymph can drain directly to multiple lymph nodes and one can collect more of the radiopharmaceutical than another (Fig. 6.6). The size of the lymph node is one parameter that determines the amount of radioactivity that can be accumulated. Its location is also relevant; a superficial lymph node has a short distance to the gamma camera or the gamma ray detection probe. Such a lymph node yields more counts than a node that contains three times as much of the tracer but lies at twice the distance. Some of the radiopharmaceutical may pass through the first lymph node and move on to subsequent nodes. A large second-echelon lymph node—or one with more active macrophages—

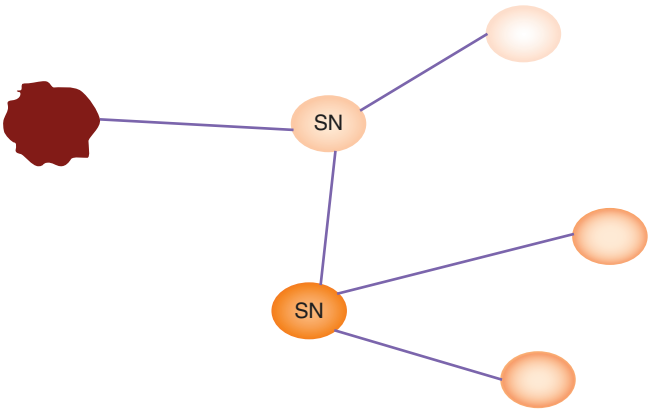

Fig. 6.6 Lymph fluid can drain directly to multiple lymph nodes and one may accumulate more of the radiopharmaceutical than another

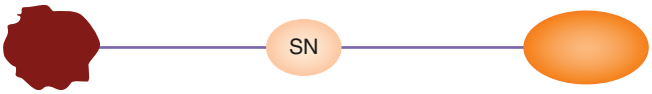

Fig. 6.7 A large second-echelon lymph node—or one with more active macrophages—may accumulate more of the radiopharmaceutical than a small first-echelon lymph node

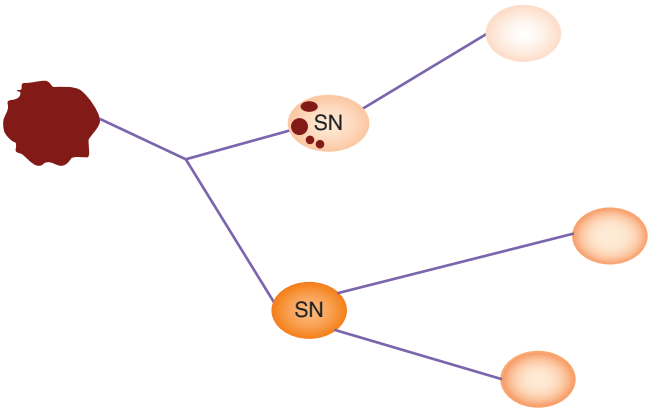

Fig. 6.8 Lymph flow to SLN hampered by metastatic disease

may accumulate more of the tracer than a small first-echelon lymph node (Fig. 6.7).

The amount of radiopharmaceutical that is accumulated by a lymph node depends on not only its position in the drainage order, but also the number of lymphatic channels that enter the node and parameters such as lymph flow speed. Another reason for a node to receive a sparse lymph supply is that the flow to that particular lymph node is hampered by metastatic disease obstructing its ingress (Fig. 6.8) [23]. So, there are a number of reasons not to classify a lymph node as a SLN based on its superior brightness on the scintigram or on the highest probe reading.

Certain surgeons relied on their gamma probe to find the SLN without preoperative imaging or use of a blue dye. They assumed that any radioactive node identified with the gamma ray detection probe is a SLN, and they defined a SLN as such. This point of view does not acknowledge the notion that some of the tracer fluid may pass through the first-tier lymph node and lodge in secondary nodes downstream that are not directly at risk of harboring metastatic disease. This definition is too liberal and too many lymph nodes may be removed as a result. One report indicated that up to 37 SLNs were to be removed from a single basin [24].

Another definition was based on the SLN-to-background count ratio. This definition also has shortcomings. Various factors determine the accumulation of the radiopharmaceutical in a lymph node, like type of tracer, size of the colloid particles if a radiocolloid is used and their surface features, size of the lymph node, metabolic activity of its macrophages, and lymph flow speed. The lymph flow speed fluctuates and depends on factors like physical exercise, time of day, medication, massaging of the injection site, and hydration state of the patient. As a result, radioactivity uptake in a lymph node to which the cancer drains is variable. In breast cancer patients, 95% of the SLNs are within an uptake range that varies from 0.001 to 2.5% of the injected radioactivity, and in melanoma patients this range is 0.06–3.6% [25]. Different surgeons used different sites for their background count reading to calculate the node-to-background ratio. Some surgeons obtained the background reading in the lymph node basin, and others used a location elsewhere in the body or even outside the body.

The SLN-to-non-SLN ratio was another parameter used to determine whether a lymph node is a SLN. This approach implies that one has to find a non-SLN first and then examine the other nodes with the probe to determine whether the designated count rate is reached. The node-to-hottest node ratio was yet another criterion. The approaches exploiting aspects of the radiopharmaceutical accumulation cannot be used in the 15–30% of the lymph nodes on a direct drainage pathway from a primary breast cancer that are not radioactive at all [26, 27]. One is left with the conclusion that the definition of a SLN cannot reliably be based on factors measurable with the gamma ray detection probe alone.

Some surgeons considered every lymph node that is stained blue to be a SLN. However, unlike the radioactive tracer, the blue dye is not retained by the macrophages in a lymph node. It just flows through and moves on to the next lymph node downstream. Rapidly, there will be a string of blue lymph nodes of which only the first one is directly at risk of containing tumor cells (Fig. 6.9).

In summary, all these alternative definitions may be correct most of the time, but they are not based on the physiol-

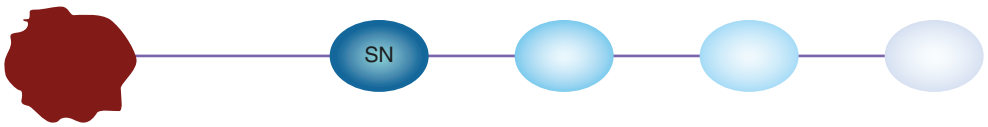

Fig. 6.9 Blue dye is not retained in the SLN. It flows through downstream and stains a string of subsequent-tier lymph nodes

ogy of lymph drainage, nor on the biology of the disease and they all have their flaws [16]. The SLN is not always the node closest to the tumor. The SLN is not just the node that is depicted first on the images, neither is it necessarily the most radioactive node, nor a radioactive node per se, nor is it always a node that is a certain number of times more radioactive or less radioactive than another node or compared to some other tissue. Not every SLN is blue, and not every blue node is a SLN.

In conclusion, the definition that a SLN is any lymph node that receives afferent lymphatic drainage directly from a primary tumor best reflects the route that the tumor cells travel and the concept of stepwise spread of cancer through the lymphatic system. However, this definition requires a meticulous technique of lymphoscintigraphy, a conscientious interpretation of the images, and a precise dissection of the afferent lymphatic ducts [28, 29]. In the occasional situation in which it is unclear whether a certain lymph node is a SLN or not, one should proceed and remove such a node.

Key Learning Points

- A SLN is best defined as any lymph node on the direct lymphatic drainage pathway from the primary tumor.
- SLNB calls for detailed lymphoscintigraphy to visualize the afferent lymphatics that identify SLNs and requires specific surgical expertise.
- A multitude of other definitions are used to simplify the procedure, but these are less accurate.

6.5 Concluding Remarks

Lymphatic mapping exploits the notion that cancer generally metastasizes first to lymph nodes and later on to distant sites. A lymph node that receives lymphatic drainage directly from the primary tumor is a SLN. SLNB was devised to identify the lymph nodes that are directly at risk and to assess whether these are involved in an early phase. A multitude of other definitions is used to simplify the procedure, but these are less accurate.

Lymphatic mapping requires a concerted effort from nuclear medicine physician, surgeon, and pathologist. Lymphoscintigraphy visualizes the afferent lymph vessel(s) and the lymph node(s) receiving lymph fluid from the lesion site and tells the surgeon where to look and how many nodes to expect. The surgeon visualizes the physiology of lymphatic drainage using a dye and exploits the radioactivity trapped in the node. The pathologist examines the node in detail.

The procedure provides prognostic information and enables more accurate staging, which guides further management. This improves the chance of survival in patients with nodal involvement from penile cancer or melanoma [30, 31]. The morbidity of the procedure is limited. Many patients with breast cancer or vulvar cancer are spared an unnecessary lymph node dissection and more patients are identified who may benefit from adjuvant systemic therapy. After description of its success in patients with these diseases, lymphatic mapping was quickly explored in other cancer types, as described in the subsequent chapters. One can conclude that lymphatic mapping with SLNB is one of the most interesting and important developments in clinical oncology in recent years and it fits in perfectly with the current trend for more individualized and conservative surgery in patients with cancer.

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