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# Patterns of lymphatic drainage after axillary node dissection impact arm lymphoedema severity: A review of animal and clinical imaging studies

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ABSTRACT

Upper extremity lymphoedema after axillary node dissection is an iatrogenic disease particularly associated with treatment for breast or skin cancer. Anatomical studies and lymphangiography in healthy subjects identified that axillary node dissection removes a segment of the lymphatic drainage pathway running from the upper limb to the sub-clavicular vein, creating a surgical break. It is reasonable to infer that different patterns of lymphatic drainage may occur in the upper limb following surgery and contribute to the various presentations of lymphoedema from none to severe.

Firstly, we reviewed animal imaging studies that investigated the repair of lymphatic drainage pathways from the limb after lymph node dissection. Secondly, we examined clinical imaging studies of lymphatic drainage pathways after axillary node dissection, including lymphangiography, lymphoscintigraphy and indocyanine green fluorescence lymphography. Finally, based on the gathered data, we devised a set of general principles for the restoration of lymphatic pathways after surgery.

Lymphoscintigraphy shows that restoration of the original lymphatic pathway to the axilla after its initial disruption by nodal dissection was not uncommon and may prevent lymphoedema. We found that regenerated lymphatic vessels and dermal backflow (the reflux of lymph to the skin) contributed to either restoration of the original pathway or rerouting of the lymphatic pathway to other regional nodes.

Variation in the lymphatic drainage pathway and the mechanisms of fluid drainage itself are the foundation of new lymphatic drainage patterns considered to be significant in determining the severity with which lymphoedema develops.

## 1. Introduction

Upper extremity lymphoedema after axillary node dissection is a well-known iatrogenic disease particularly associated with treatment for breast or skin cancers, including malignant melanoma [1,2]. Upper extremity lymphoedema causes debilitating symptoms such as heaviness, fatigue, discomfort and disfigurement. Lifelong lymphoedema causes not only physical disturbance but also psychosocial and economic issues [3,4].

The incidence of breast cancer-related lymphoedema (BCRL) is approximately 20% and is more than double this rate for patients who have axillary dissection followed by radiation therapy [5]. Sentinel node biopsy (SNB) causes less surgical damage to the lymphatics than axillary node dissection and therefore it was hoped it would minimize or eliminate BCRL. However, the long-term results of the SNAC-1 trial that randomly compared sentinel node biopsy (SNB) to axillary clearance found that while the frequency of any degree of upper extremity swelling was greater in the axillary dissection group (26%) than the SNB group (17%), BCRL remained an issue for the SNB group. On the other hand, marked lymphoedema, defined as > 20% difference in arm volume, occurred in 5.0% of patients in the dissection group and 1.7% in the SNB group—less than early published lymphoedema rates [6]. The incidence of BCRL will also change with the recent trend of de-escalation of loco-regional treatment as more patients with positive axillary nodes are now having neoadjuvant chemotherapy with current trials randomizing patients between axillary dissection, observation or radiation after a sentinel node biopsy and with improvements in radiation techniques [7,8].

*Abbreviations:* BCRL, Breast cancer-related lymphoedema; SNB, sentinel node biopsy; ARM, axillary reverse mapping; ICG, indocyanine green; SPECT, single-photon emission computerized tomography

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One possible reason for the failure of SNB in preventing BCRL may be the anatomical overlap or proximity of the arm and breast lymphatic drainage pathways. For instance, the axillary reverse mapping (ARM) technique was introduced to avoid impacting lymphatic drainage from the upper limb while not compromising breast cancer treatment [9]. Despite being an excellent surgical concept in theory, ARM was not successful in practice because crossover nodes in the arm and breast lymphatics were identified in up to 10% of cases [10]. Anatomical studies in a cadaver model and imaging study using lymphangiography in healthy subjects also confirmed the proximity of the lymph nodes draining from the arm and the breast [11–13].

The risk factors for BCRL have been assessed using multivariable regression analysis, with surgery, radiation treatment and obesity identified as the key contributors [1,14]. One crucial issue is the inability to predict which patients will develop lymphoedema before treatment, even though one in five will be affected. For example, when two patients receive both surgery and radiation to the axilla, it is unclear why one develops severe lymphoedema, while the other has a normal arm. Another issue is that lymphoedema varies in severity from localised mild disease to severe disease affecting the whole limb. To date, we haven't been successful in explaining the pathophysiology of lymphoedema to be able to address these problems.

Anatomical studies and lymphangiography in the healthy upper limb demonstrated a hierarchy of lymph nodes connected with lymphatic vessels in the axilla (Fig. 1) [11–13,15,16]. Axillary node dissection removes a segment of the lymphatic drainage pathway running from the upper limb to the subclavicular vein, creating a surgical break. It appears that the healing process enables the lymphatic system to restore lymphatic drainage from the affected limb; otherwise all patients undergoing axillary node dissection would suffer a blockage in lymphatic drainage and inevitably develop lymphoedema. Furthermore, although some authors have argued that not skeletonising the axillary vein may preserve some lymphatics, this does not explain why patients with SNB still develop lymphoedema and why rates of lymphoedema do not vary by the extent of an axillary dissection [6,17]. Thus, it is reasonable to infer, that the lymphatic drainage pathways repair themselves post-operatively in various ways and this can contribute to the various presentations of of lymphoedema from no lymphoedema through to severe disease.

In this study, we reviewed previous imaging studies of the lymphatic system in animal models and clinical studies to investigate the various patterns of lymphatic pathway repair after node dissection. We anticipated that understanding the repair process better would shed

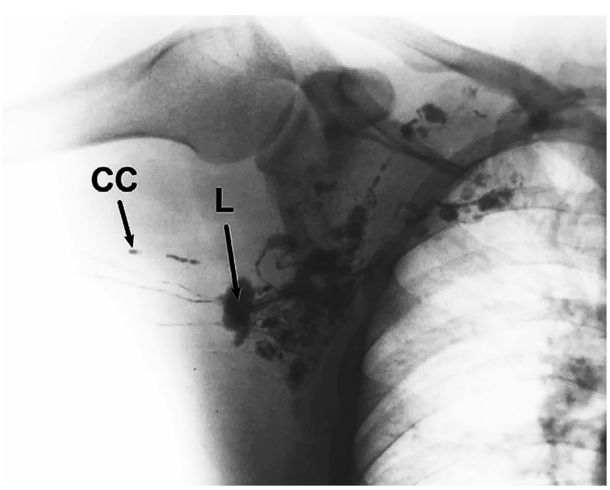


**Fig. 1.** Lymphangiography image in the axillary region in a normal subject. The lymphatic collectors from the upper limb connected to a larger lymph node in the lateral axillary region (L). The cranial collector (CC) ran to the lymph nodes in the proximal part of the axilla. (Reproduced from Ref. [13] with permission).

more light on the pathophysiology of secondary arm lymphoedema in terms of its underlying severity.

## 2. Materials and methods

Firstly, data were extracted from articles about animal experiments that investigated the repair of lymphatic drainage pathways from the limb after lymph node dissection. The animals used in these studies were mouse, rat, rabbit and canine subjects. We focused on post-operative lymphatic pathways to determine the location to which the afferent lymphatic vessels from the removed node reconnected and the drainage mechanisms that contributed to recanalization.

Secondly, we examined clinical imaging of patients after axillary node dissection and included information about lymphatic drainage pathways from the affected upper extremity. These imaging examinations included lymphangiography, lymphoscintigraphy and indocyanine green (ICG) fluorescence lymphography.

Finally, based on the gathered data, we devised a set of general principles for the restoration of lymphatic pathways after surgery. This paper discusses how these principles may aid understanding of lymphatic pathway patterns after axillary node dissection and postulates how these different patterns, as well as the lymphatic drainage mechanisms themselves, correlate with the severity of lymphoedema.

## 3. Results

### 3.1. Animal studies in post-node dissection

Recanalization of the lymphatic system after node dissection has been investigated using different animals. Furuta removed the popliteal node in rabbits and investigated lymph node regeneration in three different age groups: young, near-adult and adult [18]. He found that the lymphatic pathway was reconstructed in the surgical area, but concluded that regeneration of the lymph node was limited to the young and near-adult specimens and was negligible in adult rabbits. The excised lymph node did not regenerate in canine specimens or other rabbit studies [19–26]. This has led to the general acceptance that lymph nodes do not regenerate after surgical excision.

Surgical excision of the popliteal node was performed in different animal models with follow-up investigation of the post-operative lymphatic pathways. In all studies, the afferent lymphatic vessels reconnected to the other lymph nodes and new drainage pathways were established. Three types of change in the lymphatic system were identified:

1. the surgical break was filled with newly developed, “regenerated” lymphatic vessels [19–24];
2. the collateral lymphatic vessels re-routed to the inguinal lymph nodes, forming a new pathway (popliteal to inguinal to lumbar) not found in the healthy animal (popliteal directly to lumbar) [19,20,22,24] and
3. the collateral lymphatic vessels and dermal backflow, reflux of lymph to the lymph capillaries in the skin, contributed to rerouting of the pathway to the inguinal lymph nodes [19,24].

The author's (HS) group used a canine forelimb model to investigate changes in lymphatic pathways after surgical removal of the cervical and axillary nodes, the regional nodal sites of the forelimb. We found that collateral pathways crossed the front sagittal midline and connected to the contralateral cervical node [25,26] (Fig. 2, Supplemental video 1).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.suronc.2018.10.006.

These animal studies proved that lymphatic breaks created by lymph node dissection could be repaired with newly developed lymphatic vessels, resulting in restoration of the lymphatic pathway to a

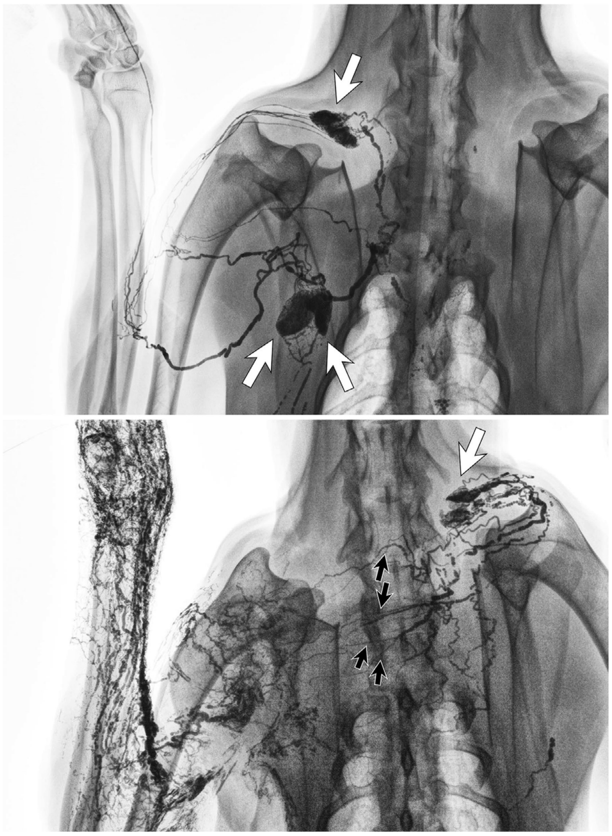

**Fig. 2.** Lymphangiography images of a canine before excision of the cervical and axillary lymph nodes (top: arrows) and six months after the lymph node dissection (bottom). The lymphatic vessels from the left forelimb crossed the sagittal midline and connected to the contralateral cervical lymph node (arrow) via regenerated lymphatic vessels (arrow heads) in the postoperative image. (Reproduced from Ref. [25] with permission).

second-tier lymph node. Collateral pathways that were not identified in the pre-operative image could be rerouted to the other regional lymph nodes. Dermal backflow also contributed to the rerouting of lymph fluid to the other nodes.

### 3.2. *Clinical studies in post-axillary node dissection*

Lymphatic pathways after axillary node dissection were investigated using different imaging examinations for patients with breast cancer or melanoma with or without lymphoedema symptoms.

#### 3.2.1. *Lymphangiography*

Lymphangiography was developed by Kinmonth in the 1950s and was useful for obtaining high-resolution radiographic images of the lymphatics [15,27]. Lymphangiography had been widely used to evaluate lymph node metastasis and lymphoedema. However, it fell out of favour in the 1980s because it was an invasive procedure requiring minor surgery to insert a cannula into a lymphatic vessel. Lymphangiography also risked worsening the lymphoedema and sometimes caused the potentially fatal side-effect of pulmonary embolism [28,29]. Despite several downsides, archival lymphangiography images are an excellent resource for demonstrating altered lymphatic pathways following axillary node dissection.

Lymphangiography in healthy subjects demonstrated that contrast media drained to the axillary nodes, without exception (Fig. 1) [13,15,30]. On the other hand, lymphatic pathways in the affected upper limb varied after axillary node dissection and included the original pathway to the axillary nodes, as well as lymphatic pathways to ipsilateral supraclavicular, internal mammary and contralateral axillary nodes (Fig. 3) [30–45].

The different patterns of lymphatic drainage pathway after axillary node dissection were reported as correlating with the severity of lymphoedema. Tsangaris et al. classified 27 patients who underwent a mastectomy and axillary node dissection into two groups based on the lymphangiographic images of lymph flow in the axilla: group 1 (lymph flow across the axilla) and group 2 (no lymph flow across the axilla or delayed lymph flow) [42]. Despite having had axillary node dissection, 22 patients (81.5%) were categorised into group 1 where the drainage pathway from the affected limbs was to the ipsilateral axillary nodes. All five patients (18.5%) in group 2 had clinically significant lymphoedema and two showed remote lymphatic drainage to the contralateral axillary nodes.

Abe performed lymphangiography for 19 patients with BCRL after axillary dissection [43]. Eighteen patients whose lymphatic vessels could be successfully visualised were categorised into 3 groups according to the lymphatic pathway in the axilla: type 1 (crossing: 13,

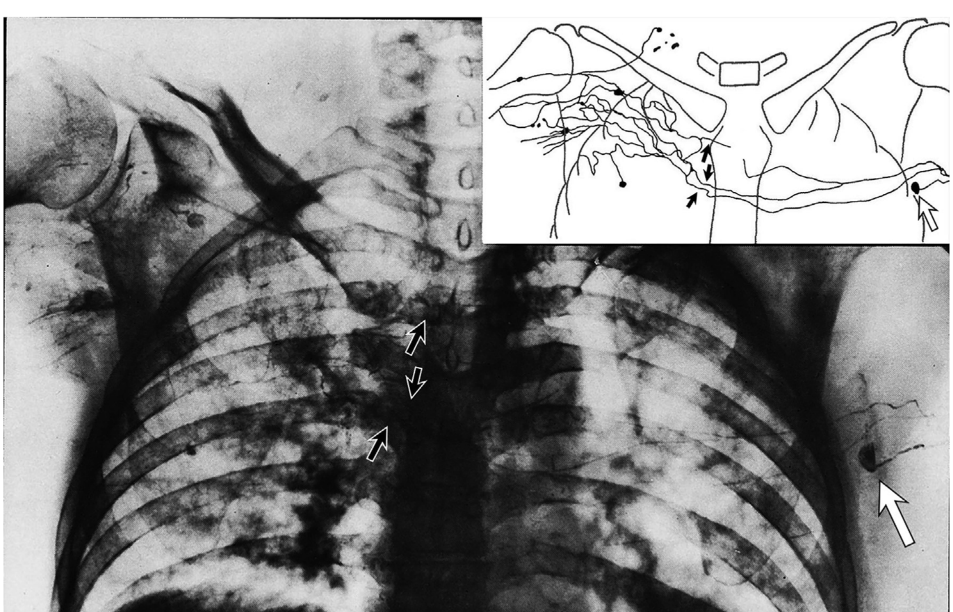

**Fig. 3.** Lymphangiography image of a patient after axillary node dissection for breast cancer. The lymphatic vessels from the right upper extremity crossed the axilla via regenerated vessels (black). The lymphatic vessels crossed the sagittal midline and connected to the contralateral axillary lymph node (white). (Reproduced from Ref. [40] with permission).

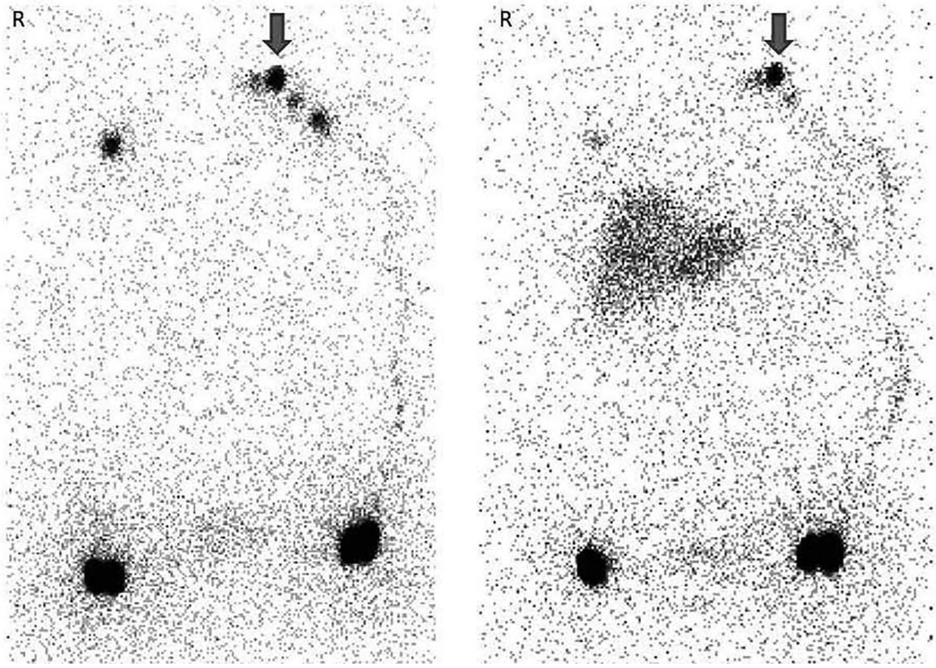


**Fig. 4.** Lymphoscintigraphy images before (left) and after (right) axillary node dissection on the left side. Lymph nodes on the operated side are in the same location (arrow) and loss of the distal nodes after dissection could be due to the operation. (Reproduced from Ref. [52] with permission).

72.2%), type 2 (collateral: 3, 16.7%), and type 3 (blocking: 2, 11.1%). For type 1 patients, the lymphatics followed their usual path through the axilla. For type 2 patients the lymphatic flow stopped at the axilla, but collateral flows were evident towards the shoulder or lateral chest-wall. In type 3, only stasis of the contrast medium at the axilla was revealed. The lymphoedema symptoms for each type correlated with mild, moderate and severe disease respectively. Abe concluded that the occurrence of BCRL was primarily dependent on the degree to which the lymphatic pathway in the axilla had been restored.

Dermal backflow occurred when the superficial lymphatic vessels were obstructed and the radio-contrast media refluxed from the lymphatic vessels to the lymphatic capillaries in the skin. Dermal backflow is one of the diagnostic imaging criteria for lymphatic congestion and is observed specifically in lymphoedematous limbs. Dermal backflow formed a bridge between the blocked lymphatic vessels and the patent lymphatic vessels and contributed to the formation of collateral pathways [37,44,45].

### 3.2.2. Lymphoscintigraphy studies

Developed in the 1950s, lymphoscintigraphy is the current imaging gold standard for lymphoedema diagnosis, particularly because it is less invasive than lymphangiography [46–49]. Lymphoscintigraphy identifies lymphoedema by tracking the movement of the radiotracer with a sequential scan that establishes the presence of regional lymph nodes and/or dermal backflow by comparing the images of the affected and unaffected limbs. While it is a versatile technique for diagnosing lymphoedema, lymphoscintigraphy is not without problems, because the tracer moves slower than in lymphangiography and ICG fluorescence lymphography and may not reach the regional lymph node during the limited scanning period. Further, lymphoscintigraphy produces low-resolution images without anatomical landmarks, which makes it difficult to document the exact anatomical position of the lymphatics unless a single-photon emission computerized tomography (SPECT) scan is also used [50].

The lymphatic status in the upper limb after axillary clearance has been investigated using lymphoscintigraphy. Bourgeois et al. studied 313 patients with breast cancer who underwent a radical mastectomy with an axillary node dissection [51]. They found that there was a total absence of visualization of the axillary nodes in 35.8% of patients. Szuba compared pre- and post-operative lymphoscintigraphic images of 30 patients with breast cancer who underwent an axillary dissection. He reported that 86.7% of patients had axillary nodes present after surgery (Fig. 4) [52]. These studies suggest that lymphatic drainage along the original route to the ipsilateral axillary nodes was re-established in most cases.

### 3.2.3. Indocyanine green (ICG) fluorescence lymphography

The technique of ICG fluorescence lymphography was initially developed to identify the sentinel nodes for breast cancer treatment and was later applied to lymphoedema assessment [53–55]. ICG lymphography has been used to diagnose lymphoedema and assist in lymphovenous anastomosis and lymph node transfer surgeries to locate the lymphatic vessels and nodes [57,58]. Compared to lymphangiography and lymphoscintigraphy, ICG lymphography has the advantage of performing lymphatic imaging without radiation. ICG is a water-soluble, low-viscous solution that moves faster than the radiotracer used in lymphoscintigraphy. Lymphatic vessels and dermal backflow can be observed in real time. The limitation of ICG lymphography is that only lymphatics within a 1–2 cm depth from the skin surface can be detected by the near infrared imaging system [53,54].

ICG lymphography has also been used for staging lymphoedema by means of the amount or quality of dermal backflow identified in the limbs [56–58]. The area of dermal backflow aids understanding of the pathological condition of the underlying lymphatic vessels [59]. For patients with lymphoedema, dermal backflow was present over the obstructed lymphatic vessels and extended to connect to patent lymphatic vessels. Tashiro and at el. identified collateral pathways to the supraclavicular lymph node in breast cancer patients after axillary node dissection [60]. Our clinical experience has revealed that ICG lymphography is useful for imaging assessment of BCRL by revealing lymphatic drainage pathways and the mechanisms of lymphatic fluid drainage, either lymphatic vessels or dermal backflow. (Fig. 5, Supplemental video 2, 3 and 4).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.suronc.2018.10.006.

Fig. 5. Indocyanine green (ICG) fluorescence lymphography images of the patients after axillary node dissection. ICG was injected into points on the medial wrist (black) and flow direction is indicated in white. ICG was carried through the lymphatic vessel (top), or a mixture of lymphatic vessel and dermal backflow (middle, bottom). The ICG drained to the parasternal region (top, bottom) and the supraclavicular region (middle). Of note, the direction of flow in the lymphatic vessel in the front chest (top, bottom) was opposite to the normal pathway. Each patient's image can be viewed in the Supplemental Video 2 (top), 3 (middle) and 4 (bottom).

## 4. Discussion

A better understanding of normal lymphatic anatomy is essential to identify post-operative changes of lymphatic drainage pathways by providing a basis for comparison. Anatomical studies in a human cadaver model and lymphangiography in healthy subjects indicate that the superficial lymphatics in the upper limb drain to two regional lymphatic basins: the axillary nodes and the supraclavicular nodes (Fig. 6A) [61–65]. The axillary nodes, which are involved dominantly with the lymph drainage from the upper extremity, are lateral (brachial), central and apical nodes usually referred to as level 1 to 3 respectively in oncology [66].

Anatomically, the lateral nodes in the axilla are where the axillary lymphatic cascade in the upper limb starts. There are two optional pathways that may bypass the lateral lymph nodes. The lateral lymphatic pathway runs along the cephalic vein and connects directly to the supraclavicular node [16,62,64,65]. A part of the medial lymphatic vessel occasionally passes the supratrochlear node at the elbow, merges with the deep lymphatic vessel along the brachial artery and connects to the central lymph nodes in the axilla [16,65]. These pathways may work as collateral drainage pathways when the medial pathway is interrupted, or the lateral axillary nodes only are removed, as in a level 1 dissection.

The animal imaging studies proved that lymphatic pathways could change after node dissection and afferent lymphatic vessels of the removed lymph node could reconnect to the second-tier lymph nodes in the same region via regenerated lymphatic vessels, or to other regional nodes via regenerated lymphatic vessels and/or dermal backflow [19–26].

It is reasonable to consider that the lymphatics may also regenerate themselves for patients with breast cancer after axillary node dissection. Lymphoscintigraphy revealed hot nodes in the axilla in more than half the cases and lymphangiography demonstrated that the lymphatic channels in the affected limb could reconnect to residual axillary nodes. The lymphatic system must possess the capability to regenerate itself by filling the surgical break and repairing the original drainage pathway to the ipsilateral axilla [31–38,51,52].

Lymphoscintigraphy and lymphangiography in both animals and humans demonstrated collateral vessels leading to the contralateral nodes (Figs. 2 and 3, Supplemental video 1) [25,26,39,40]. When patients underwent an axillary node dissection, lymphatic vessels were affected not only in the upper limb, but also in the ipsilateral anterior chest, because the axillary nodes are the dominant lymphatic basin in the whole forequarter region [12,16,61,67,68]. For example, acute or chronic breast oedema is identified following breast cancer treatment [69,70]. The sagittal midline is the watershed of the lymphatic system. The dermal lymphatic capillaries can be identified around the midline, but lymphatic vessels in the subcutaneous fat layer are absent [16,67,68]. Lymphangiography studies in canine and human subjects after lymph node dissection demonstrated that the lymphatic vessels crossed the front midline horizontally and connected to the contralateral cervical and axillary lymph nodes respectively [24,25,40]. The lymphatic vessels have valvular structures at 2–3 mm intervals that regulate one-way flow. The horizontal vessels carried lymph fluid in the opposite direction in the ipsilateral chest from the surgery site to the front midline (Figs. 2 and 3, Supplemental video 1). They crossed the sagittal midline where normally there are no lymphatic vessels present. These facts suggest that either a segment of, or an entire horizontal lymphatic vessel, was regenerated post-operatively to form the collateral pathway to the contralateral nodes.

Tsangaris and Abe postulated that the type of post-operative lymphatics in the axilla could determine the severity of lymphoedema [42,43]. This seems a reasonable proposition because re-establishment of the original pathway to the ipsilateral axilla may provide less resistance than collateral routes connecting to distant lymph nodes. We propose that the mechanism of lymph fluid drainage is an additional factor in determining the degree of lymphoedema. In this review, three types of rerouting were identified that enabled the afferent lymph vessels of the removed lymph nodes to connect to the other regional lymph nodes, via either the regenerated lymphatic vessels or dermal backflow, or a combination. The lymphatic capillaries contributing to the dermal backflow are smaller than the lymphatic vessel and lymphoedema may manifest itself more severely if the dermal backflow interferes with the reconstructed drainage pathway. The variety of post-operative lymphatic pathways from the affected upper limb is summarised from the reviewed data and illustrated schematically in Fig. 6.

The use of imaging to detect post-operative lymphatic pathways has potential clinical applications. For example, it enables us to screen patients predisposed to lymphoedema in the subclinical condition. Akita et al. investigated breast cancer patients using ICG lymphography before and at regular intervals after sentinel node biopsy or axillary node dissection [71]. Qualitative evaluation was applied to categorise the lymphatic imaging patterns into 5 types ranging from normal to an advanced condition. An abnormal lymphatic pattern was identified in

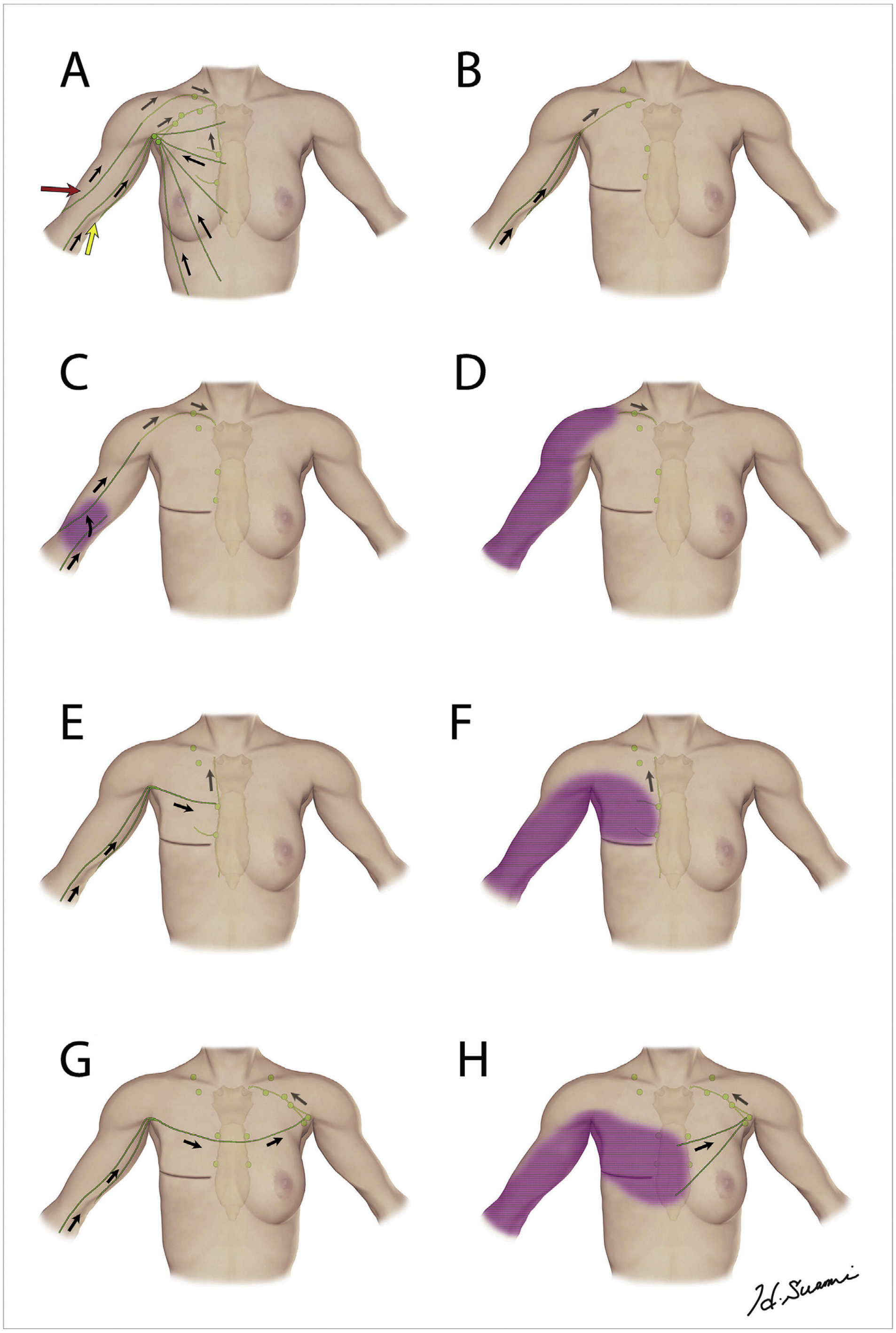


**Fig. 6.** Schematic diagram in the forequarter representing the lymphatic pathway variation from the upper extremity after axillary node dissection as summarised from the reviewed data. Flow direction is indicated in black. The normal lymphatics in the upper limb drain to the supraclavicular lymph nodes (red) and the axillary lymph nodes (yellow) as a control (A). The drainage pathways are to the ipsilateral axillary (B), supraclavicular (C,D), internal mammary (E,F), and contralateral axillary nodes (G,H). Lymph fluid could be carried by regenerated lymphatic vessels (B,E,G), the lateral pathway (C) or dermal backflow (D,F,H).

25.5% of affected upper extremities and clinical lymphoedema requiring compression therapy was found in 17.9% of the upper extremities in this population. This study succeeded in ruling out lymphoedema in 74.5% of post-axillary surgery subjects because no abnormalities were identified in the upper extremities at the initial one-month post-operative examination.

Manual lymphatic drainage (MLD) has long been the mainstay of conservative lymphoedema treatment [72]. Identification of post-operatively altered drainage pathways may help refine and improve current massage techniques. The principle of MLD is to decongest lymph fluid in an oedematous region by shifting excess fluid to non-congested areas. Imaging examinations can illustrate in which direction the fluid should be moved using a personalized MLD approach.

Lymphoscintigraphy is the current gold standard for imaging the lymphatic system and ICG fluorescence lymphography is a new imaging tool to assess the lymphatic system. The two examinations are complementary, with each having its own advantages and disadvantages. There have been rapid advancements in diagnostic imaging of the lymphatics. The MR lymphography technique has been used to attempt to visualise the lymphatic vessels with and without contrast media, a procedure similar to, but less invasive than, lymphangiography [73–75]. With the potential for more detailed lymphatic imaging in the future, a knowledge of both normal lymphatic anatomy and post-operative changes is essential to better understand the pathophysiology of lymphoedema for each individual patient.

## 5. Conclusion

We reviewed lymphatic pathways from the affected limb after node dissection in animal and clinical imaging studies. Regeneration of lymphatics with repair of the original pathway to the axilla was not uncommon after an axillary dissection and this may contribute to the prevention of lymphoedema. Various collateral drainage pathways were identified using lymphangiography and ICG fluorescence lymphography. Three types of rerouting were identified, one via regenerated lymphatic vessels, the other via dermal backflow or both mechanisms. Different drainage pathways and the drainage mechanisms themselves are significant factors in predicting the severity of lymphoedema after an axillary dissection.

## Conflicts of interest

The authors have nothing to disclose.

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