In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma

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CHAPTER 7

Lymphatic drainage patterns in breast cancer patients who previously underwent mantle field radiation

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Abstract

Introduction: Lymphatic drainage patterns from the breast have been described in the past. Drainage may change after radiation of a breast or its regional lymph node basins and this may have implications for lymphatic mapping afterwards. The aim of this study was to determine the lymphatic drainage patterns in breast cancer patients with a previously radiation breast and lymph node regions.

Methods: Between January 1999 and November 2008, 22 sentinel node procedures were performed in breast cancer patients who had undergone mantle field radiation due to Hodgkin’s lymphoma. Lymphatic drainage patterns were analyzed based on pre-operative lymphoscintigraphy and sentinel lymph node biopsy. The results were compared to the drainage patterns in patients without previous breast procedures.

Results: Sentinel nodes were found in the axilla in 19 patients (86%) and nine patients (41%) also had drainage towards extra-axillary regions. Sentinel nodes were more often found outside the axilla compared to the patients in our earlier study (33%, p=0.04), and the non-identification rate was also higher (14% versus 3%, p=0.01). Five patients (23%) had involved sentinel nodes. These were harvested from the internal mammary chain in two of them. No lymph node recurrences were observed during a median follow-up time of 49 months.

Conclusion: Lymphatic mapping is feasible and yields a lymph node in 86% of the breast cancer patients after previous mantle field radiotherapy for Hodgkin’s lymphoma. Non-visualization and extra-axillary nodes are more frequently encountered than in patients without a history of mantle field radiation. The finding of involved nodes suggests that sentinel node biopsy improves staging. Long-term follow-up will determine the sensitivity of the procedure in this specific situation.
Introduction

Studies of long-term survivors after treatment for Hodgkin’s lymphoma have shown an increased risk of secondary cancers.1-4 In particular, there is an increased risk of breast cancer in female patients who have been treated with a mantle field radiation or similar radiation fields to supra-diaphragmatic lymph node regions with partial exposure of breast tissue.5-8 It is estimated that 90% of all breast cancers developing after radiotherapy for Hodgkin’s lymphoma can be attributed to the previous irradiation.1,3,9 Awareness of the relatively high risk of breast cancer in Hodgkin’s lymphoma survivors has led to screening with mammography or magnetic resonance imaging (MRI) in follow-up protocols.

Radiation can influence microvasculature and damage the capillary network which manifests itself as telangiectatic vessels that increase over time.10 Studies have shown that repair of damaged endothelium by angiogenesis is inhibited by the radiation.11 A similar damage and aberrant repair may occur in lymphatic micro-vessels. We hypothesize that damage to the lymphatic micro-vessels may perturb the drainage pattern in the irradiated breast and in its regional lymph node basins. This may have consequences for the lymphatic drainage pattern from a breast tumour and therefore for sentinel node detection. This procedure, although not yet part of standard management in this patient group, has been performed in our institution during the last decade.

The aim of this study was to determine the lymphatic drainage routes from the breast to the axillary and extra-axillary lymph nodes, based on results of lymphatic mapping and sentinel node biopsy, in patients who have previously undergone mantle field radiation due to Hodgkin’s lymphoma. The results were compared to the drainage patterns in patients without previous treatment of the breast, which have been studied at our institution in the recent past.12

Patients and methods

The study population consisted of 22 breast cancer patients who had undergone mantle field radiation for Hodgkin’s lymphoma, which is 1.0% of the 2,154 breast cancer patients who underwent sentinel node biopsy between January 1999 and November 2008. The median age of the patients was 51 years (range 31-67 years). All patients had received mantle field radiation to the neck, the axilla and the mediastinum, overlapping part of the breast. The lymphatic regions in the neck, axilla and mediastinum received a prescribed radiation dose of 36 - 40 Gy.9 About 4 Gy was directed to the area under the shielding blocks over the lungs (figure 1). The medial and upper outer quadrants of the breast are exposed to a dose ranging from 36 to 40 Gy.
Pathological proof of breast cancer was obtained in all patients. The median disease-free interval between the mantle field radiation and breast surgery was 270 months.

Figure 1: Mantle field radiation markings on the skin of a patient showing the extent of the exposed breast tissue.⁹

Figure 2: Simulator film of a mantle field irradiation from 1974 (not the same patient as in figure 1).
BC: position of the subsequent breast cancer developing in 2002 in the axillary part of the field that includes the upper outer quadrant of the right breast.
with a range of 61 to 390 months. Six of the 22 patients received wide-local excision and sentinel node biopsy and sixteen patients mastectomy with sentinel node biopsy. Sixteen patients (73%) had their breast tumour in the upper outer quadrant, an example of such a tumour is shown in figure 2.

A two-day protocol was used for the sentinel node procedure. On the first day, an intratumoural injection of 120 MBq technetium-99m nanocolloid (Nanocoll®, GE-Healthcare, Eindhoven, the Netherlands) was given in a volume of 0.2 ml. Static images were obtained at ten minutes, two hours and four hours after radiotracer administration. A dual-head gamma camera equipped with low-energy high-resolution collimators (Vertex®, Philips, Eindhoven, the Netherlands) was used for imaging. Both anterior and lateral images were routinely obtained and additional images if needed. A cobalt-57 flood source was placed behind the patient to outline the body contour. A sentinel node was defined as a lymph node upon which the primary tumour drains directly.13

Single photon emission computed tomography with CT scanning (SPECT/CT) was introduced in December 2006 and was performed when conventional images failed to visualize a sentinel node in the axilla.14 SPECT/CT was performed immediately after the four-hour conventional images using a hybrid system (Symbia T, Siemens, Erlangen, Germany) without re-injection of the radiopharmaceutical. After correction for attenuation and scatter, fused SPECT/CT images were generated and displayed in both two- and three-dimensional projections for anatomical localization of sentinel nodes and surrounding tissues. The location of a sentinel node was marked on the skin with indelible ink. A second dosage of the radiopharmaceutical was given in case of non-visualization and conventional lymphoscintigraphy was repeated.

The next day, 1 ml patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was administered in the breast cancer immediately before the operation. Sentinel nodes were pursued in the axilla and in all other regions indicated by lymphoscintigraphy. All harvested lymph nodes were fixed in formalin, bisected, embedded in paraffin, and cut at a minimum of six levels at 50 to 150 μm intervals. Pathological evaluation included haematoxylin-eosin and immunohistochemical staining (CAM 5.2; Becton Dickinson, San Jose, CA, USA). Axillary node dissection was only performed if an involved sentinel node was found in the axilla.

The patients were followed at our own institution with particular attention to the lymph node fields, using ultrasound if necessary. The median follow-up duration was 49 months (range 1-99 months).

Patient characteristics, lymphoscintigraphy results and operative findings outcome were recorded prospectively. The lymphatic drainage patterns were compared to the drainage patterns in patients without previous treatment of the breast (figure 3).

The Chi-square test or the Fisher exact test was performed to evaluate differences in drainage between various patient groups. Statistical analyses were performed in SPSS 15 (Version 15, for Windows, SPSS Inc, Chicago, IL, USA).
Table 1. Lymphatic drainage patterns in the 22 patients with a previously radiated breast.

<table>
<thead>
<tr>
<th>Drainage pattern</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Non-identification</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Axilla only</td>
<td>10 (45)</td>
</tr>
<tr>
<td>Axillary and elsewhere</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Axilla and internal mammary chain</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Axilla and supraclavicular fossa</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Axilla and breast</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Axilla, internal mammary chain and breast</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Axilla, internal mammary chain and interpectoral fossa</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>22 (100%)</td>
</tr>
</tbody>
</table>

Results

Preoperative lymphoscintigraphy revealed 35 sentinel nodes in 19 of the 22 patients (86%). All visualized sentinel nodes were intraoperatively harvested. Surgical exploration of the axilla using blue dye and the gamma ray detection probe yielded two additional blue and radioactive sentinel nodes in two patients who only had internal mammary chain sentinel nodes on the preoperative lymphoscintigram. Axillary exploration did not reveal a sentinel node in three patients without a visualized node on the lymphoscintigrams and, these patients underwent direct axillary dissection. Ultimately, a mean of 1.7 sentinel nodes were identified per patient with a range of zero to four.

Sentinel nodes were found in the axilla in 19 patients (86%) and elsewhere in nine patients (41%) (table 1 and figure 4). This latter percentage is higher than the 33% in the patients in our earlier study in whom no previous treatment of the breast and surrounding lymph node regions had been carried out (p= 0.04), and the non-identification rate was also higher (14% versus 3%, p= 0.01).12
Figure 3. Lymphatic drainage pattern of 700 primary breast cancer patients, calculated from the results of a previous study.12 (Legend figure 1, chapter six)

Figure 4. Location and incidence of sentinel nodes after previous mantle field radiation.
Five patients had sentinel node involvement (23%). In three patients, the positive sentinel node was harvested from the axilla and prompted completion dissection. Two patients had both a positive axillary sentinel node that had not been visualized on the preoperative images and an involved internal mammary chain node. These patients received axillary node dissection, but radiotherapy to the internal mammary chain region was omitted since further radiation would exceed the tolerance of underlying normal tissues such as the heart. No lymph node metastases were found in three patients with persisting non-visualization who received axillary clearance. No lymph node recurrences were detected in or outside the axillae during follow-up.

**Discussion**

This study describes the lymphatic drainage pattern in 22 Hodgkin’s lymphoma patients who had received mantle field radiation and developed breast cancer afterwards. A series including a similar number of such patients who were subjected to sentinel node biopsy has not been published before. The sentinel node detection rate was 86% using lymphoscintigraphy and intraoperative exploration with the help of blue dye and the gamma-ray detection probe. This percentage is somewhat less than in previously untreated breast cancer patients (96.9%), and the percentage of non-visualization was higher (14% versus 3%). These findings show that sentinel node biopsy is feasible in these patients but that not all sentinel nodes may have been detected. The 41% incidence of drainage to nodes outside the axilla was also more than the 33% in formerly untreated patients. The rather high incidence of internal mammary chain sentinel nodes (32%) is remarkable since the previous radiation was directed to the mediastinum including these nodes that had therefore received the full dose of 36-40 Gy.

The 23% of patients with involved nodes is comparable to the rate in untreated patients (26-32%). This suggest that sentinel node biopsy was accurate. Radiotherapy could not be given to the internal mammary chain in the two patients with involved nodes in this region, due to the previous mantle field irradiation. An involved extra-axillary sentinel node may lead to subsequent systemic treatment, even if this would not have been applied based on the aspects of the primary tumour. Two axillary sentinel nodes that were not visualized on the preoperative images but were harvested using blue dye and the gamma-ray detection probe harbored metastases. It is likely that the extensive tumour growth in these nodes prevented the accumulation of sufficient radioactivity to be picked up by the imaging technique. This finding not necessarily indicates that sentinel node biopsy is unreliable in previously radiated breast cancer patients, but it emphasizes the importance of the exploring the axilla anyway and demonstrates the sensitivity of the intraoperative tools.

No lymph node recurrences were detected in a median follow-up time of 49 months. This is a satisfying follow-up duration, although the risk of nodal recurrences is likely...
to persist. The median time between the mantle field radiotherapy and the breast cancer surgery was 23 years. It has been described that the risk of radiation-induced breast cancer begins to increase ten years after the radiation exposure. After fifteen years, the standardized incidence ratio is at its peak. This state of augmented risk seems to remain high until at least 30 years following the mantle field radiation. The highest risk is observed in patients who were under twenty years of age at the time of radiation treatment. Patients who have not been treated with chemotherapy are also more at risk. This observation can be related to the influence of premature menopause induction by gonadotoxich chemotherapy, which reduces the breast cancer risk. The degree of damage that is caused by radiation of the blood vessels and presumably the lymph vessels is dependent on the dose of radiation per fraction and the total dose, although there is a considerable inter-patient variation. The hypothesis that this damage causes an alteration of the lymphatic drainage pattern appears to be correct, given the differences between the patterns in radiated and not radiated breast cancer patients. But it is uncertain whether this change in the lymphatic pathways means that sentinel node biopsy is a less accurate staging tool in these patients. The percentage of tumour-positive sentinel nodes that were detected and the absence of lymph node recurrences account for at least some evidence of its sensitivity. It can be hypothesized that the lymphovascular damage is already established by the time the breast cancer develops, so that the sentinel node procedure is able to show the actual route that detached tumour cells travel. This is in contrast to breast cancer patients who had undergone recent surgical treatment of the breast, as has been shown by a study of patients who were subjected to lymphatic mapping before and shortly after excision of a breast lesion resulting in a different drainage pattern in 68% of the patients. We conclude that, compared to untreated breasts, lymph drainage from cancer in patients who received mantle field radiation many years previously occurs less often to the axilla and more often to nodes elsewhere. A sentinel node can be identified in 86% of these patients. Pursuing extra-axillary sentinel nodes improves staging. Sentinel node biopsy is feasible in these patients and seems reliable. Definite conclusions on the sensitivity of the procedure require a larger study population and longer follow-up.
References


