Clinical relevance and refinement of the sentinel node procedure in breast cancer and melanoma
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Citation for published version (APA):

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LYMPHATIC MAPPING WITH TRACER ADMINISTRATION INTO THE PRIMARY BREAST CANCER

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INTRODUCTION

Various aspects of the tracers used to find the sentinel node in breast cancer patients are controversial. Different tracers are used on different continents. Other elements of debate concern the injection volume, radioactivity dose, colloid characteristics and particularly the site of injection. Investigators debating the injection site can loosely be divided into two camps: those who advocate a superficial injection site, such as the subareolar lymphatic plexus, the subdermal plane or the skin of the breast, and those who prefer a deep tracer administration in or around the primary tumor. A superficial injection technique is felt to more often visualize lymphatic channels and lymph nodes whereas a deep tracer administration better reflects the actual drainage pattern of the primary cancer.

DEVELOPMENT OF THE INTRA-TUMORAL INJECTION TECHNIQUE

At The Netherlands Cancer Institute, tracers are injected into the tumor using a 25 Gauge needle (Figure 1). The $^{99m}$Tc-nanocolloid (Nanocoll$^\text{TM}$, Amersham Cygne, Eindhoven, the Netherlands) is deposited as a bolus and patent blue dye (Blue Patenté V, Laboratoire Guerbet, Aulnay-sous-Bois, France) is distributed over the tumor. Over the past years, we have encountered numerous surgeons and nuclear medicine physicians who failed to understand this approach or even expressed outright concerns over its ethical acceptability. Several manuscripts describing our work have been rejected for publication solely because of the intralosomal injection technique. In the present paper, the reasons for adopting the intratumoral injection technique are described, and its advantages and disadvantages are discussed.

At The Netherlands Cancer Institute, lymphatic mapping in breast cancer was begun shortly after Morton's original description of this approach in melanoma. Application of the lymphatic mapping in breast cancer had not been described or even suggested in the literature. The technique had to be developed from scratch. It was felt best to inject the tracers into the primary breast cancer because drainage from the very lesion was what we were interested in. It was feared that lymphatic watersheds might exist in the breast and that various parts of the breast might drain to different lymph nodes. We wanted the tracers to travel the exact same route as the disseminating tumor cells. A small volume of 0.2 ml was chosen for the radioactive tracer to disturb the normal physiology of lymph drainage as little as possible. A dose of 1 ml of blue dye was chosen in analogy to Morton’s technique in melanoma. A breast cancer can be small and scirrhouss but leakage of tracer from the tumor was thought to be without unfavorable consequences as long as the fluid would not diffuse beyond the immediate vicinity and would not cross a lymphatic watershed.

SAFETY OF INTRA-TUMORAL INJECTION

Animal experiments have shown that massaging of the tumor increases the risk of lung distant metastases. This knowledge made us initially wonder whether intralosomal injection would force tumor cells into the blood stream with the same deleterious outcome. These fears were resolved when we noticed how the pathologist performs some twenty passes through a breast cancer for fine needle aspiration cytology. The true-cut needle technique (Allegiance Health Care Corporation, McGaw Park, IL, USA) is even more traumatizing. Also, the average breast cancer is present for five to ten years before it is diagnosed. Tumor cells detach from the primary lesion all the time. The rate of tumor cell shedding has been measured in rat mammary carcinomas and was found to be 3.2 million cells per 24 hours per gram tumor tissue. There is
no evidence that an injection into a tumor is enough to release additional cells into the circulation. These observations make one appreciate that, if it were true that extra cells are to enter the blood stream because of the intralesional injection, their numbers are unlikely to have a measurable impact on the prognosis. Virtually all tumor cells that are shed from a solid tumor solely as a consequence of manipulation are ephemeral. The notion that such cells may give rise to clinically relevant metastases represents an oversimplification of the complex sequence of steps that are required of metastatic tumor cells.

**Scientific Justification**

Frequently asked questions are whether there are lymphatic vessels present in a tumor and whether a tracer drains from a tumor. Yes, there are and yes it does: a sentinel node was identified in all of our last 50 patients.

A research program was developed leading to stepwise incorporation of sentinel node biopsy into practical clinical management. Patients scheduled to undergo a mastectomy were studied first. Patent blue dye was injected into the breast cancer when the patient was on the operating table. Mastectomy was performed while at the same time the dye was taken up by the lymphatic system and flowed to the regional nodes. The specimen was taken to the Department of Pathology and there it was dissected. The tumor was found to be stained blue as intended. A blue stained lymphatic channel running to the axillary tissue was identified and such a channel was carefully dissected until it drained into a blue stained lymph node. Thirty patients were studied in this fashion. A tumor-positive sentinel node was found in ten patients. In six of these patients, the sentinel node was the only tumor-positive node. There were no false negative cases. This study demonstrated the sequential nature of lymphatic dissemination.

Sentinel node biopsy with intratumoral injection of the tracers was followed by completion axillary node dissection in a subsequent study of 136 patients. Both sentinel node and other axillary nodes were examined by immunohistochemistry staining. A sentinel node was identified in 126 patients (93%). Three sentinel node biopsies were false negative (sensitivity 95%). The particle concentration and radioactivity dose were modified to improve the results. Based on these results, routine axillary node dissection was abandoned. Since then, 531 patients underwent lymphatic mapping with intratumoral injection of the tracers. A sentinel node was identified in 516 (97%), with a false-negative rate of 3.1%.

**Figure 1.** The tracer fluid is injected into the primary lesion site.
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ADVANTAGES

Administration of tracers into the primary breast cancer has several advantages. On average, a mere 0.16% of the injected dose ends up in the sentinel node. Some 95% of the radioactivity dose remains at the injection site. The ensuing large number of scattered gamma rays from the injection site may overshadow the far smaller number of counts emitted from the sentinel node, preventing its detection with the gamma ray probe. An advantage of injecting a small volume into the tumor is that lumpectomy will remove this radioactivity at the injection site facilitating recovery of the sentinel node. Removal of the collimator increases the sensitivity of the probe considerably and makes the procedure even easier.

An interesting observation is that intratumoral and peritumoral injections visualize sentinel nodes outside the axilla. Such nodes are not seen after superficial tracer administration. Extra-axillary nodes are present in up to 27% of the patients. Retrieving these nodes led to a change in the management of 17% of our patients.

In patients with non-palpable breast cancer, intralesional tracer administration enables not only sentinel node retrieval but also simultaneous probe-guided excision of the primary lesion. In fact, better margins are obtained with this approach as compared to wire-guided excision.

CONCLUSIONS

We submit that the intratumoral route of tracer administration has been carefully researched and makes sense from theoretical and practical point of view. The sentinel node identification rate is 97% with intralesional tracer administration, which is similar to the results obtained with other routes of administration. Randomized studies have not been done. It is too early to tell how the sensitivities of the various approaches compare. Long-term follow up of patients with a tumor-free sentinel node and without axillary node dissection will provide us with that information.

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