

EDITORIAL

**CHROMOLYMPHOGRAPHY, LYMPH NODE
SURGERY AND DETECTION OF LYMPH NODE METASTASES:
CURRENT STATE AND FUTURE**

The clinical value of chromolymphography needs to be updated as little activity in this area has been noted in recent years (see *Commentary* by Chernomorsky, S). After the introduction of computer tomography, the indications for chromolymphography, like diagnostic conventional oil contrast lymphography, for visualizing regional lymph nodes decreased rapidly. However, experience with computer tomography and subsequently with magnetic resonance imaging has shown that lymph nodal metastases without marked lymphadenopathy can be missed by these computed imaging methods. Although oil contrast lymphography may delineate the intranodal architecture and therefore the likelihood of metastases with equivocal computerized scans, its cumbersomeness (involving a cut-down in lymphatic cannulation) and side effects (e.g., oil embolism to the lungs) makes its resurgence as a diagnostic tool problematic. Chromolymphography using chlorophyll and Lipiodol to color lymph nodes never achieved popularity, having similar drawbacks of conventional lymphography, the impurity of the chlorophyll, and the fact that tissues saturated with chlorophyll as opposed to black or blue dyes were difficult to delineate from surrounding structures. Accordingly, the return of conventional lymphography with chlorophyll and Lipiodol is unlikely no matter how improved (purified) the chlorophyll becomes. On the other hand, chromolymphography is as good as endolymphatic therapy and both are worthy of reconsideration. After

radical retroperitoneal lymphadenectomy as performed commonly for uterine cervical carcinoma, the value of chromolymphography is limited. Here, fatty tissue is removed along with embedded lymph nodes. These radical dissections, although complete and accurate has poor selectivity. Paradoxically, only lymph nodes which are not grossly involved are removed. Thus, if metastatic lymph nodes are palpable at the beginning of operation, the laparotomy is usually aborted and the patient treated by irradiation. Ironically, therefore, a large number of non-involved (healthy) lymph nodes (up to 80 per patient) are removed while potentially non-visualized small lymph nodes with metastases may remain in the body. Because most women with uterine cancer that undergo surgery are already relegated to "low staging", the histology of most lymph nodes removed show no metastasis. Moreover, when patients are compared with and without lymphadenectomy, no difference in survival is realized (8).

In most clinics, radical retroperitoneal lymphadenectomy is deemed obligatory until a reliable method for detecting lymph node metastases (both microscopic and macroscopic) is found. Whether imaging by positron emission tomography (PET scanning) can fulfill this expectation is as yet not known. Until then, perhaps chromolymphography can substantially modify the role of retroperitoneal lymphadenectomy (e.g., its extent and selectivity). If the extent of operative dissection and injury can be lessened and the

complication rate can be reduced, preservation of fatty tissue, which contains vegetative nerves, is of signal importance for young men undergoing radical retroperitoneal lymphadenectomy to stage urologic cancer. With more selective dissection, the complications of retrograde ejaculation, impotence, and infertility can be avoided.

Chromolymphography can be performed before embarking on lymphadenectomy by injecting guajazulen, a dark blue lipid soluble dye, via a dorsal pedal lymphatic (2). After preliminary animal experiments, this approach was used in 11 patients. Each demonstrated dark blue retroperitoneal lymph nodes at the time of lymphadenectomy 1-3 days later. The disadvantage of this agent is the need to use a lipid solvent (analogous to Lipiodol). This oil compresses lymph nodal parenchyma and can initiate respiratory distress from oil embolism.

To circumvent these drawbacks, aqueous blue dyes (patent blue V and isosulfan blue) encapsulated in liposomes were developed for preoperative chromolymphography (3-5). Intraoperative lymph node visualization can alternatively be done using a carbon suspension with mean particle size of 150 nm (1). After this latter suspension was injected into the gastric wall of 10 patients with gastric cancer undergoing gastrectomy with regional nodal dissection, 76% of healthy lymph nodes and 69% of involved lymph nodes were found blackened with carbon. In other words, only 3 of 4 lymph nodes removed by this operation were actually stained black. The rest of the lymph nodes had to be identified by the "classical" all inclusive radical dissection thus limiting the clinical value of this labeling method.

The problem of axillary lymphadenectomy in management of breast cancer differs somewhat from retroperitoneal lymphadenectomy for uterine cancer. Radical retroperitoneal lymphadenectomy is performed primarily for therapy (despite the fact that the resected lymph nodes are often without metastases). In contrast, axillary

lymphadenectomy nowadays is mainly done for diagnostic staging (although the removed lymph nodes often contain metastases). In the past, adjuvant treatment of breast cancer has been restricted to patients with metastatic axillary lymph nodes. Recent data suggest, however, that even nodal-negative patients may benefit from adjuvant chemo or hormonal therapy. In many centers, the rationale for performance of axillary lymphadenectomy for breast cancer has moved from "diagnostic" to "prognostic". As with retroperitoneal nodal dissection, however, axillary lymphadenectomy indiscriminantly removes adjacent fatty tissue with the risk of subsequent peripheral lymphedema. This drawback of axillary lymphadenectomy raises the question as to how non-involved lymph nodes can be preserved while metastatic lymph nodes are selectively excised. In this regard, chromolymphography has only limited value as lymph nodes with microscopic metastases typically stain normally because lymph flow remains intact.

Color staining of normal lymph nodes can be used, however, to resolve special issues. In the treatment of malignant melanoma of the skin the question arises, whether tumor has already seeded the regional lymph node basin. If the lymph nodes are uninvolved, then lymphadenectomy is not worthwhile. To examine regional nodal involvement, the blue staining ("mapping") of lymph nodes draining the skin tumor site can be performed (6,7). If the lymph node nearest the site of the primary melanoma ("sentinel" node) is histologically free of tumor, then more radical lymphadenectomy is not done. The false-negative rate is less than 1%. Because the blue dye (patent blue V or isosulfan blue) is administered in aqueous solution, it diffuses out rapidly from the lymphatics. Accordingly, to obtain sufficient staining of lymph nodes, the dye injections are repeated every 20 minutes. The procedure is therefore time-consuming, although it is recommended that regional nodal dissection be performed promptly. More experience with this technique is needed.

Staining alone is not used to decide whether lymph nodes should or should not be excised. Thus, lymph nodes with metastases large enough to cause cessation of afferent lymph flow may not stain at all but can be identified at operation by its characteristics of large size and palpability.

Lymphoscintigraphy after intradermal injection of radionuclides adjacent to a tumor site shows promise in detecting small lymph node metastases. The error rate, however, is still too high to reliably detect metastases with this method.

In experimental investigations using MR images after endolymphatic administration of dextran-coated superparamagnetic iron oxide particles (average size 47 nm), lymph node metastases of VX2 rabbit tumor larger than 2 mm could be detected (9). Detection was based on signal reduction of healthy lymph nodes after injection of contrast medium. Stainable iron was not found within metastatic nodules. The authors recommend, however, that only tumor-free lymph nodes from highly tumorous lymph nodes can be consistently differentiated.

Besides PET scanning, the future in nodal marking for metastases probably belongs to antibodies directed against specific tumor cell surface markers injected directly into the lymphatic system. Liposomes as a lipoidal carrier have already demonstrated their superior properties for this purpose. They can carry both specific antibody on their surface and a radionuclide (for gamma-camera detection) in their inner compartment. Perhaps, these liposomes containing tumor-specific antibodies can also carry blue dye to "map" the tumor drainage area thereby raising the accuracy of nodal involvement and avoiding unnecessary radical lymphadenectomy. Chromolymphography alone is likely to be useful only if most of the lymph nodes to be dissected are lymphographically accessible and some selective removal is possible. In an analogous fashion, if such endolymphatic diagnosis is possible then endolymphatic therapy with antitumor drugs may someday substitute for curative radical

lymphadenectomy to treat metastatic regional lymph nodes.

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