Can Manual Treatment of Lymphedema Promote Metastasis?

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ABSTRACT

Complete decongestive therapy (CDT; alternatively known as complete decongestive physiotherapy) is a treatment program for patients diagnosed with primary or secondary lymphedema. CDT incorporates manual lymphatic drainage (MLD), a technique involving therapeutic manipulation of the affected limb. There are several contraindications to performing CDT. Relative contraindications include hypertension, paralysis, diabetes, and bronchial asthma. General contraindications include acute infections of any kind and congestive heart failure. Malignant disease is also widely considered a general contraindication; a current vogue concept is that MLD will lead to dissemination and acceleration of cancer. However, cancer research supports the contention that this therapy does not contribute to spread of disease and should not be withheld from patients with metastasis. The intent of this article is to review these data.

KEY WORDS: cancer metastasis, complete decongestive therapy, lymphedema, manual lymphatic drainage

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The purpose of this article is to examine the scientific evidence surrounding the issue of lymphedema and the suggestion that malignancy and the presence of metastasis may place a patient at risk when receiving complete decongestive therapy (CDT) and manual lymphatic drainage (MLD). The International Society of Lymphology states that, theoretically, massage and mechanical compression could promote metastasis by mobilizing dormant tumor cells.[1] This concept is promoted in several published documents on the treatment of lymphedema, stating that active malignancy is a contraindication for the use of CDT.[2–6] A book geared toward patient education by Burt and White suggests that lymphatic massage could move cancer cells to a new area and potentially spread the cancer.[2] Foldi and colleagues also list CDT as a relative contraindication, stating that the therapist should refrain from applying MLD in the area of the body that is directly affected by the tumor.[7] However, with this stated, Foldi clearly asserts that CDT does not cause metastasis and can be used in the treatment of malignant lymphedema to improve quality of life.[8]

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Lymphedema is a disease process in which there is an abnormal accumulation of protein-rich lymph fluid due to a low-volume (mechanical) insufficiency of the lymphatic system. Lymphedema can be classified as primary (congenital) or secondary. The latter is commonly caused by surgery, radiation therapy, or trauma. Three stages of lymphedema exist:

- Stage I, reversible lymphedema (Figure 1), consists of an edematous limb that is soft to palpation and has pitting edema. This stage is named for the ability of the lymphedema to temporarily resolve after elevation of the limb for a prolonged period of time.
- Stage II, spontaneously irreversible lymphedema (Figure 2), consists of an edematous limb that is much firmer to palpation because of increased fibrosis and soft tissue scarring. This stage of lymphedema will reverse somewhat but not completely with limb elevation.
- Stage III, lymphostatic elephantiasis (Figure 3), develops when the limb becomes grossly enlarged. It also presents with hardening and thickening of the dermal tissues and polyps of the skin. The name originates from the resemblance of the dermis to that of an elephant. This stage of lymphedema shows no reduction in swelling with prolonged elevation.

Lymphedema is most often analyzed and studied in breast cancer patients, but it may occur whenever there is a disruption of the lymphatic system from surgery, radiation therapy, or trauma. It may be just as debilitating in the

Figure 1 Stage 1—reversible lymphedema.

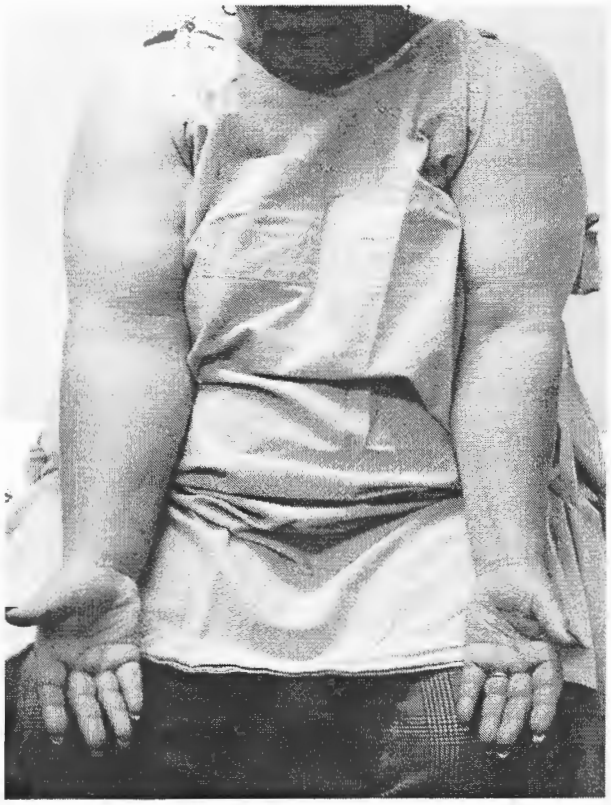

Figure 3 Stage III—lymphostatic elephantiasis.

Figure 2 Stage II—spontaneously irreversible lymphedema.

breast cancer patient after modified radical mastectomy followed by radiation to the chest wall as in the patient with lower-extremity melanoma after a groin dissection. Lymphedema is a progressive disease that advances through all three sages, albeit slowly, if left untreated. Treatment is available for all stages, but with progression into the latter stages, treatment becomes more difficult and is likely to produce a less-than-optimal outcome.

LYMPHEDEMA AND BREAST CANCER

Patients who undergo axillary lymph node dissection (ALND) or radiation therapy for breast cancer have a 6 to 30% risk of developing of lymphedema.[9] This risk is increased in the presence of nodal disease, by the extent of breast surgery and axillary dissection performed, and by the delivery and port encompassed by the radiation field. When a patient has an ALND or undergoes radiation therapy, lymphatic flow is impaired and the patient is considered to be in a subclinical state of lymphedema. This state is characterized by the absence of any measurable girth changes of the affected limb as compared with the unaffected limb. If the girth difference of the affected limb as compared with the unaffected limb becomes 2 cm or greater at any one measurement site, the measurement is considered significant and the patient is given a diagnosis

of secondary lymphedema. There are several treatment options at this point: vasopneumatic compression devices, compression garments, surgery, and CDT. The use of CDT is becoming much more widely accepted and is now considered standard of care by the International Society of Lymphology.[10]

In an effort to decrease the toxicity of treatment, more conservative breast surgeries are now performed and the sentinel lymph node biopsy (SLNB) has been developed. A recent randomized trial by Purushotham and colleagues examined the morbidity both physically and psychologically after SLNB compared with ALND in radiotherapy patients.[11] A significant reduction was seen in physical and psychological morbidity after SLNB. However, whereas SLNB reduces the likelihood of lymphedema in patients without axillary nodal metastases, ALND remains the standard of care for those patients with involved lymph nodes.

CDT is a useful therapeutic program for patients diagnosed with lymphedema. The goal of treatment is not to "cure" lymphedema but, rather, to decrease limb edema to a minimal level with maintenance of a reduced girth to prevent or potentially eliminate infections. The patient's participation in the program is crucial for a successful outcome; therefore, the patient must commit to all components of the program prior to the initiation of treatment.

CDT is a two-phase therapeutic program that consists of a treatment phase (phase I), and a maintenance phase (phase II). The treatment phase includes four components: MLD, skin and nail care, compression bandaging, and therapeutic exercise. The maintenance phase consists of self-care using all of these components in addition to the use of a compression garment. Patient education relating to lymphedema and precaution guidelines for arm and hand care are strongly emphasized throughout the program.

MLD is a technique used to increase the lymph vessel pumping rate to move stagnating fluid from an edematous area to other regions of the body that can accept and continue with the normal processing and elimination of the lymph fluid. This procedure requires a very light application of pressure secondary to the location of the superficial lymphatic vessels just below the skin. The direction of movement with this technique is always distal to proximal, forcing the evacuation of excess lymphatic fluid from the edematous limb. The sequence and type of manual techniques are determined for each patient on an individual basis depending on the specific area of increased edema as well as the stage of lymphedema presented.

Unfortunately, in many arenas, a new lore has emerged that states that MLD exacerbates or contributes to disease progression. The disconcerting end to which these fears have been taken is a widespread prohibition of MLD in patients with recurrent or metastatic disease. Owing to the perpetuation by well-meaning but inaccurate concerns of patients and practitioners unaware of the pathobiology of metastasis, many patients who could benefit from MLD or CDT are being deprived of the opportunity.

METASTASIS

Metastasis of cancer, in most cases, implies an inability of providers to cure the disease. It does *not* imply an inability to treat symptoms. This is true with respect to pain, tumor masses, bleeding, and obstructed breathing; it is also true with respect to lymphedema. What is necessary is an awareness by practitioners that cancer is a *biologic* process rather than a *rational* process. History serves as a useful teacher here. In 1889 Stephen Paget described clinical observations of 735 autopsies of patients who died of breast cancer.[12] He coherently outlined the argument:

> What is it that describes what organs shall suffer in a case of disseminated cancer? If the remote organs in such a case are all alike passive and, so to speak, helpless—all equally ready to receive and nourish any particle of the primary growth which may "slip through the lungs," and so be brought to them,—then the distribution of cancer throughout the body must be a matter of chance. But if we can trace any sort of rule or sequence in the distribution of cancer...then the remote organs cannot be altogether passive or indifferent as regards embolism.[12]

His data were unequivocal. Of his cases, 241 women had autopsy evidence of liver metastasis but only 17 had splenic lesions. This peculiar distribution cannot be explained by anatomy alone. Paget remarked, "The spleen has, so to speak, the same chances as the liver; its artery is even larger than the hepatic artery; it cannot avoid embolism."[12] As expansion, he described the results of 340 autopsies of patients who died of sepsis; in these, liver abscesses were present in 66 cases and splenic abscesses in 39.

Further, discrepancies were noted within organs and between cancers. In his series, Paget did not document breast cancer metastasis to the radius, ulna, or fibula. The humerus was involved in 10 cases, the femur in 18, and the skull in 36. He noted than in prior reports of autopsies for melanoma, although bone metastases were common, there were no humeral lesions and only a single femoral metastasis.[12] In retrospect, it was recognized 110 years ago that metastasis is not simply a function of cancer cells' ability to get to various parts of the body but also to grow when they get there.

The requisite steps for metastasis have since been described.[13] Recent work has elegantly documented heterogeneity within tumors—in other words, some tumor cells have all the necessary requirements to metastasize and thrive, some have some of the functions, and some have

none.[14] Although some cells may escape into the blood and lymphatic system, very few of them develop into clinical metastases. Ruitler and colleagues give one explanation: "This low efficiency may be a temporary absence of a suitable microenvironment once the tumour cells escape from this original tissue compartment."[15]

In sum, each cancer exists uniquely within each patient. Each patient exerts a singular immune response and metabolism, which serves as an individual "test tube" for that person's malignancy. The lesson for practitioners of MLD and CDT is that elevations in venous pressure cannot provide individual cells with capabilities that did not exist at lower pressures.

There are several examples of known cancer deposits that do not grow into clinical problems:

- Mechanical shunting procedures are used to relieve symptoms caused by excessive fluid accumulation in the brain, pleura, or abdomen. When used in malignancy, these procedures provide direct infusions of tumor cells into the abdomen or bloodstream.[16,17] An autopsy review of 15 patients who had undergone peritoneovenous shunt placement for incurable abdominal malignancy revealed that over one-half of patients had no detectable hematogenous metastases at autopsy a median of 9 weeks postoperatively. One of the seven patients with hematogenous metastases noted at autopsy had such disease noted at the time of shunt placement, and the other six patients may have had such disease preoperatively, given their disease process.[17] Another study of 17 patients undergoing pleuroperitoneal shunt procedures for malignant pleural effusion reported no clinical evidence of peritoneal dissemination of disease with a median follow-up of over 6 months.[16]
- After radical prostatectomy, up to 66% of patients with clinical stage B prostate cancer will have malignant cells at the margins of resection.[18,19] However, of these patients only about two-thirds will experience clinical recurrence at 15 years. This fact has led some to state, "Just because the surgical margins are positive does not mean the patient has residual tumor."[20]
- In the randomized B-04 trial of the National Surgical Adjuvant Breast and Bowel Project,[21] 40% of patients randomized to receive modified radical mastectomy had pathologically involved axillary lymph nodes. Given the randomized nature of the trial, a similar number of patients would be expected in the patient cohort that had no axillary dissection performed initially. However, only 18% of that cohort developed subsequent clinical evidence of lymph node metastasis.
- Patients with carcinoma of the lung are frequently found to have malignant cells on bronchial brushings at time of bronchoscopy or on sputum cytology. Presumably, the cells thus sampled are present in the entire tracheobronchial tree proximal to the lesion. However, the frequency of suture-line recurrence after sleeve resection is 5 to 9%.[22,23]
- In endometrial cancer, the presence of malignant cytologic cells within the peritoneum is widely considered to be a poor prognostic sign.[24] Unfortunately, the degree of poor prognosis is not agreed upon since only 7% of such patients in one large study progressed with peritoneal disease if no therapy was delivered to the abdomen.[25]
- Recent literature documents the use of reverse transcription-polymerase chain reaction technique in patients undergoing resection of breast,[26,27] colorectal,[28] or prostate cancer.[29] This test may document the presence of tumor cells in the blood circulation or bone marrow of patients at time of presentation. Although most studies report that patients with such a finding fare worse than patients without it, this presence of tumor cells does not guarantee recurrence and patients with known metastatic disease may have negative testing.[30] This finding alone is not enough to determine the patient's prognosis.

The most recent blow to the mindset against MLD in metastatic disease is found in the emerging literature describing sentinel node sampling of the axilla in breast cancer. Using this technique, proponents maintain that full axillary dissection should be predicated on the presence or absence of metastatic disease in the sentinel axillary node—the first node to reveal dye when it is injected into the tumor site intraoperatively.[31] Using this technique, the primary lesion is resected and dye injected around the tumor bed. The sentinel node is found by its color and sampled.[31] Dye transit time is measured in minutes. Thus, any presumption on the part of the patient or therapist that MLD facilitates the spread of a tumor ignores the fact that it was probably already there.

Other data come from the examination of SLNB in patients with cutaneous melanoma. There are isolated cases reported in which a patient may have developed an in-transit metastasis after starting CDT; it has also been suggested that SLNB increases the incidence of in-transit metastases. The most recent findings from van Poll and colleagues refute this premise.[32] They found that the in-transit metastasis was higher in patients undergoing elective nodal dissection (24.2%) compared with patients with positive sentinel nodes with immediate dissection (10.8%). This is supported by other investigators.[33] Hopefully, the phase III multicenter Selective Lymphadenectomy Trial will unequivocally answer this question.

SUMMARY

Lore becomes a hindrance to progress when it perpetuates a flawed way of thinking. Such was the case in the early 1900s after Koch's postulates seduced caretakers of the

times into thinking that a rationalistic approach could be applied to medicine.[34] For decades, an anatomically based, "common-sense" construct of metastasis supplanted the seed and soil theory proposed by Paget. It fell to recent research to bring back into focus the fact that tumor biology, not host anatomy, is the critical aspect of cancer metastasis. Research confirms that an "optimal microenvironment" is necessary for metastasis.[14] This fact, once recognized by us and taught to our patients, will facilitate the appropriate treatment, even in the presence of incurable disease.

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