**Review**

**Significance and Mechanism of Lymph Node Metastasis in Cancer Progression**

Kenji Kawada and Makoto Mark Taketo

**Abstract**

The effect of local therapy, such as surgical lymph node (LN) dissection and radiotherapy, on the survival of cancer patients has been debated for decades. Several lines of recent clinical evidence support that LN metastasis plays significant roles in systemic dissemination of cancer cells, although the effects of surgical LN dissection on survival was downplayed historically because of controversial data. Molecular studies of LN metastasis suggest that the microenvironment within LNs, including chemokines and lymphangiogenesis, can mediate the metastatic spread to the sentinel LNs, and beyond. It has been demonstrated that chemokine receptor CXCR3 is involved in LN metastasis, and its inhibition may improve patient prognosis. Although it remains to be determined whether local therapy is best pursued through LN dissection or through a combination of resection with radiation, prevention of regional metastases is an important goal in the treatment of cancer patients to achieve a better survival.

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Patients with advanced cancers have a significant risk of local recurrence and distant metastasis after surgical resections of the primary tumors. Systemic therapy to prevent distant metastasis has been emphasized to improve the survival of cancer patients, but the effect of local therapy has been debated for decades, as reviewed by Punglia et al. (1) and summarized below. The most frequently used strategy to control local recurrence includes radical resection combined with LN dissection (lymphadenectomy) and local radiation therapy. Regarding local therapy, three clinical viewpoints have been proposed. In the early last century, William Halsted proposed that breast cancer is a local disease that spreads primarily in a predictable, stepwise manner from the primary tumor to the regional lymphatics and then systemically to distant organs (2). Local regional LNs are the commonest and earliest site of metastasis of solid tumors, and his idea provided the justification for radical breast-cancer surgery with extended LN dissection (2). In reaction to the “Halstedian” theory, the “systemic” theory arose. Bernard Fisher and others proposed the view that breast cancer is a systemic disease from the beginning and that LN dissection is merely useful for prognostic information, but does not affect overall survival, suggesting more important role of hematogenous dissemination to vital organs (liver, lungs etc.) in metastasis (3). Thus, effective systemic therapies were emphasized in breast-cancer treatment, which indeed helped to improve the overall survival. As a third hypothesis, the “spectrum” theory balanced these two opposing strategies (4). Cancer cells develop metastatic potential as tumors grow through their clinical evolution. Accordingly, the LN involvement is of prognostic importance not only because it indicates a more malignant tumor biology, but also because persistent disease in LNs can be the source of subsequent fatal metastases. In fact, results of some recent clinical trials support this notion. Namely, improved local therapy is causally associated with better overall survival in several types of cancer as exemplified below.

1) Evidence from clinical trials

a) Breast cancer: Two (i.e., Canadian and Danish) prospective randomized trials demonstrated that, after mastectomy, the addition of radiation therapy and adjuvant chemotherapy not only decreased local recurrence but also improved overall survival, indicating that local treatment prevents recurrence from generating fatal metastases (5, 6). A recent meta-analyses also presented the findings from 78 randomized clinical trials that improved local control during first
5 years resulted in a statistically significant improvement in the overall survival at 15 years, and
that the survival benefit was similar either by extensive surgery or by radiation therapy (7).

With the widespread introduction of the sentinel LN biopsy procedure, the question was
raised about how to deal with potential and additional LN metastases in case of a positive
sentinel LN. Micrometastases in regional LNs were associated with a reduced disease-free
survival with early-stage breast cancer (8). To investigate differences in regional control, survival,
and long-term morbidity between axillary LN dissection and radiation therapy, an international
multicenter phase III trial was initiated in 2001, and is still ongoing (9).

b) Gastric cancer: The need for radical LN dissection for curative treatment of gastric cancer
continues to be debated. Two large randomized trials from the Netherlands and UK that
compared the less extended D1 dissection (lymphadenectomy limited to the perigastric LNs)
with the D2 dissection (lymphadenectomy extended to hepatic, gastric, cardiac and splenic LNs)
failed to show a survival benefit for the D2 procedure (10, 11). In these studies, however, lack of
experience with the surgical skills and postoperative care appeared responsible for the high
morbidity (~45%) and mortality (~12%) of the patients who underwent D2 dissection (Table 1).

The American Intergroup study showed that chemoradiotherapy after no or limited
lymphadenectomy (D0 or D1 dissection) decreased the local recurrence rate and increased
overall survival, suggesting that chemoradiotherapy eliminated the residual LN metastases that
could be removed by D2 dissection (12). In 2006, a prospective randomized trial in Taiwan
showed a significant benefit in overall survival for a D2 dissection over D1 alone, without
increased operative mortality (13). In this trial, all the surgeons had already performed at least 80
D2 operations, and there were no deaths in either group (Table 1). In a surgical trial to compare
two different operative methods, participating surgeons should be experienced equally in both
techniques. These results suggest that adequate local treatment is essential for effective treatment
of gastric cancer.

In 2008, a prospective randomized trial in Japan showed no improvement in overall
survival with D2 dissection plus para-aortic nodal dissection (PAND) as compared with D2 alone.
This trial was performed by experienced surgeons in 24 specialized hospitals with a high volume
of cases, and resulted in very low mortality rates (0.8%) and good long-term survival in both
groups (14). The result may suggest that para-aortic LN metastasis is a systemic, not local, disease, and that PAND is an unworthy and excessive procedure against advanced gastric cancers.

c) Rectal cancer: In the United States, extended LN dissection in rectal cancer was performed in the 1950s, but the effectiveness of lateral pelvic LN dissection was not accepted because it led to an increase in blood loss, and urinary and sexual dysfunctions without further survival benefit (15). Preoperative radiotherapy reduced the relative risk of local recurrence, although without significant survival improvement (16, 17). Although a recent meta-analysis comparing extended and non-extended lymphadenectomy of the lateral pelvic LN showed no overall difference in cancer-specific outcome (18), this study has limitations such as varying protocols, different levels of surgical expertise, different patient populations and different time periods. In many Western countries, current standard therapy for lower rectal cancer is total mesorectal excision (TME) with preoperative radiotherapy.

In Japan, on the other hand, lateral pelvic LN dissection has been performed extensively along with TME in advanced rectal cancer, which contributed to the reduced local recurrence and improved survival in retrospective multicentre studies (19). A retrospective analysis suggests that lateral pelvic LN dissection can be equivalent to the preoperative radiotherapy in terms of the curative effect for patients with lower rectal cancers (20). It is worth noting that a phase III prospective randomized trial is ongoing, assessing the effectiveness of lateral pelvic LN dissection (JCOG 0212).

Similar situations have been reported for lung cancer (21), endometrial cancer (22) and esophageal cancer (23, 24). In stage I-IIIA non-small cell lung cancer, a meta-analysis of randomized controlled trials suggests that complete mediastinal LN dissection is associated with improved survival (21). In endometrial cancer, comparative cohort study reports that para-aortic LN dissection (PAND) has survival benefits, and that pelvic LN dissection alone might be an insufficient surgical procedure for patients at intermediate or high risk of recurrence (22). In adenocarcinoma of the esophagus, one randomized controlled trial suggests that in patients with 1 to 8 metastatic LNs, extended transthoracic esophagectomy with en bloc LN dissection results
in improved 5-year survival compared with limited transthiatal resection (23). On the other hand, in pancreatic cancer, 3 randomized controlled trials suggest that extended LN dissection does not result in survival benefit (25-27). Although there is no doubt that the presence of LN metastases worsens prognosis of a patient, unambiguous evidence to support LN dissection is still lacking. For many solid tumors, the role of LN dissection is yet controversial, and may depend on the tumor type and the stage of patient presentation for diagnosis. Namely, cancers of the breast, colon and stomach are often diagnosed as local diseases, whereas pancreatic cancer is found after they have progressed to the systemic diseases. Accordingly, well-designed randomized controlled trials are required to evaluate the systemic vs. local therapy in a scientific manner.

2) Molecular mechanisms of LN metastasis

Cancer metastasis appears to form through a chain of events where organ selectivity by the tumor cells is largely determined by physical factors (blood and lymph flows) and biological molecules that are expressed in the tumor microenvironment. As described above, several lines of evidence are beginning to show that LN metastasis not only provides the prognostic information, but also plays active roles in developing distant metastases to the vital organs, causing eventual lethality. However, little is known about its molecular mechanisms. Questions remain whether tumor cells are trapped by LNs, causing a lag phase in tumor dissemination, whether LN metastases just serve as evidence of tumor cell transit through the LNs, or whether the LNs promote spreading of the tumor cells by amplifying them and serving as a launch pad for further systemic metastasis (28, 29). As the lymph flows into the systemic circulation through the thoracic duct or lymphovascular shunts, LN metastasis can be regarded as a side loop of the hematogenous metastasis circuit.

Recent studies suggest that the least efficient steps in metastasis are the survival and growth of the micrometastatic foci and their persistence that affect colonization, indicating the importance of interactions between the ‘seed’ (cancer cell) and ‘soil’ (microenvironment). Of the different components that affect the organ selectivity, instrumental roles have been attributed to interactions between chemokine receptors on cancer cells and their ligands in the target organs (30). To date, several sets of chemokines and their receptors have been suggested to play important roles in the metastatic organ selectivity, and one of the best-studied examples is the
CXCL12-CXCR4 axis in breast cancer metastasis to the bone. Regarding the direct role of chemokines in LN metastasis, recent reports suggest critical roles for CXCR3, CXCR4 and CCR7 (31-34). Importantly, these three receptors are involved in the recruitment and patterning of several types of immune cells to LNs, suggesting that cancer cells often acquire these receptors and are controlled by their ligands in a manner analogous to the immune cell interactions.

Although early studies to describe chemokine receptors and melanoma or breast cancer did not detect receptor CXCR3, it has been demonstrated recently that CXCR3 plays the critical role in LN metastasis of melanoma and colon cancer cells, but not in their hematogenous metastasis (31, 32). Upon construction of B16F10 mouse melanoma cell derivatives with reduced CXCR3 expression by antisense RNAs, their metastatic activities have been investigated after subcutaneous inoculations into mouse footpads. The metastatic frequency of these cells to popliteal LNs was markedly reduced compared with control B16F10 cells, without affecting hematogenous metastasis to the lung or liver. In addition, human colon cancer cells were constructed that expressed CXCR3 cDNA (DLD-1-CXCR3), and compared with controls by rectal transplantation in nude mice. In 6 weeks, 59% of mice inoculated with DLD-1-CXCR3 showed macroscopic metastases in para-aortic LNs, whereas only 14% of those did with the control. Metastasis to the liver or lung was rare, and unaffected by CXCR3 expression.

In 92 human colon cancer specimens, expression of CXCR3 was found in 31 (33.7%) cases, most of which had LN metastasis (32). Importantly, the patients with CXCR3-positive colon cancer showed significantly shorter survivals than those without CXCR3. The patients with CXCR4-positive tumors also had a significant poorer prognosis, but its effect was less than that of CXCR3. In addition, the patients with tumors double positive for CXCR3 and CXCR4 had a significantly poorer prognosis than those with tumors positive only for CXCR4 or the double negatives (Figure 1). In breast cancer, high CXCR3 expression has also been reported to be associated with poorer prognosis (35). These results demonstrate that activation of CXCR3 stimulates cancer metastasis preferentially to the draining LNs with poorer prognosis, implicating a critical role of LN metastasis in overall patient survival (32).

More results have emerged recently in support of the role for CXCR3 in the metastasis of melanoma and neuroblastoma, and cancers of colon, breast, ovaries, and prostate. Namely,
several laboratories have provided data that CXCR3 strengthens the invasion-related properties of cancer (36) and that CXCR3 facilitates lung metastasis of breast and colon cancers (37, 38). In addition, lymphangiogenesis within the sentinel LNs is also associated with tumor metastasis to distant sites (39). These results indicate that the microenvironment in LNs, including chemokines and lymphangiogenesis, can mediate the metastatic spread of tumor cells to the sentinel LNs, and beyond.

For decades, the oncology community has focused on adjuvant therapies in an effort to prevent distant metastasis. Although the effects of local recurrence on patient survival was downplayed, or even denied, prevention of local recurrence is getting to be appreciated as a key goal for many types of cancer. In the meantime, it is yet to be determined whether regional treatment of cancer is best pursued through LN dissection or a combination of resection with radiation. It is also worth noting that economic factors on the health insurance system need to be evaluated carefully in establishing the therapeutic strategy on metastasis. We should be able to overcome tumor metastasis with a better understanding of the interplay between the cancer cells and their microenvironment not only in hematogenous but also LN metastasis.

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References


27. Farnell MB, Pearson RK, Sarr MG, et al. “A prospective randomized trial comparing


Table 1. Four randomized controlled trials of gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>5-year survival rate</th>
<th>perioperative morbidity</th>
<th>perioperative mortality</th>
<th>participating surgeons/hospitals</th>
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<tr>
<td><strong>Taiwan trial (13)</strong></td>
<td></td>
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<td>single hospital 3 experienced surgeons</td>
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<tr>
<td>D2/D3</td>
<td>111</td>
<td>59.5 %*</td>
<td>17 %**</td>
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<tr>
<td>D1</td>
<td>110</td>
<td>53.6 %</td>
<td>7 %</td>
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<td><strong>Dutch trial (10)</strong></td>
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<tr>
<td>D2</td>
<td>331</td>
<td>47 %</td>
<td>43 %**</td>
<td>10 %**</td>
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<td></td>
<td></td>
<td>33 surgeons</td>
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<tr>
<td>D2</td>
<td>200</td>
<td>33 %</td>
<td>46 %**</td>
<td>13 %***</td>
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<tr>
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<td>35 %</td>
<td>28 %</td>
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<tr>
<td><strong>Japan trial (14)</strong></td>
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<td>D3 (D2+PAND)</td>
<td>259</td>
<td>70 %</td>
<td>28.1 %</td>
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<td>D2</td>
<td>263</td>
<td>69 %</td>
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* P < 0.05 compared with D1 (log-rank test)
** P < 0.01 compared with D1 (Fisher’s exact test)
*** P < 0.05 compared with D1 (Fisher’s exact test)
Legend to Figure 1. Survival curve (Kaplan and Meier estimates) by expression of CXCR3 and CXCR4 in colon cancer (27).
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