Impact of Multiple Lymphatic Channel Drainage to a Single Nodal Basin on Outcomes in Melanoma

James K. Wall, MD; Marilyn Florero, BS; Neil A. Accortt, PhD; Robert Allen, MD; Mohamed Kashani-Sabet, MD; Eugene Morita, MD; Stanley P. L. Leong, MD

Objective: To determine the impact of multiple lymphatic channels (MLCs) on outcome in melanoma.

Design: Retrospective cohort study.

Setting: Academic tertiary care center.

Patients: Of 1198 consecutive selective sentinel lymphadenectomies performed from 1995 to 2000 for primary invasive melanoma, 502 patients were identified with extremity or truncal melanoma that drained to a single nodal basin. Three cohorts were formed based on lymphatic channels (none, single, and multiple). Tumors with drainage to multiple nodal basins as well as all head and neck tumors were excluded.

Main Outcome Measures: Multiple variables, including patterns of lymphatic drainage, were analyzed for impact on disease-free and overall survival.

Results: Demographics were similar among groups, with a median follow-up of 5.6 years. Univariate analysis revealed MLCs as an independent risk factor for both disease-free (P = .04) and overall survival (P = .003). Multivariate analysis confirmed that tumor depth, sentinel lymph node status, and MLCs were risk factors for both disease-free and overall survival. Kaplan-Meier analysis showed worse survival in the MLCs group.

Conclusions: Our study reveals that MLCs are an independent risk factor for recurrence and mortality in melanoma. Multiple lymphatic channels may facilitate the process of metastasis.

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Elective sentinel lymphadenectomy, as described by Morton et al, is now the standard of care for staging of melanoma and breast cancer and may have applications in other cancers. The sentinel node is routinely identified by injecting blue dye, a radiotracer, or both at the primary tumor site. Lymphoscintigraphy evaluates the uptake of a radiotracer and provides a map of lymphatic channels leading to sentinel nodes prior to selective sentinel lymphadenectomy. It is routinely used in treating melanoma, particularly truncal tumors in which the draining nodal basin may not be predictable or in which there may be multiple draining nodal basins. The usefulness of lymphoscintigraphy has been questioned in breast cancer in which lymphatic drainage is consistent, usually to the ipsilateral axilla, and aberrant patterns of drainage do not affect the surgical management. Several patterns of lymphatic drainage, including single vs multiple channels to single vs multiple nodal basin, have been described (Figure 1).

Predictors of outcome in melanoma are numerous. The American Joint Committee on Cancer staging system includes Breslow thickness, ulceration, and sentinel lymph node (SLN) status as the most important prognostic factors. Melanoma of the trunk is known to carry a worse prognosis than that of the extremities. Many believe this is because of the possibility of lymphatic spreading to multiple channels creating more than 1 gatekeeper. Studies of signaling markers indicate that there may be a role of such growth factors, like vascular endothelial growth factor C, in the flow and delivery rate of cancer cells through lymphatic channels. Clinically, it has been postulated that an increasing number of lymphatic channels might allow a greater possibility of cancer cell mobilization and spread. However, there is mixed data in the literature as to the impact of multiple channel drainage. Jacobs et al showed no increase in metastases associated with dual basin drainage in truncal melanoma. However, it is well established that multiple channel drainage to multiple nodal ba-
sins holds a worse prognosis for patients with truncal melanoma. Despite what seems to be equivalent rates of metastases to the SLN, patients with multiple channels of drainage to multiple nodal basins have a worse outcome. What remains unclear is the role of multiple channels independent of multiple nodal basins in patient outcome. We aimed to determine the impact on survival and recurrence of multiple channel drainage to a single nodal basin in melanoma.

**METHODS**

After attaining approval from the institutional review board at the University of California, San Francisco, we performed a retrospective review of 1198 patients who underwent selective sentinel lymphadenectomy for melanoma between 1995 and 2000. Patients with head and neck melanoma as well as patients with lymphatic channels to multiple nodal basins were excluded. A total of 502 patients were identified with extremity or truncal melanoma that drained to a single nodal basin.

Clinical and pathologic data were collected by reviewing clinic records, a tumor registry, and a death registry until October 2005. Complete pathologic data could not be recovered on all patients whose primary biopsies were performed by a referral institution, partially limiting the number of patients in the multivariate analysis of survival and recurrence. The interval to recurrence and death was calculated from the date of selective sentinel lymphadenectomy.

Lymphoscintigraphy was performed within 24 hours of the operation by intradermal injection of technetium Tc99m sulfur colloid. Injection at the primary tumor or biopsy site was followed by immediate dynamic imaging to assess lymphatic channels. Delayed static imaging was then acquired to assess radiocolloid uptake by the SLN(s). Attending radiologists interpreted the results as no channels, single channel, or multiple channels to a single nodal basin.

Operative procedures were performed by 1 of 2 surgical oncology attendings, as previously described. All patients underwent wide local excision of the primary tumor based on standard guidelines. Selective sentinel lymphadenectomy was performed using dye, a technetium Tc 99m radiotracer, or a combination of the two. Complete axillary lymphadenectomy was offered to all patients with metastatic disease in the SLN(s).

Patients were divided into 3 groups based on the lymphoscintigraphic finding of no channels, a single channel, or multiple channels to a single nodal basin. Analysis of survival and recurrence was limited to the patients with a single lymphatic channel (SLC) and multiple lymphatic channels (MLCs). Patients with no lymphatic channels were excluded because of the small size of this cohort and unknown etiology of having an SLN without visible drainage on lymphoscintigraphy. Survival and recurrence curves were calculated using the Kaplan-Meier method. The log-rank test was used for univariate analysis of patients. The Cox proportional hazards regression model was used for multivariate analysis. P values < .05 were considered significant.

Five hundred two patients underwent lymphoscintigraphy followed by selective sentinel lymphadenectomy. Patients were divided into 3 groups based on drainage patterns of none, single channel, and multiple channels, with 10.7%, 58.8%, and 30.5% of patients in each group, respectively. Median follow-up was 5.6 years with no significant difference between the groups. Mean age and sex distribution was also similar among groups (Table 1).

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**Table 1. Patient Demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>None</th>
<th>SLC</th>
<th>MLCs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>54 (10.7)</td>
<td>295 (58.8)</td>
<td>153 (30.5)</td>
<td>502</td>
</tr>
<tr>
<td>No. of male patients (%)</td>
<td>30 (55.6)</td>
<td>168 (56.6)</td>
<td>84 (55.3)</td>
<td>282 (56.2)</td>
</tr>
<tr>
<td>Mean age (range), y</td>
<td>49.8 (1-83)</td>
<td>52.4 (8-96)</td>
<td>54.4 (2-87)</td>
<td>52.7 (1-96)</td>
</tr>
<tr>
<td>Median follow-up, y</td>
<td>5.6</td>
<td>4.9</td>
<td>5.8</td>
<td>5.6</td>
</tr>
</tbody>
</table>

**Table 2. Primary Tumor Location**

<table>
<thead>
<tr>
<th>Location</th>
<th>None</th>
<th>SLC</th>
<th>MLCs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper extremity</td>
<td>14 (10.5)</td>
<td>94 (70.7)</td>
<td>25 (18.8)</td>
<td>133 (26.5)</td>
</tr>
<tr>
<td>Trunk</td>
<td>24 (11.2)</td>
<td>117 (54.9)</td>
<td>72 (33.8)</td>
<td>213 (42.4)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>16 (10.2)</td>
<td>84 (53.8)</td>
<td>56 (35.9)</td>
<td>156 (31.1)</td>
</tr>
</tbody>
</table>

Abbreviations: MLC, multiple lymphatic channel; SLC, single lymphatic channel.
Upper extremity, lower extremity, and truncal location composed 26.5%, 31.1% and 42.4% of all primary tumor sites, respectively. Among the 3 groups, truncal melanoma was the most common melanoma in each group. The primary tumor site was similar among the 3 groups (Table 2). Tumor characteristics of the SLC and MLCs groups from available pathology are presented in Table 3.

In the analysis of overall survival, MLCs were an independent risk factor for decreased survival ($P = .003$). The multivariate analysis revealed primary tumor thickness, SLN status, lymphovascular invasion, and MLCs status as significant risk factors for decreased survival (Table 4). In the analysis of recurrence, MLCs were an independent risk factor for early recurrence ($P = .04$). The multivariate analysis revealed primary tumor thickness, SLN status, mitosis grade, and MLCs status as significant risk factors for early recurrence (Table 5). Figures 2 and 3 show the Kaplan-Meier survival curves for the 2 groups with respect to overall survival and disease-free survival. There was a significant difference between SLCs and MLCs for overall survival and a trend toward early recurrence in the MLCs group.

**Table 3. Tumor Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SLC</th>
<th>MLCs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>46 (15.9)</td>
<td>26 (17.5)</td>
<td>72</td>
</tr>
<tr>
<td>Negative</td>
<td>244 (84.1)</td>
<td>123 (82.6)</td>
<td>367</td>
</tr>
<tr>
<td>Thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 mm</td>
<td>32 (10.9)</td>
<td>32 (20.9)</td>
<td>78</td>
</tr>
<tr>
<td>1.0-2.0 mm</td>
<td>142 (48.1)</td>
<td>72 (47.1)</td>
<td>215</td>
</tr>
<tr>
<td>2.0-4.0 mm</td>
<td>86 (29.2)</td>
<td>27 (17.7)</td>
<td>113</td>
</tr>
<tr>
<td>&gt; 4.0 mm</td>
<td>35 (11.9)</td>
<td>22 (14.4)</td>
<td>57</td>
</tr>
<tr>
<td>Mitosis grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>57 (26.3)</td>
<td>25 (25.5)</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>114 (52.5)</td>
<td>60 (61.2)</td>
<td>174</td>
</tr>
<tr>
<td>3</td>
<td>46 (21.2)</td>
<td>13 (13.3)</td>
<td>59</td>
</tr>
<tr>
<td>Regression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24 (10.0)</td>
<td>15 (14.6)</td>
<td>39</td>
</tr>
<tr>
<td>No</td>
<td>216 (90.0)</td>
<td>88 (85.4)</td>
<td>304</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (9.5)</td>
<td>15 (13.9)</td>
<td>38</td>
</tr>
<tr>
<td>No</td>
<td>219 (90.5)</td>
<td>93 (86.1)</td>
<td>312</td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (23.5)</td>
<td>27 (24.1)</td>
<td>85</td>
</tr>
<tr>
<td>No</td>
<td>189 (76.5)</td>
<td>85 (75.9)</td>
<td>274</td>
</tr>
</tbody>
</table>

Abbreviations: MLC, multiple lymphatic channel; SLC, single lymphatic channel; SLN, sentinel lymph node.

**Table 4. Results of the Log-rank Test and Cox Proportional Hazards Regression Model for Survival**

<table>
<thead>
<tr>
<th>Model</th>
<th>$\chi^2$</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate model$^a$</td>
<td>8.7029</td>
<td>1.8 (1.2-2.6)</td>
<td>.003</td>
</tr>
<tr>
<td>MLCs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate model$^b$</td>
<td>14.7283</td>
<td>2.4 (1.5-3.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SLN positive</td>
<td>14.5335</td>
<td>1.6 (1.3-2.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thickness</td>
<td>11.4403</td>
<td>2.0 (1.4-3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MLCs</td>
<td>6.501</td>
<td>0.5 (0.3-0.8)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: MLC, multiple lymphatic channel; SLN, sentinel lymph node.

$^a$ $n = 443$.

$^b$ $n = 345$.

**Figure 2.** Kaplan-Meier analysis of overall survival.

**Figure 3.** Kaplan-Meier analysis of disease recurrence.
CONCLUSIONS

Our study reveals that MLCs are an independent risk factor for recurrence and mortality, regardless of the nodal basin drainage pattern in melanoma. By implicitly studying the lymphatic channels, we have further delineated the role of the lymphatic system in the transition from local to metastatic melanoma. The relevance of multiple channel drainage may be applicable to other tumors with a tendency to spread via lymphatics. We hope that an understanding of the clinical relevance of multiple channel drainage combined with further investigation into biological mechanisms of lymphatic spread of cancer cells may lead to new and innovative approaches in the control of metastatic disease.

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Previous Presentation: This paper was presented at the 78th Annual Meeting of the Pacific Coast Surgical Association; February 18, 2007; Kohala Coast, Hawaii; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

REFERENCES


Richard Essner, MD, Santa Monica, California: I would like to thank Drs Goodnight and Hart, and the PCSA [Pacific Coast Surgical Association] for allowing me the opportunity to discuss the paper by Wall and his associates from UCSF. The debate on the surgical management of the regional lymph nodes in melanoma begun [sic] over 100 years ago when the British surgeon Herbert Snow first advocated elective lymph node dis-
section, based on the observation that melanoma metastasized first to the regional lymph nodes, and early surgical removal of all of the draining lymph nodes would reduce the morbidity from local regional relapse and potentially diminish the incidence of distant metastases and improve survival.

Since Snow’s early observations, multiple retrospective and 4 randomized clinical trials have failed to confirm the original hypothesis of the therapeutic value of elective lymph node dissection, yet many of these studies could not be expected to achieve a survival benefit, as almost 80% of patients with intermediate thickness melanoma will have tumor-negative dissections and therefore can’t benefit from lymph node dissection.

As an alternative to elective lymph node dissection in 1990, Morton devised lymphatic mapping and sentinel lymph node dissection as a minimally invasive approach to the regional lymph nodes. This technology has revolutionized our approach to the regional lymph node and allows surgeons to identify those patients to have high-risk melanoma, ie, those with tumor-positive sentinel node and eliminates complete lymph node dissection in all other patients.

A number of histologic factors have been used to determine which patients are at risk for tumor-positive sentinel node. Tumor thickness, Clark level, ulceration, regression, lymphovascular invasion, and mitotic rate are some of the features of the primary, which are used to evaluate a patient’s risk of having lymph node metastases. Leong, and co-authors from UCSF must be commended for their work as they have been at the forefront of research focusing on the mechanisms that are important in lymphangiogenesis and lymph node metastases. In this paper, the authors have focused on visual imaging of lymphatic channels. Five hundred two patients underwent lymphatic mapping and sentinel lymph node dissection. Lymphoscintigraphy films were re-evaluated to examine the number of lymphatic channels directed toward a single lymph node basin. Patients were divided into 3 groups: no visualized channels, single channel, or multiple lymphatic channels. Patients found to have multiple lymphatic channels had a worse survival than single channel or no visualized channels, suggesting the multiple lymphatic channels pattern allowed for easier passage of tumor cells from primary to more distant sites. I suspect either the innate anatomy of the patient or tumor-derived stimulation of lymphatic channels may be the cause of the multiple lymphatic channels pattern.

Other factors, including tumor thickness, sentinel node status, and lymphovascular invasion were also significantly related to outcome. The mechanisms of lymphangiogenesis and transport of tumor cells through the lymphatics is not understood in humans. These results suggest another factor may be important for understanding the biology of melanoma metastases. My questions to Drs Leong and Wall are:

1. What was the technique used for lymphoscintigraphy? Did the technique vary based on location of the primaries (ex- tremity vs trunk), age of the patient, method of biopsy of the primary (shave biopsy vs excisional biopsy), or time from initial injection of the radiopharmaceutical to imaging? Were all the lymphoscintograms reviewed by the same radiologists?

2. A variety of factors appeared to relate to multiple lymphatic channels status. Older patients, ulcerated and thick (>4 mm) primaries, along with those having regression and lymphovascular invasion tended to have a higher rate of multiple lymphatic channels. Do you have any explanation? Should we expect patients with higher “risk” primaries to have multiple lymphatic channels? Is multiple lymphatic channels a surrogate marker of aggressive tumor biology?

3. Was the rate of sentinel node and nonsentinel node metastases higher for patients with multiple lymphatic channels vs single channel vs no visualized channels? Would you expect patients to have higher rates of in-transit metastases with the multiple lymphatic channels pattern?

4. Why did you exclude patients with head and neck primaries and those with multiple lymph node basins identified by lymphoscintigraphy? Would you expect patients with multiple lymphatic channels and multiple basins (as compared to no lymphatic channels visualized and 1 basin) have the worse outcome of patients undergoing sentinel node biopsy?

5. Do you have any thoughts as to the mechanism of multiple lymphatic channels? Is it related to VEGF-C [vascular endothelial growth factor C] expression at the primary?

Dr Leong: Thank you, Dr Goodnight, for being the modera-
tor of this session on surgical oncology. Thank you, Dr Essner, for reviewing our manuscript. I appreciate your comments. I agree with you that your group including Dr Morton, you, and other colleagues have revolutionized the biology of solid cancer to bring us to a new level with the development of sentinel lymph node concept. With the dawn of the sentinel lymph node era, the approach to solid cancer has changed. Globally, there are probably 3 major hypotheses to explain cancer metastasis, initially proposed by Dr William Halsted with the primary cancer spreading first to the regional lymph node before metastasizing to the distant sites. Based on an extensive breast cancer database, a systemic hypothesis was developed by Dr Bernhard Fischer with systemic dissemination at the inception of cancer growth in the primary site. Subsequently, the data show that neither of the 2 hypotheses fitted perfectly well, so Dr Samuel Hellman from Harvard postulated a spectrum hypothesis, in which metastasis is a progressive process with early cancer spreading to regional lymph nodes first and cancer disseminates as progression takes place.

The sentinel lymph node concept and the clinical outcome with respect to sentinel lymph node status and survival fit nicely with the spectrum hypothesis. It has been found that 98% of early breast patients may be cured of their disease without recurrence.

We know that melanoma, if intervened in its early stage, can be potentially cured. And yet, at a certain point, it would spread to the sentinel lymph nodes. Within the period of progression in the sentinel lymph nodes, vascular invasion might ensue, resulting in stage IV disease, for which surgical resection is quite limited. Thus, there is a paradigm shift to resect cancer as early as possible.

In today’s presentations, the melanoma, breast cancer, colon cancer, and pancreatic cancer data all have a thematic point that the lymph node is a critical station for cancer spread. When the lymph node is involved, it indicates that the tumor burden has increased to a significant level for further systemic metastasis being consistent with the spectrum hypothesis.

Now, to specifically answer Dr Essner’s question. In terms of the technique, it is very well standardized. Basically, we inject intradermal technetium sulfur colloid for dynamic imaging. With the dynamic flow, which means that you have to watch the channels right after injection, we will be able to appreciate single and multiple channels much better. Still, in certain situations, it would be nice to have a 3-D dynamic rotation of the patient, which we don’t; particularly in the groin area it could be very helpful. The technique was the same for different locations of the primary melanoma. Although more than 1 nuclear medicine physician was involved with the lymphoscintigraphic reading, they agreed uniformly with the definition of single and multiple lymphatic channels.

With respect to other melanoma high risk factors, multivariate analysis showed that multiple lymphatic channels were an independent high risk factor with respect to disease-free and overall survival. However, the rate of sentinel lymph node positivity is similar in the single and multiple channel group. Our original hypothesis was that multiple lymphatic channels
would facilitate the cancer cells to spread to the sentinel lymph nodes much easier. Therefore, the chance of sentinel lymph node positivity would be significantly increased, but that is not the case. We are not able to correlate the lymphatic channel with the in-transit metastasis, as the incidence of in-transit metastasis is too low for statistical analysis.

We did not include the head and neck patients, because the head and neck lymphatic drainage system is much more complex. We want to simplify this study by just addressing the difference between single vs multiple channels. As to the number of nodal basins, it has been found that multiple nodal basins tend to have a worse prognosis as stated in this paper. In this study, we are only interested in a single basin in which single and multiple channels are being compared.

Finally, the mechanism of multiple lymphatic channels in melanoma metastasis is still being pursued. Perhaps when there are multiple channels there could be an increased number of lymphovenular connecting channels to allow the cancer cells to move from the lymphatic channels into the vascular system. This transfer of cancer cells through the lymphovenular channels may explain that the disease-specific survival is significantly lower in multiple lymphatic channel group and yet there is no difference in sentinel lymph node positivity between the single and multiple channel group. Another reason could be due to the flow, which may be increased in the multiple lymphatic channel group. Dr David Nathanson from Henry Ford Hospital in Michigan has demonstrated that in the animal model, transport of cancer cells may be enhanced with increased lymphatic flow. The last reason could be explained on the molecular level with expression of increased VEGF-C in the primary melanoma and research is ongoing in this area. Further, we are collaborating with Dr Marlys Witte at the University of Arizona to isolate the lymphatic channels leading to the sentinel lymph nodes and study the molecular profile of the endothelial cells of these channels.

James E. Goodnight Jr, MD, Sacramento, California: We will wind up shortly, but I cannot resist. Did these nasty melanomas just get lucky? Do they have a bunch of routes to the node, or are they in fact building their own bridges to the nodes?

Dr Leong: That is an excellent question because there is evidence from Harvard that there is actually de novo synthesis of lymphatic channels induced by the melanoma cells.

Dr Goodnight: Those nasty buggers are building their own bridges. Dr Ko, Dr Bilchek, Dr Wong, obviously it is going to be hard to do that anatomically in GI [gastrointestinal] cancers, but is the potential there that a molecular marker of this phenomenon would tell you that the bad GI cancer is doing the same thing. Is that a possibility?

Clifford Y. Ko, MD, Los Angeles, California: I think that there are many molecular markers that are now being examined and, unfortunately, not uncommonly with conflicting or inconsistent results. A probable step in the right direction would be to combine the data in some kind of systematic way to help elucidate effectiveness, predictability, etc. I think organization is needed, and of course time will tell.

Dr Goodnight: Dr Wong, you see what you have done. Now I am going to have to wrap myself around the concept of multiple lymphatics as well as node ratios.

Jan H. Wong, MD, Honolulu, Hawaii: It has been a tough afternoon for you, hasn’t it?

Dr Ko: I have one question for Dr Leong. Is 2 worse than 1, and is 3 worse than 2?

Dr Leong: The number of patients is too small for such an analysis, but I think with multiple centers, and I would like to mention that we do have a sentinel lymph node working group that can organize such a study.

Dr Goodnight: Thank you very much. The poster session awaits us. I certainly want to thank Drs Iddings, Hsiang, Wong, Tomlinson, and Wall for just a beautiful set of presentations. This is a rich set of papers as much as anything for the massive issues that they touch on. The lowly lymph node indeed has a new lease on its existence in a new era. It is quite exciting. I want to thank the panelists. Thank you very much, indeed, gentlemen. Thanks to the audience for your staying power and the program committee for taking a new stand. This has been dramatically interesting to me. Thank you.

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