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Clinical patterns of metastasis*

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Abstract In human solid cancer, lymph node status is the most important indicator for clinical outcome. Recent developments in the sentinel lymph node concept and technology have resulted in a more precise way of examining micrometastasis in the sentinel lymph node and the role of lymphovascular system in the facilitation of cancer metastasis.

Different patens of metastasis are described with respect to different types of solid cancer. Expect perhaps for papillary carcinoma and sarcoma, the overwhelming evidence is that solid cancer progresses in an orderly progression from the primary site to the regional lymph node or the sentinel lymph node in the majority of cases with subsequent dissemination to the systemic sites. The basic mechanisms of cancer metastasis through the lymphovascular system form the basis of rational therapy against cancer. Beyond the clinical patterns of metastasis, it is imperative to understand the biology of metastasis and to characterize patterns of metastasis perhaps due to heterogeneous clones based on their molecular signatures.

Keywords Cancer metastasis · Sentinel lymph nodes · Lymphovascular system

Introduction

Clinical aspects of lymph node metastases

Substantial data exists that indicates no survival difference between patients who undergo regional node dissection and those who undergo lesser dissections or no dissection, for melanoma, head and neck cancers, gastric, colorectal cancers, and particularly breast cancers. These clinical studies all confirm the indicator function, or statistical relationship, but question the outcome- governing role of lymph node metastases [1]. Thus, the purpose of a sentinel node biopsy or regional node dissection is not to improve survival, since that has not been clearly demonstrated, but to collect diagnostic and prognostic information to help select systemic therapy to improve prognosis. Since patients do not die of regional disease, but from systemic metastases in vital organs, prognosis can only be improved by preventing distant micrometastases from occurring or developing in the vital organs. When clinically node-negative breast cancer patients do not have axillary dissection with breast conservation and

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radiation therapy, the clinical risk of axillary recurrence may be 2% or less [2–4]. Thus, not only do we not jeopardize patient's lives by not dissecting the axilla in breast cancer, but we do not jeopardize them regionally because of a very low regional recurrence rate. In patients at extremely low risk for axillary nodal metastases, such as mammographically discovered, low grade T1a or T1b cancers without lymph vessel invasion or poor nuclear grade, even sentinel node evaluation may be avoided. Sentinel node biopsy will be useful in patients with a modest incidence of lymph node metastases (5% or more) and where the primary tumor features would not allow decisions about systemic therapy. Finally, traditional axillary dissection may be appropriate in primary breast or thyroid cancers with clinical metastases to remove a palpable lesion that might undergo progressive growth and create local palliative problems. In a clinically positive axilla, when confirmed by fine needle aspiration cytology, one might argue that axillary dissection has therapeutic benefit since it removes a palpable lesion and results in extremely low rates of axillary recurrence.

In recent years, there has been a dramatic decrease in the size, grade, lymph node metastases rate, probably due to downstaging of breast cancer from the impact of extensive mammographic screening [5]. The current median maximum diameter of all breast cancer in the State of Rhode Island is only 1.5 cm and the lymph node metastasis rate is only 26% [5]. Of invasive breast cancers discovered only mammographically, the median maximum diameter is about 1 cm, the positive node rate is less than 20% and few are of high grade [6–8]. Eighty percent of breast cancer sentinel node biopsy programs in the United States use routine immunohistochemical staining of multiple sections of the sentinel nodes without, at present, understanding the meaning of such special techniques, discovered micrometastases. For example, the results of one report are biologically implausible, since a single IHC discovered micrometastasis in a single lymph node 10 years later in a retrospective subset analysis of 20 patients out of almost 1,000 decreased the survival rate by as much as 50% [9]. Such a dramatic survival decrement associated with a few metastatic cells is greater than that seen when the patient has one to three lymph node macrometastases in traditional analysis. This particular study, while originally a randomized controlled trial, was subjected to this retrospective selective subset analysis by pathological redefinition of axillary lymph nodes. Thus, it cannot be taken at face value. The current and most appropriate clinical biologic model (the "Spectrum" model) [10] supplants the previous "Fisherian" model, which assumed that all breast cancers were systemic from their onset, which in turn had displaced the "Halstedian" lymphatic- system-dominant model [11] that controlled thinking until the 1970's. In Halsted's time, it was assumed that lymph nodes were filters and only when the filter was filled with cancer cells did further cells "spill over" into the distant lymphatic vessels, which led directly to distant organs [11]. In the "Spectrum" model [10], the size and evolving features of the genetically unstable cancer undergoes continued growth, and results in greater virulence, increased likelihood of metastatic spread, a greater dose of cancer cells, and increasing risks of death. The vast majority (>75%) of current early breast cancers correspond to this model, in which ability to metastasize increases as size and resultant biological potential increases. Very small cancers with few exceptions have little ability to develop clinical metastases [12]. Dramatic clinical evidence of the selective nodal metastatic pattern exists in differentiated thyroid cancer in younger, low-risk patients [13]. None of the published risk group definitions indicate that lymph node metastases have a relationship to survival. This unique clinical situation with very frequent nodal metastases but excellent survival is replicated in carcinoid cancers of the gastro-intestinal tract [14, 15]. The frequency of lymph node metastasis without distant organ metastasis in these two may help us to understand the role of lymph node metastasis in general in a more scientifically logical way.

Patterns of metastasis in malignant melanoma

Melanoma usually progresses from an *in situ* growth phase to a radial growth phase in which it expands into a vertical growth phase, which is associated with increased risk of metastasis. Nodal status is the most important predictor of clinical outcome in melanoma [16, 17]. In the pre-sentinel lymph node (SLN) era, several retrospective studies noted that the regional nodal basin was the most common site of metastasis. Patients with primary lesions ranging from 0.76 to 1.5 mm thick developed nodal recurrence 25% of the time within 3 years. When the Breslow thickness increased to 1.5 to 4 mm, the percentage of nodal metastasis increased to 60% within 3 years. On the other hand, systemic metastasis was less common but its incidence was also correlated with the thickness of the primary tumor. Patients with primary lesions from 1.5 to 4 mm thick developed systemic metastasis in 15% of the time within 5 years of the diagnosis [18]. These retrospective studies indicate that, in general, during the early phase of melanoma proliferation, the pattern of metastasis to the regional nodal basin is the predominant one, but a minority of the patients will develop systemic disease. In an autopsy series of 216 melanoma patients, the lymph nodes and lungs were the most frequent sites of involvement [19]. In addition, melanoma was found in multiple organs, indicating that in late stages of the disease, dissemination was widespread. On the basis of the autopsy reports, it was evident that clinical and histologic features did not predict patterns of metastasis. When melanoma disseminated widely, survival was usually short, but when dissemination was limited, survival

was longer. Indeed, isolated metastases could potentially be resected, resulting in longer survival, but patients with multiple metastasis usually did quite poorly. The relationship between Breslow thickness and the sentinel node status is linearly correlated. Because of the accuracy of harvesting the SLNs as a staging method, the 6th edition of the American Joint Committee on Cancer for melanoma has been revised to incorporate SLN status [20]. Melanoma progression can be further defined in terms of primary melanoma proliferation, metastasis to the SLNs or distant sites, progression from SLNs to non-SLNs, progression from SLNs or from non-SLNs to systemic sites [21]. In general, the process of metastasis takes place in an orderly fashion from the primary site to the regional SLNs before disseminating systematically. Occasionally, early blood-borne metastasis may occur.

The role of harvesting the SLNs is to provide accurate staging at the initial diagnosis of primary invasive melanoma of 1 mm or greater [22]. The staging procedure is often accurate, resulting in reduced morbidity and cost when compared with an elective lymph node dissection. Several recent studies have shown that SLN status is a strong and reliable prognostic indicator [23]. The IHC negative group can further be subgrouped when paraffin-embedded tissues are used [24]. Both SLN and polymerase chain reaction (PCR) negative patients enjoy survival approaching nearly 100%, indicating that indeed melanoma with no metastasis to the SLN(s) can potentially be cured. Patients who are SLN negative but PCR positive have a significantly high recurrence rate in comparison to the SLN negative and PCR negative group. When paraffin-embedded SLNs from 162 IHC-negative patients were further studied using multimarker real time PCR, 41 (25%) showed positive signals; 5-year rates of recurrence were 40%, 63% and 78% when SLNs expressed 1, 2, and $\geq$3 melanoma markers, respectively, versus only 4% for PCR-negative SLNs ($p \leq 0.001$). This difference suggests that the IHC method fails to detect 25% of SLN micrometastasis. Thus, PCR is not only more sensitive than IHC in detection of micrometastasis in SLNs, but also clinically significant for recurrence. This is consistent with the high cure rate of patients with early invasive primary melanoma [25].

Early diagnosis of melanoma through education and surveillance should be encouraged. Since treatments for metastatic melanoma are still limited, it is imperative for oncologists to detect and resect an early cancer as soon as possible.

Patterns of metastases in breast cancer

Autopsy studies of women dying of breast cancer suggest that widespread metastatic disease with bones (70%), lungs (66%) and liver (61%) are the most common sites of spread. However, with early-stage breast cancer, the most common site for metastatic involvement is the regional nodal basin and specifically the SLN. In fact, the status of the SLN is the most powerful predictor of recurrence and survival in women with early-stage breast cancer. Lymph node staging is important in women with breast cancer in order to control local-regional disease, select patients for adjuvant therapy, identify the most important prognostic factor, and perhaps contribute to a survival benefit.

The SLN procedure in women with breast cancer has proven to be a win/win situation and very quickly has become the standard for the surgical approach to staging the axilla [26, 27]. Lymphatic mapping and SLN biopsy have proven to be a low morbidity procedure and at the same time provide the most accurate staging due to the fact that a more detailed examination of the SLN is now possible [28]. This more detailed examination of the SLN may include more sectioning, immunohistochemical staining or even RT-PCR assays for metastatic disease and provides the most sensitive and accurate staging information of the modal brain patients. Approximately 1356 patients with invasive breast cancer or ductal carcinoma in situ (DCIS) have been registered to the two breast programs at the Moffitt Cancer Center (MCC) and the Lakeland Regional Cancer Center (LRCC) in Florida. Lymphatic mapping and SLN biopsy were performed as part of the primary treatment of the breast cancer, with a combination mapping technique using either a parenchymal breast injection or an injection into the subareolar plexus of radiocolloid and blue dye. The SLN was harvested, after which a complete lymph node dissection was performed, if the SLN was positive. Detailed examination of the SLN consisted of multiple sections and immunohistochemistry staining. More recently intra-operative RT- PCR using mammoglobin and cytokeratin markers have been evaluated. The success rate of SLN identification in the axilla was 98%. Detailed examination of the SLN resulted in 28.6% of the patients with metastases, 60% of whom had disease confined to the SLN. Of the 809 women who had a negative SLN biopsy, two experienced a regional nodal recurrence after a follow-up period of 60 months. Cytokeratin staining "upstages" approximately 10% of the node-negative population defined by routine histology [29]. Intra-operative RT-PCR analysis of the SLN through the Veridex GeneSearch study has the potential of giving the surgeon immediate feed-back as to the status of the SLN with the same sensitivity of standard pathology, avoiding a completion lymph node dissection as a second procedure.

In published studies, missed micrometastatic disease is correlated with a worse outcome. There have been 25 studies of the clinical relevance of missed micrometastatic disease in breast cancer over the last 50 years and 6/7 of the largest studies that actually have enough statistic power to

determine small differences in outcome have shown that patients upstaged after a more detailed examination of the regional basin or SLN have increased recurrence rates and poorer survival than patients who are not. In Germany, studies have shown that bone marrow mictometastases is additive to regional nodal staging, a finding that may be confirmed in the ACOSOG Z-10 study. Data would suggest that due to the more accurate nodal staging methods that are standard today, women with breast cancer that is staged as node-negative with the lymphatic mapping procedure will have a much better prognosis than women staged as node-negative with an axillary node dissection in the past. Lymphatic mapping and SLN biopsy have proven to be the least morbid and most accurate methods for performing regional nodal staging and are the standard of care for women with breast cancer. Bone marrow staging [30] and SLN staging may "ultrastage" the woman with breast cancer and begin to identify groups of women who may be spared the toxicity and expense of adjuvant chemotherapy.

Patterns of metastasis in head and neck cancer

The lymphatic system of the head and neck is complicated [31–35]. An extensive analysis of 2044 medical records of patients with squamous cell carcinomas of the head and neck who had not received prior treatment led Lindberg to divide nine lymph node regions on each side and, additionally, the parited lymph nodes [36]. The lymph fluid of the upper aerodigestive tract is drained via about 300 regional cervical lymph nodes, which are divided according to the current classification established by Robbins [37] into nine lymph node levels (level I–VI).

Due to the fact that the prognosis of patients suffering from squamous cell carcinoma of the upper aerodigestive tract depends significantly on the presence or absence of lymph node metastasis, the question of detecting clinically occult lymph node metastases is still important concerning the management of the clinical N0 neck. The published rate of lymph node metastasis depends on the location of the primary tumor, with values from 12% to over 50% (median, 33%) [38–40]. Numerous authors favor elective treatment of the lymphatic region (neck dissection) if the presence of occult lymph node metastasis can be expected with a probability of 20% or more. However, other authors prefer to adopt a "wait and see" strategy, although this requires both great compliance from the patient and great expertise on the part of the responsible physician to identify metastasis early. Another argument in favor of elective neck dissection versus a "wait-and-see" strategy is the significant deterioration of the survival rate when neck disscetion is due after clinical disease is defected [41–43]. The elective treatment of the regional lymphatic drainage can generally be performed either surgically or radiotherapeutically. The choice of one of these procedures generally depends on the therapy of the primary tumor. An advantage of elective neck dissection over radiotherapy is that the histological examination of the neck dissection specimen can give important information for deciding therapy, as well as about the prognosis [44]. Thus, the sentinel node concept for squamous cell carcinomas of the upper aerodigestive tract is quite appealing. Contrary to what is done in cases of malignant melanoma and breast cancer, the technical performance of dynamic lymphoscintigraphy of the head and neck should not be limited to the isolated description of the injection point and the first draining lymph node station. An adequate evaluation and anatomic assignment of the draining lymph node station is improved by the additional description of the head and neck silhouette [45]. Furthermore, limits and pitfalls of SLNs for head and neck squamous carcinoma discussed elsewhere [46] illustrate that an advanced intranodal tumor growth with extracapsular metastatic spread, leads to a significant reduction of the radiotracer uptake [35, 47]. Even small, clinically unsuspected lymph nodes may reveal extracapsular tumor growth with resulting lack of radiopharmacon accumulation [48, 49]. The lymphatic drainage directions of the different primary tumor sites of the upper aerodigestive tract described by our group using the above mentioned method emphasize the validity of this procedure. The results correspond to the classic images of the regional lymphatic drainage. The dominating metastatic region of pharyngeal and laryngeal carcinomas is mainly level II and less commonly, level III. Carcinomas of the anterior oral cavity drain mostly into level I and less commonly into level II. Accordingly, neck dissection of these lymph node levels can be expected to include the majority of clinically occult metastases.

With this background, it must still be clarified whether the intraoperative identification of the radiolabeled SLN is appropriate to reduce the extent of selective neck dissection in the suspected N0 neck, or whether neck dissection can be completely avoided in the case of histologically-proven tumor-free SLN. Opponents of such a procedure argue that selective neck dissection already has a morbidity that must be considered. Supporters of sentinel lymphadenectomy stress both protecting the intact, i.e. non-metastatic, cervical lymph node systems and reducing the extent of surgery. Scarring contractures, paresthesia, and persisting lymph edemas can be reduced by a selective SLN dissection.

Current research aims to optimize surgical access to the SLNs. Alternative approaches, such as video-assisted endoscopic surgery techniques are very interesting as they are already established, especially in the fields of gynecology and visceral surgery [50–52]. The first results on endoscopically performed selective lymphadenectomy led to the assumption that this method of lymph node dissection could achieve some significance in the therapy of the clinical N0 neck, provided that it is based on the SLN concept [53].

However, the techniques would have to be optimized. Furthermore, prospectively collected data should be gathered and analyzed. Within such an investigation, it would make sense to examine frozen sections of the excised lymph node. Depending on the histopathological result, a surgical resection of the lymphatic drainage in the form of a selective neck dissection could then be indicated. At present, the technical diversity and importance of endoscopic lymphadenectomy in the neck shows scientific and clinical potential. The question about the significance of the procedure, however, can not yet be answered conclusively.

Patterns of metastasis in upper GI cancer

The spreading pattern of upper GI cancer is not one of orderly progression. Understanding this pattern is essential to planning the therapeutic strategy. SLN mapping has provided us with the evidence-based information on the lymphatic drainage route from GI cancer. Although distant metastasis is associated with hematogenous mechanisms of cancer dissemination, some organ metastases are closely related to the lymphatic spread.

Lymphatic spread

Anatomical skip metastases were found in 50%–60% of esophageal cancers and 20–30% of gastric cancers in a retrospective analysis of the location of solitary metastases [54, 55]. Sano et al. reported that the perigastric nodal area close to the primary tumor is the first site of metastasis in 62% of gastric cancers, based on a retrospective analysis of cases of solitary metastasis [56]. From these clinical observations, extended radical procedures such as esophagectomy with three-field lymph node dissection and gastrectomy with D2 lymphadenectomy have become recognized as standard procedures in Japan, even for clinically node negative cases [57, 58]. However, a significant increase of morbidity and mortality after these invasive procedures was reported in randomized trials [59, 60]. To eliminate the need for highly invasive surgery in all cases, SLN mapping may be used to obtain individual information that can be used to modify the surgical procedure and other multi-disciplinary approaches.

Several studies supporting the validity of the SLN concept in upper GI cancers have been reported in the past few years [61–64]. The increasing prominence of endoscopic surgery since the early 1990's has changed surgical thinking in the field of GI surgery. Now the application of SLN mapping in the management of GI malignancies is a riveting topic in surgical oncology. Based on promising results from single institutional studies, multi-center prospective trials for SLN mapping for gastric cancer are on-going in Japan [65]. Lymphatic spread from Barrett's cancer is different than that from squamous cell carcinoma in the same location. The incidence of anatomical skip metastases from Barrett's cancer is relatively low [66]. This discrepancy might be attributed to the anatomical and functional alterations of lymphatic drainage routes by associated chronic inflammation with gastro-esophageal reflux disease.

Distant organ and other metastases

In esophageal cancer, hematogenous metastasis is also as common as lymphatic spread, according to clinical experience and autopsy data [67, 68]. Intramural metastasis is the characteristic metastatic pattern of esophgeal squamous cell carcinoma and closely related to lymphatic and distant dissemination and poor prognosis [69]. Gastric metastasis from esophageal cancer is also closely related to poor prognosis and to location of the primary lesion (middle thoracic location), size of tumor (>7 cm), histologic type (undifferentiated) and depth of invasion (T4) [70]. Sites of hematogenous recurrence in patients with esophageal cancer are related to the location of primary lesions. Lung metastases are associated with cervical lymph node metastases from upper esophageal cancer, and liver metastases are associated with thoracic metastases from lower esophageal cancer [71]. These observations suggest that the lymphogenous organ metastases exist in some of the patients with upper GI cancer. Yamagata et al. found lymphogenous liver metastasis by lymphaticovenous communication in an animal model [72]. This phenomenon was clinically supported by Kumagai et al, who demonstrated the correlation of liver metastasis and lymphatic advancement in gastric cancer [73]. Peritoneal dissemination is a common metastatic pattern of gastric cancer. Peritoneal dissemination is observed as a initial recurrence in 20–30% of patients who underwent curative surgery for gastric adenocaricinoma and is related to the diffuse type of the distal tumors [74]. Distant recurrence is related to the intestinal type of the proximal tumors [74]. The overall recurrence rate after curative surgery for early gastric cancer is generally low (1.9%). In this patient population, node-positive cases showed a relatively high rate of recurrence (10.7%) and differentiated tumors showed a 2.3% rate of hematogenous metastasis [75].

Patterns of metastasis in colorectal cancer

Our knowledge of the patterns of metastasis in colorectal cancer is incomplete due to the limited resolution of imaging techniques, the possible sampling errors during surgical procedures, and the inclusion of patients with advanced disease in autopsy series. Almost 50% of patients with colorectal cancer have distant tumor spread at the time of their diagnosis. The most common sites for tumor spread are the regional

Table 1 Metastasis from colorectal cancer in autopsy series [76]

Lymph nodes	52%
Liver only	26%
Lung only	10%
Liver and Lung	36%
Peritoneal	25%
Spleen and Heart	<10%
Brain, Kidney, Thyroid, Bone	<3%

lymph nodes, the liver, the lung, and the peritoneal cavity (as shown in Table 1) [76].

For patients without disseminated disease, metastasis to the regional lymph nodes is the most important prognostic factor. Many studies have demonstrated that adjuvant therapy improves survival in patients with lymph node metastasis. The risk of nodal metastasis increases with the level of tumor penetration in the bowel wall; it is approximately 10% for tumors penetrating into the submucosa, 22% for tumors penetrating into the muscularis propria, and 56% for tumors that reach the pericolonic fat. Tumor grade also seems to have an impact on the risk of nodal metastasis; patients with poorly differentiated and undifferentiated tumors have a higher risk of nodal metastasis than patients with well or moderately differentiated tumors. Tumors with some histological features such as lymphatic vessel invasion and blood vessel invasion also have a higher risk of nodal metastasis than tumors without such histological features. The patterns of lymph node metastasis are different for tumors of the colon and rectum, and should therefore be considered separately. The regional lymph nodes in the colon are classified in four groups: the epicolic nodes, distributed along the vasa recta in the wall of the colon and epiploic apendices; the pericolic nodes, distributed along the marginal vessels; the intermediate nodes, distributed along the vessels, such as the sigmoidal, left colic, middle colic, and ileocolic; and the central or apical nodes, located along the inferior mesenteric and superior mesenteric vessels. Lymph node metastases in colon cancer occur primarily to the pericolic nodes (97% of patients with nodal metastasis), intermediate nodes (27% of patients with nodal metastasis) or central nodes (11% of patients with nodal metastasis) [77, 78].

Metastasis to the pericolic nodes occurs mostly within 7 cm from the primary tumor. The average distance of nodal metastasis from primary tumor increases with T stage; it is 2.5 cm for T1 tumors, 5 cm for T2 tumors, and 7 cm for T3 tumors. Metastases occurring 10 cm from the primary tumor are exceptional [77]. Skip metastasis to the central nodes without involvement of the pericolic lymph nodes occurs infrequently. In rectal cancer, the main lymphatic spread is upwards to the mesorectal lymph nodes located along the superior rectal vessels [79]. In most rectal cancer patients, nodal metastasis lay within the mesorectum, 3 cm or less from the primary tumor, but in almost 25%, nodal metastasis occurs near the bifurcation of the superior rectal vessels [80]. As in colon cancer, lymphatic spread progresses upwards in an orderly fashion, but in some patients, spread can be discontinued [80]. The presence of nodal metastasis in the mesorectum distal to the primary tumor occurs in up to 20% of patients. Most of these metastases are located within 2 cm from the lower margin of the primary tumor; nodal metastases beyond 4 cm are exceptional [81–83].

Tumors in the lower third of the rectum can spread along the middle rectal vessels towards the internal ileal nodes. Metastasis to the internal ileal nodes occurs in 12% of patients with rectal cancer undergoing radical surgery and this proportion increases with tumor penetration in the rectal wall [84].

Tumors involving the anal canal can metastasize to the inguinal lymph nodes. The number of lymph nodes retrieved from surgical specimens and analyzed pathologically varies significantly. It depends primarily on the, size of the tumor, the surgical technique and the diligence of the pathological exam [85].

The number of nodes harvested directly influences the staging of colorectal cancer; the higher the number of nodes retrieved, the higher the probability of finding nodal metastasis [86]. Data from several studies suggests that a minimum of 12 nodes should be analyzed for adequate staging [87]. Several studies have demonstrated that the total number of nodes retrieved had a significant impact on patient survival [88, 89]. Unfortunately, only 37% of patients undergoing curative surgery for colorectal cancer in the United States undergo adequate lymph node evaluation [90]. Analysis of the distribution of metastatic disease in autopsy series had contributed to the development of a cascade hypothesis that metastatic disease develops in discrete steps, first to the liver, then to the lung, and finally to other sites. In a series of 1541 autopsies from different centers in the United States and Europe, Weis et al. found that only 15% of patients without liver metastasis had metastasis to the lung or other organs, compared to 52% of patients with liver metastasis. Seven percent of patients without liver metastasis had metastasis to distant organs other than lung, compared to 27% of patients with liver metastasis, and 55% of patients with liver and lung metastasis [91]. According to the cascade hypothesis, the distribution of metastasis in distant organs would be correlated with target organ blood-flow, with the exception of the bone marrow and thyroid.

The pattern of distant metastasis is slightly different in patients with rectal cancer than in patients with colon cancer. In rectal cancer patients, metastasis to the liver is as common as metastasis to the lung. The high frequency of lung metastasis has been attributed to the potential hematogenous spread of distal rectal cancer through the inferior iliac veins and the

inferior vena cava. Animal studies have demonstrated a streamlined flow of portal blood to the liver. Blood derived from the superior mesenteric vein tends to flow though the right lobe of the liver, whereas blood derived from the splenic and the inferior mesenteric veins flows preferentially though the left lobe of the liver. This streamlined flow has been thought to be the potential cause of the preferential location of the liver metastasis within the liver—depending on the site of origin of the tumor in the different segments of the large bowel. Several studies have demonstrated that metastases from colorectal cancer are twice as common in the right lobe of the liver than in the left, but this predominance is independent of the location of the primary tumor [92]. The role of SLNs in staging of colorectal cancer will be discussed in this issue (Aikon et al. pg 269–277).

Patterns of non small cell lung cancer

Non-small cell l lung cancer (NSCLC) now accounts for nearly 85% of all newly diagnosed lung cancers in the United States. Lung cancer has recently eclipsed hepatocellular carcinoma as the dominant cancer killer worldwide, with an estimated 1.2 million lives claimed annually. In the United States, lung cancer kills more people than colorectal, prostate and breast cancers combined. In 2004, approximately 168,000 people were diagnosed and approximately 155,000 patients succumbed to their disease for an average 14.5% survival rate. Survival remains comparatively abysmal for this dominant cancer killer worldwide, due to late stage at diagnosis, comparatively ineffective systemic control agents and lack of better understanding of the molecular pathogenesis of the disease [93].

Recently, much discussion has taken place regarding the role of spiral CT screening for at risk populations. A large randomized prospective trial has been initiated comparing spiral CT to chest X ray. Fifty-thousand patients have been enrolled countrywide within the past year and half. This new focus on early detection should lead to earlier stage at diagnosis and higher chance of cure. In concert with this have been the developments of minimally invasive surgical techniques for anatomic resections and the emerging role of SLN mapping for intra-operative staging and decision making [94]. Regional and mediastinal nodal involvement in lung cancer portends a worse survival. In fact, in the later 1980's to early 1990's, intra-operative determination of mediastinal nodal disease (N2 stage IIIa) was found to have less than 15% long-term survival despite "complete" resection. This led several investigators to study the use of induction chemotherapy and chemo-radiotherapy for locally advanced, stage IIIa disease. This has become, in most centers, the accepted new standard of care [95–97]. Yet, even with induction regimens and successful complete resections, positive long-term outcomes remain challenging due to the innate biologic aggressiveness of most NSCLCs (in particular, adenocarcinomas) and their propensity for early dissemination. As a result, newer techniques for accurate intra-operative and pre-operative staging are required and emerging. PET scanning and CT/PET in lung cancer, like in many solid organ cancers, has become an important tool for accurate non-invasive staging. In most cases of NSCLC, PET upstages at least 20–25% of patients, thereby preventing futile thoracotomies. Intra-operative SLN staging may be used in addition to pre-operative PET and PET/CT to identify patients with regional (hilar N1) and locally advanced (ipsilateral mediastinal N2) prior to resection to allow more accurate staging and use of combined modality therapies [98].

Over the past five years, several investigators and thoracic surgeons, especially groups in Japan and the United States [99–103], have been pioneering the use of intra- operative SLN mapping for early stage NSCLC patients. As a whole, they have developed several techniques that now focus on the use of direct primary tumoral injection with typically radiolabeled technetium colloid as well as trypan blue dyes to map nodal patterns and to determine feasibility and locations of SLN. Numerous reports over the past few years have demonstrated refinements in techniques and have validated the concept of SLN mapping. In most series, that unfortunately are small phase I pilot studies, SLNs are identified in the vast majority of cases and confirmed intra-operatively by both frozen section H&E staining and scintigraphy. The success rates vary from 60–95% in these small series. What the true role is for SLN mapping in NSCLC remains controversial. Unlike in breast and melanoma surgery, where sentinel node determination has been well studied and can preclude larger more debilitating regional node dissections, in the chest, most node dissections, even radical mediastinal lymphadenectomies, are reasonably well tolerated. Yet, the ability to determine by SLN testing the rational need for complete hilar or mediastinal node dissection especially by minimally invasive surgical techniques is attractive. Undoubtedly, as experience grows with the use of SLN detection, fewer radical node dissections will be done or required for truly early stage lesions (T1N0 Stage Ia).

In summary, the role of SLN mapping in NSCLC is evolving. Early pilot studies have confirmed the feasibility and general reliability of the technique (typically incorporating a technetium colloid with intra-operative scintigraphy detection) but routine implementation has yet to occur. The advantages of SLN for lung cancer may be less critical than for other surgical oncologic procedures in which regional node dissections have more morbidity (lymph edema, nerve injury, etc). Yet, as the technique becomes more refined and more thoracic surgeons become versed in SLN detection, it is likely that it will become an important part of the thoracic surgeon's armamentarium. Advances in both the clinical

delivery of care, earlier detection, and more effective, rationally designed systemic targeted agents hold great promise for increasing survival rates for patients with NSCLC.

Why is papillary thyroid cancer to the regional nodes relatively "benign"?

As a human clinical model of a highly selective, organ-specific lymph node metastatic pattern, papillary thyroid carcinoma in young "low risk" patients is very pertinent. These young patients have a pattern of frequent (75%) regional nodal metastases when routine nodal resections are performed, but uncommon (<3%) distant metastases, (entirely confined to the lung when they occur), and a 99% disease-free survival rate at 20 years after treatment [13]. This selective nodal metastatic pattern is mimicked in carcinoid and islet cell tumors of the foregut and midgut organs such as the stomach, duodenum, pancreas, and intestine [14]. Nodal metastases are required to even define carcinoma in many pancreatic islet cell tumors, since histological criteria alone do not clearly differentiate malignant from benign. Lymph node metastases are common but are not controlling influences on survival, since that is determined entirely by distant vital organ metastases, particularly the liver in carcinoid tumors or islet cell cancers, or the lung in low-risk thyroid cancers. This pattern of specific "lymph node only" metastases without the poor prognosis arising from vital organ metastases (liver, lung, brain) mimics the animal research studies mentioned [1, 11, 104–115] that elaborate organ-specific metastatic patterns.

Dramatic clinical evidence of the selective nodal metastatic pattern exists in differentiated thyroid cancer in younger, low-risk patients [13]. None of the published risk group definitions indicate that lymph node metastases have a relationship to survival. This unique clinical situation of very frequent nodal metastases but excellent survival is replicated in carcinoid cancers of the gastro-intestinal tract [14]. The frequency of lymph node metastasis without distant organ metastasis in these two human cancers is consistent with the data from laboratory and animal research. It may also help us to understand the role of lymph node metastasis in a more scientifically logical way.

Despite frequent differentiated thyroid cancer lymph node metastases detected histologically, few patients actually develop clinical regional nodal metastases. However, 25% of young patients present because of clinically palpable cervical metastases from small occult thyroid cancers. The same is true for carcinoid tumors of the small intestine, where the desmoplastic reaction and bulk of lymph node metastases causes clinical bowel obstruction, even when the primary carcinoid tumor is very small and asymptomatic. Jejunal (midgut) carcinoid primary tumors 5 mm or less in diameter have a lymph node metastasis rate of 70%, and carcinoids between 5 and 10 mm in diameter have rate of 94%. The organ specificity of nodal metastases is here again uniquely displayed, but also occurs in other cancers.

Why does sarcoma metastasize via the vascular system rather than the lymphatic system?

Sarcoma is unique from other types of cancer in that its prognosis depends on its grade rather than its specific histological type. Except for epitheloid sarcoma and angiosarcoma, which may spread to regional lymph nodes, most of the other types, including rhabdomyosarcoma, leiomyosarcoma, chondrosarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, lymphangiosarcoma and fibrous hystiocytoma, spread via the vascular system to the lungs most of the time [116]. A recent study by Billingsley [117] has shown that pulmonary metastasis is the predominant distant site of metastasis (23%), and that metastatic cells would spread via the venous circulation and settle in the lungs as metastatic foci. Genetically, sarcomas fall into two main categories. One category is characterized by a tumor-specific translocation that seems to be central to the pathogenesis of the tumor, and indeed is being incorporated as diagnostic criteria. The other category is characterized not by recurring, tumor-specific genetic alteration, but by complex karyotypes that are characteristic of severe genetic and chromosomal instability. Most sarcomas have abnormalities in the RB or p53 gene. **S**pecific genetic alteration leads to activation of specific tyrosine kinase growth-factor receptors, sarcomas have been successfully treated with drugs that specifically inhibit the activated kinase receptor [118].

Recent molecular studies have yielded greater insight to the biology of sarcoma, with even a therapeutic target against the *c*-kit receptor as in gastrointestinal stromal tumor (GIST) [119]. Additional studies using recently identified molecules of lymphangiogenesis may be applied to detect if such molecules are indeed absent in sarcoma. It is crucial to understand the molecular mechanisms of why sarcoma, unlike melanoma or carcinoma, seldom spreads through the lymphatic system.

Conclusion

In human solid cancer, lymph node status is the most important prognostic indicator for the clinical outcome of patients. Recent developments in the SLN concept and technology have resulted in the application of this innovative approach to define the first draining or SLN to which the cancer may have metastasized [22, 24]. The underlying thesis in solid cancer biology is that metastasis generally begins with an

orderly progression, spreading through the lymphatic channels to the SLN in the nearest LN basin. Thus, the logical approach is to harvest that specific SLN for thorough analysis. The critical issue to be defined is the role of the SLN in the process of lymphatic metastasis. Over the past two decades, advances have been made in understanding the functional anatomical, cellular and molecular aspects of the lymphovascular system. Significant advances have been made in the study of molecular events of metastasis through the lymphovascular system. Advances in SLN technology have made it possible to study micrometastasis in the SLN. Follow-up data has shown that about 80% of metastasis follows an orderly pattern of progression via the lymphatic network, whereas about 20% of the time, systemic metastasis occurs, bypassing the lymphatic system. Malignant melanoma has been proven to be the most ideal tumor model for studying the role of the SLN. Subsequently, selective SLN procedure has been applied to breast cancer, colon cancer and other types of solid cancer. Beyond the technical aspects of harvesting the SLN, the implication of micrometastasis remains to be defined. Harvesting the SLNs makes it useful as a clinical staging procedure, and opens up new opportunities to study micrometastasis and its evolution within the SLNs. The basic mechanisms of cancer metastasis through the lymphovascular system form the basis for rational therapy against the progression of metastasis and the molecules involved in the process of metastasis. New molecular and genetic tools may be used to understand the mechanisms of lymphatic and hemotogenous routes of metastasis. If such mechanisms can be understood, new therapeutic advances may be developed to prevent the process of micrometastasis. Research on multifaceted aspects of micrometastatsis including proliferation and differentiation of various clones from the primary tumor, the acquisition of adhesion molecules, the process of lymphangiogenesis versus angiogenesis, and host interaction with the microscopic tumor may lead to better understanding of mechanisms of metastasis and help us to develop therapeutic strategies to prevent the process of micrometastasis. Rather than targeting larger tumor burdens such as Stage IV disease, targeted adjuvant clinical trials can be developed for high- risk patients after they have had a definitive surgical resection.

Thus, in the future, we may be able to abandon some aspects of our surgical or systemic attack on development of clinical cancer metastases, such as lymph node removal or use of toxic chemotherapy, and instead, consider more physiological and less traumatic approaches to blocking the highly manipulable multi-step physiological process of metastatic progression. The future biological models of clinical cancer behavior will have to incorporate aspects of understanding the metastatic cascade, and particularly the host factors that permit progressive growth to clinical metastases.

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