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The Role of Lymph Node Staging for Clinical Decision Making in Patients with Solid Cancers

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The treatment of solid tumors is based on consideration of the 3 most important biologic factors affecting prognosis: 1) local extension of malignant tissue, 2) lymphatic dissemination, and 3) hematogenous spread. Currently, the TNM classification system of malignant tumors, periodically updated by the International Union Against Cancer (UICC) (1) and the American Joint Committee on Cancer (AJCC) (2), is used to describe the tumor status of a patient. The "TNM" acronym indicates that the staging system takes into account the local extent of the primary "tumor," its dissemination to locoregional lymph "nodes," and the presence of distant "metastases." Staging is intended to: 1) estimate the "life cycle" of a tumor; 2) assess the location and extent of malignant disease; 3) estimate the prognosis, risks of recurrence, and risks of mortality; 4) plan treatment (local and systemic therapy); 5) correlate anatomy and pathology with outcomes of disease and treatment; 6) unify reporting of clinical trials, and 7) increase knowledge of cancer biology.

The TNM system, originally developed about 50 years ago, defines a common, internationally accepted classification system for epithelial and connective tissue tumors at 44 anatomic sites (1,2). Specific criteria are described to define the locoregional extension of the primary tumor and the involvement of regional lymph nodes, and to identify distant metastases.

Radionuclide studies have been used for more than 50 years to demarcate the extent of tumor involvement. The neurosurgeon Sweet used beta detectors in the operating room to identify the tumor margins (3). This was followed by anecdotal reports by Pochin from London and Müller from Zurich, who used Geiger counters connected to needle probes to detect ^{131}I in residual thyroid tissue in patients undergoing thyroidectomy.

Despite this auspicious beginning, it was another 40 years before intraoperative radionuclide techniques became part of mainstream clinical care. An additional development that helped advance the field was radioimmunoscintigraphy, which in turn led to radioimmunoguided surgery. Surgeon Martin Jr., helped design a handheld gamma probe to detect residual/recurrent colorectal cancer during surgical exploration of the abdomen using anti-carcinoembryonic antigen (anti-CEA) monoclonal antibody (B72.3) labeled with ^{125}I (4). Use of the probe improved staging by searching for micro- and macroscopic tumor residues (indicated as R1 and R2, respectively). The intraoperative probe technology was particularly useful in identifying micrometastases and isolated tumor cells in lymph nodes, which is difficult when relying only on standard histologic procedures (hematoxylin and eosin, or H&E, staining). Combining use of the probe in the operating room for specific node identification with immunohistochemistry and molecular biology-based techniques (such as the polymerase chain reaction, or PCR) (5) greatly improves sensitivity in the detection of metastatic involvement of lymph nodes. These procedures modify tumor stage, often resulting in upstaging (6). While lymph node mapping and especially sentinel lymph node biopsy are invasive, they can spare the patient unnecessary aggressive node dissections.

Radioguided sentinel lymph node biopsy has become a standard surgical procedure. Proposed initially for penile cancer, it has been extended to melanoma and breast cancer, supplemented by vital or fluorescent dyes (7) administered at the time of sentinel node harvest. A number of studies are underway to determine the value of sentinel lymph node mapping in tumors affecting the head and neck, upper aerodigestive tract, thyroid, salivary glands, lungs, stomach, uterus, external genitalia, prostate, colorectal, and others (Table 8-1).

Effective radioguided sentinel lymph node biopsy requires a team consisting of the surgeon, a nuclear physician, and a pathologist (8) to optimize the technique of radioisotope and dye injection, the site of injection, the modality of sentinel lymph node identification (by color and radioactivity counting), excision and handling of the sentinel lymph node, and histology. The team must agree

Table 8-1. Intraoperative clinical applications of the gamma probe in different oncologic indications.

Indication of	Tumor type	Clinical utility
Sentinel lymph node by intra- or peritumoral administration of ^{99m}Tc-colloids	Breast cancer	++
	Melanoma	+
	Skin cancer	++
	Penile/vulvar cancer	++
	Colon cancer	±
	Lung cancer	±
	Head and neck cancer	±
Tumor deposits by tumor-seeking agents (monoclonal antibodies, ^{99m}Tc-sestamibi)	Colon cancer	±
	Ovarian cancer	−
	Breast cancer	−
	Medullary thyroid cancer	+
	Melanoma	−
	Neuroblastoma	±
	Parathyroid adenoma	++
Bone abnormalities by ^{99m}Tc-diphosphonate	Osteoid osteoma	++
	Bone lesions suspected for bone metastasis	++
Occult tumors by intratumoral administration of an isotope tracer	Occult breast cancer	++

Legend:
++ = proven clinical value
+ = may be of clinical value
± = clinical relevance insufficiently evaluated
− = proven not to be of clinical value
Source: Adapted from Ell PJ, Gambhir SS, eds. *Nuclear Medicine in Clinical Diagnosis and Treatment*. Vol 1. Edinburgh: Churchill-Livingstone; 2004:217–227, with permission from Elsevier.

on specific issues that include the site of radiocolloid injection (e.g., in case of breast cancer intratumoral, peritumoral, intradermal, or subareolar) (9,10), as well as the type and size of the radiocolloid particles, which are known to affect both the velocity of migration of radiocolloids and their retention pattern in the nodes (11).

Although the techniques work, false-negative cases (i.e., a sentinel lymph node free from metastatic involvement in the presence of other lymph nodes that are found to be metastatic at histology) occur with small but significant frequency. In addition, different distributions of the radiotracer and the vital dye in the nodal basin continue to occur in about 15% of cases. In a recent editorial, Goit (12) addresses the biological variables that possibly cause these events (13).

The sensitivity of immunohistochemistry and sentinel lymph node biopsy has led to the identification of small tumor cell clusters (i.e., <0.2 mm). It is unclear if these isolated tumor cells have the potential to produce metastatic disease (e.g. proliferation or stromal reaction) or invade blood vessel walls and sinusoid spaces in a lymph node.

The most recent revision of the TNM system (1,2), based on results from several large-scale studies and consensus conferences (14–17), suggests classifying the histopathologic status of sentinel lymph node(s) as: 1) "pNX(sn)" when no data are available; 2) "pN0(sn)" when the sentinel lymph node was analyzed and found to be free from metastasis, or 3) "pN1(sn)" when the sentinel lymph node was analyzed and found to harbor metastasis. In particular, isolated tumor cells are not to be taken into account (especially if identified with molecular biology techniques); thus a lymphatic basin where only isolated tumor cells were detected is classified as pN0, and there is no reason for upstage migration (Table 8-2).

Table 8-2. Example of correct notation for staging of isolated tumor cells and micrometastases.

Lymph node biopsy	Histologic finding	Size of lesion*	Notation
	1 node IHC positive	0.1 mm	pN0 (sn) (i+)
SLND	1 node H&E positive	0.1 mm	pN0 (sn)
SLND	1 node IHC positive	1.0 mm	pN1mi (sn) (i+)
SLND	1 node H&E positive	1.0 mm	pN1mi (sn)

Legend:
*Isolated tumor cells are defined as metastatic lesions no larger than 0.2 mm in diameter. Micrometastases are defined as metastatic lesions between 0.2–2.0 mm diameter. Metastatic cell deposits seen with immunohistochemical staining alone are considered to be equivalent to those seen on standard H&E staining.
H&E—hematoxylin and eosin staining
IHC—immunohistochemistry
SLND—sentinel lymph node dissection
Source: Data from and used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-New York, www.springeronline.com.

Radioguidance and Staging in Tumors

Melanoma

Sentinel lymph node biopsy is accepted worldwide as the method of choice to stage regional lymph nodes in patients with melanoma, even at unexpected/abnormal draining sites (which have a frequency of about 5%) (18). Because there are often many nodes (radioactive and/or colored), it is difficult to establish which are the true sentinel lymph nodes. In the Sunbelt Melanoma Trial of 1,184 patients, it was found that sometimes the most radioactive lymph node was negative for metastatic involvement, whereas other, less radioactive lymph nodes were metastatic (13.1% of cases) (19). It appears reasonable therefore to recommend resection and histologic analysis of all "blue" nodes and nodes with radioactivity count rates greater than 10% of the ex-vivo count rate of the node with the greatest radioactivity. This approach should reduce the risk of false-negative biopsies.

Another issue concerns the reliability of the histologic analysis of the node. A consensus is emerging that frozen section and H&E staining alone have too low a sensitivity for clinical use, since they demonstrate metastasis in less than 50% of the lymph nodes that actually harbor melanoma cells (20). Additional analysis with step sections and immunohistochemical staining increases the sensitivity.

Radioguided surgery is particularly useful in patients with melanomas that are located in the perineum, since lymph drainage is clinically ambiguous. These lesions may drain to nodes in the groin, iliac, and obturator regions, as demonstrated by lymphoscintigraphy (21,22).

Regional lymph node metastases (N1 to N3) define stage III disease and are cardinal prognostic variables for patients with cutaneous melanoma. In 580 patients whose sentinel lymph nodes (identified using dye and lymphoscintigraphy) were found to be free from metastasis, the status of the sentinel node was the single most powerful prognostic factor after Breslow thickness (23,24). Since patients with melanomas <1.0 mm thick rarely have nodal disease (25), sentinel node biopsy is not commonly performed in this group, but should be considered when negative prognostic features such as ulceration or Clark level IV to V invasion are present (26). For patients with melanomas that are >1 mm thick, sentinel node staging can be considered for prognostic purposes, and to evaluate eligibility for clinical trials and the need for adjuvant therapy. Accurate staging can identify patients whose risk of recurrence is sufficiently high to justify adjuvant systemic treatment.

Breast Cancer

The sixth edition of the TNM classification system introduced important changes in the classification of regional nodes in breast cancer, specifically: 1) modifying the role of metastatic involvement for lymph nodes of the internal mammary chain; 2) including again the supraclavicular lymph nodes (whose metastatic involvement is now defined as N3 and no longer as M1); and 3) adopting the definition of clinical apparent metastases for internal mammary nodes on the basis of imaging and physical examination (with the exclusion of lymphoscintigraphy). Micrometastases in lymph nodes (0.2–2 mm) are classified as pN1, and the parameters include the number of metastatic nodes (up to 3, between 4 and 9, or more than 10 involved, respectively) and the simultaneous presence of metastases in the axillary, and/or the internal mammary chain, and/or the supraclavicular lymph nodes (1,2).

According to the new classification, staging of the axilla can be based on either axillary dissection or sentinel lymph node biopsy. In the first instance, resection of the first level lymph nodes (lower axilla) is required for histopathologic classification. The specimen usually contains 6 or more lymph nodes; if less than 6 nodes are examined and they are negative for metastatic involvement, the classification is pN0.

In the case of sentinel lymph node biopsy, if only the sentinel node is resected and examined (without total axillary dissection), this factor is reported with a specific notation, for example pN1(sn). Although some investigators have reservations about this approach (27), the revised TNM classification recognizes that sentinel lymph node biopsy (including both lymphoscintigraphic mapping and intraoperative gamma probe detection) plays an important role in the care of patients with breast cancer. Nevertheless, consideration should be paid to some limiting factors of the procedure, such as partial lymphatic drainage to the internal mammary chain (in about 17% of the cases, if the radiocolloid is injected peritumorally), depending on the location of the primary tumor within the breast (28).

It is unclear whether lymphatic mapping and sentinel lymph node biopsy should be performed in patients with ductal carcinoma in situ. By definition, an in-situ breast cancer should not yet have invaded the lymphatic channels, yet foci of microinfiltration can be observed at extensive histopathology of some resected cancers that had been defined as in situ before resection (29). Another issue concerns the possibility of predicting metastases in nonsentinel nodes, when the sentinel lymph node is positive for metastasis (an event reported to occur in about 50% of the cases) (30). A confounding variable in patients treated with neoadjuvant chemotherapy before surgery is fibrosis of the lymphatic channels, which can raise the rate of false-negative sentinel lymph node biopsies in up to 33% of cases (31).

It is generally agreed that the combined use of a dye and radiotracer yields better identification rates (32,33).

The intraoperative analysis of the excised sentinel lymph node using "touch imprints" is fast, convenient, and highly sensitive for detecting tumor cells in the lymph node (34). On the other hand, staging of a residual tumor (R0, R1, R2) is not influenced if a marginal, apical, or sentinel node is metastatic (35).

Preoperative lymphoscintigraphy has become the standard of practice in breast cancer patients to detect nonaxillary sentinel lymph nodes (such as those of the internal mammary chain, as well as those located in the supraclavicular, subclavicular, and interpectoral regions, or the lateral and medial intramammary lymph nodes).

One prognostic factor is the number of positive axillary lymph nodes, based on at least a level I or II axillary dissection and a detailed histologic evaluation. As the number of involved lymph nodes rises, relapse rates increase and survival rates decrease. A second important factor is tumor size. Other factors such as patient age, hormone receptor status, and HER2/neu status are of lesser importance than node status and tumor size. Historical information suggests that patients with negative lymph nodes have a 60% to 75% 10-year disease-free survival, whereas those with positive lymph nodes have a 25% to 30% 10-year disease-free survival. The 1998 result of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated a proportional reduction in the risk of relapse and death in node-positive and node-negative disease for patients treated with adjuvant therapy. However, proportional risk reductions translate into larger absolute benefits for higher risk patients with node-positive disease than for lower risk patients with node-negative disease. While the absolute benefit of treating node-positive patients with chemotherapy is large enough to warrant the potential risks, it is reasonable to wonder whether the same is true for patients with node-negative disease (36).

Head and Neck Cancers

The usefulness of sentinel lymph node biopsy in tumors of the thyroid (37,38), salivary glands, or squamous cell cancers of the head and neck is still not established. It is clear that lymphoscintigraphic mapping identifies bilateral draining basins, suggesting nodal sites that can be sampled for staging, leading to selective nodal dissection or conservative management (39–41). In the neck, there are about 200 lymph nodes, with many separate anatomic structures adjacent to one another, so often the primary tumor and draining lymph nodes are in close proximity. On the other hand, elective neck dissection reveals lymph node metastases in an average 30% of clinically N0 patients, so in about 70% of patients this operation is unnecessary. Even the most advanced nuclear medicine imaging method, positron emission tomography (PET, which is useful for detecting local recurrences), is largely ineffective for evaluating tumor status of the sentinel lymph node(s), as well as of the second-echelon and contralateral nodes (42). Thus, lymphoscintigraphic mapping holds promise for guiding surgery, although larger trials and further experience (with longer follow-up studies) are necessary before radioguided sentinel lymph node biopsy becomes the standard of care for planning treatment (43,44). Different figures have been reported for clinically occult metastatic involvement of sentinel lymph node(s) identified under radioguidance: 21% of oropharyngeal cancer, 34% of squamous cell cancers of the tongue, and 34% and 45% respectively of oral and tongue cancers (45). However, in a series of 41 patients with primary head and neck cancers, radioguided sentinel lymph node identification failed in 3/9 patients with metastatic lymph nodes (46).

At the Tenth International Congress on Oral Cancer in April 2005 (Crete), investigators reported >95% negative predictive value for sentinel lymph node biopsy, suggesting that elective neck dissection should become clinical routine only in those patients with a metastatic sentinel lymph node (47). It was also noted that sentinel lymph node biopsy improves surgical staging, especially for patients with tumors located on the midline or crossing the midline, and allows better pathologic staging. Sentinel node biopsy can modify the prognostic assessment and is helpful for selecting patients for adjuvant therapies and/or more aggressive treatment protocols (48). In contrast to melanoma, here intraoperative frozen-section histopathology seems to be more reliable, since only 4 of 48 patients with metastatic involvement of the sentinel lymph node were missed on frozen-section analysis (49). Advances in molecular biology techniques (based on 1-step reverse-transcriptase polymerase chain reaction) also make it possible to detect metastases within an intraoperative timeframe (50). Lymphoscintigraphy is greatly improved when single photon emission computed tomography (SPECT) images are recorded and when the technique is used in combination with ultrasonography (51). Furthermore, lymphoscintigraphic mapping of the sentinel node can reduce the rate of complications (52), especially those related to unnecessary modified radical neck dissection (53). There was general consensus on the feasibility and usefulness of lymphoscintigraphic mapping for sentinel node identification and radioguided biopsy, leading to discovery of micrometastases in clinically N0 oral and oropharyngeal cancers (54–57).

Head and neck cancers are associated with a 20% to 30% incidence of occult cervical lymph node metastases, even with a clinically negative examination. These observations have led to the generally accepted need for elective lymph node neck dissection as part of standard surgical management (58,59). Patients who did not

undergo elective dissection were more likely to present with more advanced neck disease when disease recurred than those who opted for prophylactic lymph node dissection. The presence of lymph node metastases dictates the use of combination surgery and postoperative external radiation therapy. Surgery alone is reserved for those situations in which only a single lymph node is involved and where there is no extension of disease beyond the lymph node capsule.

Gastrointestinal Tract

Both blue dye and radiocolloids are used for lymph node mapping and identification of the sentinel node in patients with cancer of the gastrointestinal tract. Interstitial injection is performed either submucosally around the tumor (during endoscopy prior to surgery) or subserosally (during open or laparoscopic surgery) (60–62).

In esophageal cancer, a close correlation has been found between the number of sentinel lymph nodes (identified with the use of ^{99m}Tc-labeled rhenium sulphide), lymph node status, pathologic stage, and the number of metastatic nodes (63). Sentinel lymph node biopsy is especially useful in minimally invasive surgery (64). Lymph nodal status is the most powerful prognostic factor in esophageal cancer, and accurate staging is necessary to distinguish potentially curable patients from those with local advanced disease. Although esophagectomy remains the standard of care in early-stage tumors (stage I, IIA), its role is being questioned in patients with locally advanced disease (stage IIB, III) because of the generally poor outcomes following surgical resection alone. The overall 5-year survival rate for patients with esophageal cancer is 20% to 25% (60% to 70% for patients with stage I disease, 5% to 10% for patients with stage III disease).

In Japan, the high incidence of gastric cancer has led to evaluation of sentinel lymph node biopsy for patients with this type of tumor. The standard treatment for early cases is gastrectomy with en-bloc lymph node dissection. Lymphatic mapping has disclosed unexpected/aberrant sites of drainage, thus guiding surgeons to perform a regional dissection approach tailored to the individual patient. Both conventional histochemistry and molecular biology techniques have been applied in the search for micrometastatic involvement of the sentinel lymph node(s) (65,66). Management of gastric cancer depends upon complete resection of the primary tumor and extensive en-bloc lymph node dissection, but as yet there is no consensus on whether more extensive dissection (D2) improves survival compared with less aggressive surgery. Several studies have demonstrated that lymph node dissection limited to the D1 level understages 60% to 75% of patients, compared to a D2 dissection (67). The number of lymph nodes containing metastasis is an accurate predictor of clinical outcome: patients with more than 15 positive lymph nodes have an unfavorable outcome, comparable to those with distant metastatic disease. Furthermore, the 5-year survival rate ranges from 78% for patients with superficial tumors and negative lymph nodes (stage IA), to 7% to 8% for patients with metastatic N2 nodes or with distant metastases (stages IIIB and IV). In patients with lymph node metastases in the resected specimen, disease recurrences and cancer-related deaths are at least 70% to 80%. Recent meta-analyses suggest that adjuvant systemic treatment may confer a small but clinically significant improvement in survival (68,69), with the benefit to node-positive patients being greater than for node-negative patients (70).

Aberrant lymph drainage leading to modification of the intended surgical approach can be identified as well in 5% to 8% of patients with colorectal cancer. Lymphatic mapping and sentinel lymph node analysis performed with molecular biology techniques can detect micrometastases in up to 14% of the cases, identifying a subgroup of patients who can benefit from adjuvant chemotherapy. In a study of 492 consecutive patients (401 with colon cancer, 91 with rectal cancer), the overall success rate for radioguided sentinel lymph node identification was 97.8%, with most of the failures occurring in rectal cancers (8.8% of the cases, versus 0.7% for colon cancer), most likely due to local submucosal lymphatic fibrosis induced by neoadjuvant radiation therapy administered prior to surgery (71). The overall accuracy rate for predicting lymph node metastases was 95.4% (with 89.3% sensitivity), while the overall incidence of skip metastasis was 10.9%.

A minimum number of lymph nodes must be assessed for accurate staging of patients with colorectal cancer, as nodal status (the number of nodes resected and the presence of micrometastases) is crucial for planning treatment after primary surgery (72). Inadequate retrieval and assessment of sentinel lymph nodes is associated with worse outcome (e.g., in stage II patients) (73). Although lymph node mapping per se (either with blue dye or radiocolloids) does not generally modify the surgical procedure (which usually follows a standardized approach), it does identify the crucial node(s) to be submitted to extensive analysis with sophisticated laboratory techniques searching for micrometastases. Adjuvant chemotherapy is performed in the positive cases. The lymphotropic agents are most frequently injected subserosally during open surgery, with a specificity approaching 100% when using the blue dye (74), and during laparoscopic procedures (75). Submucosal injection is generally performed during endoscopy prior to surgery, and the use of radiocolloids is increasing (76).

The potential advantages of lymphatic mapping for patients with colorectal cancers and malignant polyps

(77) are less obvious than for those with breast cancer or melanoma, and the procedure is generally performed in strictly controlled clinical trials. Nevertheless, for colorectal cancer the simplest and most widely applied prognostic feature is the presence of lymph node metastases in the surgical resection specimen. Accurate staging of regional lymph nodes is critical not only for its prognostic relevance, but also for the therapeutic implications. While the 5-year survival rate for patients with stage I or II colorectal cancer is approximately 80%, those with metastatic lymph nodes have an approximately 50% 5-year survival. Furthermore, the presence of lymph node metastases represents the primary indication for adjuvant chemotherapy, whose therapeutic benefits have largely been proved (78,79). In stage II (node-negative disease with the primary tumor through the muscle wall) or stage III (metastatic involvement of regional lymph nodes) rectal cancer, adjuvant chemotherapy plus concurrent radiation therapy is based on clinical observations of the high incidence of pelvic recurrences and on the significant morbidity associated with local recurrences observed following surgery alone.

Urogenital Cancers

In cancers of the bladder and prostate preoperatively staged as N0, the optimal extent of regional lymph node dissection is under debate. Preliminary reports indicate that in bladder cancer it is possible to map the sentinel lymph node even outside of the obturator fossa. If this lymph node is metastatic, nodes from the obturator fossa must be dissected and removed. Nevertheless, further study is required to elucidate all the clinical and surgical implications of sentinel lymph node biopsy. Similar considerations apply to prostate cancer, as the extent of lymph node dissection might be guided by the metastatic status of the sentinel lymph node, especially if it is found in unexpected, extraregional locations.

For testicular cancer, lymphatic mapping is still in a very early phase of clinical experience. However, for penile cancer (a typical tumor of the midline, in which bilateral lymphatic drainage is the rule) sentinel lymph node biopsy may spare unnecessary bilateral (heavy) groin lymph node dissection, a surgical procedure with a heavy burden of morbidity and side effects, and at the same time result in considerable improvement of the quality of life.

Interesting studies have been published on sentinel lymph node biopsy in patients with vulvar or cervical cancers (80–82), where lymphatic mapping is performed with blue dye and/or radiocolloids during either open or laparoscopic surgery. In a multicenter study of 232 patients, the identification rate of the sentinel lymph node ranged from 15% to 100%, and was not affected by preoperative neoadjuvant chemotherapy. Intraoperative lymphatic mapping with sentinel node biopsy may affect the care management of patients with these tumors, leading to more accurate detection of lymph node metastases and reduced postoperative morbidity (in case a lymphatic basin assessed as free from metastases based on sentinel lymph node findings is not submitted to extensive lymph node dissection). The success rate in sentinel lymph node identification is generally high, and the status of the node plays an important role in the selection of more or less aggressive therapeutic approaches (83). Nevertheless, before definite evidence is accumulated, "it can be stated only that such procedure may permit a reduction in the amount of surgery" (84).

Regional lymph node status is a major prognostic factor for the therapeutic strategy of gynecologic malignancies. Early cervical cancer is treated with surgery and/or radiotherapy; surgery consists of radical hysterectomy and pelvic lymphadenectomy. However, metastasis in pelvic lymph nodes is found in only 15% of the women with stage Ib cervical cancer (85,86), and thus the vast majority of these patients does not benefit from a surgical treatment associated with considerable morbidity (nerve and vessel damage, lymphedema) (87). As in other applications of surgical oncology, sentinel lymph node biopsy could represent a definite advantage to select women for whom lymphadenectomy is really necessary.

Similar considerations also apply to patients with vulvar cancer, a condition in which the status of the regional lymph nodes is crucial for therapeutic decision-making. Standard treatment includes bilateral inguinofemoral lymphadenectomy, but this surgery is associated with high rates of short-term and long-term morbidity, and only 10% to 26% of the patients with vulvar cancer have inguinal metastases. Therefore, the majority of early-stage patients unnecessarily undergo overtreatment (i.e., lymphadenectomy with an ensuing negative impact on quality of life). Sentinel lymph node biopsy could ensure accurate lymph node staging as a prerequisite to implement less aggressive treatments, especially in patients with early vulvar cancer (88).

Conclusions

Regional lymphatic mapping with sentinel lymph node biopsy is becoming increasingly important in clinical oncology. This procedure can improve lymph node staging and guide the subsequent treatments (systemic neoadjuvant and adjuvant chemotherapy, radiation, and surgery), especially for melanoma, breast cancer, and squamous cell carcinoma of the vulva (and penis). In the sixth edition of the TNM classification system of malignant tumors (1,2), the status of the sentinel lymph node

is specifically included in the staging of regional lymph nodes for patients with breast cancer or malignant cutaneous melanoma.

Large-scale single-institution and multicenter trials are being conducted concerning both the clinical and technological aspects of the procedure. Among the latter worth noting are the development of cordless gamma probes for easier handling during surgery (89) and the semi-conductor or solid-state miniature gamma camera, which can overcome some limitations of the non-imaging gamma probe, in particular to avoid leaving residual sentinel lymph nodes in the surgical bed (90).

Global interest in this topic became evident with the establishment of the International Sentinel Node Society in Yokohama in 2002, during the Third International Sentinel Node Congress. This scientific association's stated goals are: 1) to promote the concept of the sentinel lymph node in the scientific and medical community and to stimulate its use; 2) to foster an interdisciplinary interchange of knowledge; 3) to hold periodical international meetings; 4) to conduct educational activities and increase professional skills; 5) to stimulate clinical and laboratory research; and 6) to encourage and facilitate collaborative clinical trials. During the society's recent congress in Los Angeles (December 3–6, 2004), experts from around the world (surgeons, nuclear medicine specialists, pathologists, and medical oncologists) gathered to discuss the many different aspects of this topic. The interest of the international oncologic community in sentinel lymph node biopsy and other forms of radioguided surgery has also been demonstrated by the growing space devoted to such topics in "organ-oriented" meetings focusing on different solid cancers.

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