Sentinel Lymph Node Biopsy for Breast Cancer: A Suitable Alternative to Routine Axillary Dissection in Multi-Institutional Practice When Optimal Technique Is Used

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Purpose: **Previous studies have demonstrated the feasibility of sentinel lymph node (SLN) biopsy for nodal staging of patients with breast cancer. However, unacceptably high false-negative rates have been reported in several studies, raising doubt about the applicability of this technique in widespread surgical practice. Controversy persists regarding the optimal technique for correctly identifying the SLN. Some investigators advocate SLN biopsy using injection of a vital blue dye, others recommend radioactive colloid, and still others recommend the use of both agents together.**

Patients and Methods: **A total of 806 patients were enrolled by 99 surgeons. SLN biopsy was performed by single-agent (blue dye alone or radioactive colloid alone) or dual-agent injection at the discretion of the operating surgeon. All patients underwent attempted SLN biopsy followed by completion level I/II axillary lymph node dissection to determine the false-negative rate.**

Results: **There was no significant difference (86% *v* 90%) in the SLN identification rate among patients who underwent single- versus dual-agent injection. The false-negative rates were 11.8% and 5.8% for single- versus dual-agent injection, respectively ($P < .05$). Dual-agent injection resulted in a greater mean number of SLNs identified per patient (2.1 *v* 1.5; $P < .0001$). The SLN identification rate was significantly less for patients older than 50 years as compared with that of younger patients (87.6% *v* 92.6%; $P = .03$). Upper-outer quadrant tumor location was associated with an increased likelihood of a false-negative result compared with all other locations (11.2% *v* 3.9%; $P < .05$).**

Conclusion: **In multi-institutional practice, SLN biopsy using dual-agent injection provides optimal sensitivity for detection of nodal metastases. The acceptable SLN identification and false-negative rates associated with the dual-agent injection technique indicate that this procedure is a suitable alternative to routine axillary dissection across a wide spectrum of surgical practice and hospital environments.**

J Clin Oncol 18:2560-2566. ***© 2000 by American Society of Clinical Oncology.***

FOR NEARLY A CENTURY, axillary lymph node dissection has been considered an essential component of breast cancer management. However, axillary dissection can result in significant morbidity. Complications of axillary dissection include pain, paresthesia, seroma, infection, limitation of shoulder motion, and lymphedema. Lymphedema, which occurs in 6% to 30% of patients after axillary dissection, is a particularly troubling lifelong problem for which there is no curative therapy.[1,2] The long-term consequences of axillary dissection on quality of life can be substantial, even among those who have apparently normal postoperative recovery.[3]

Sentinel lymph node (SLN) biopsy is a minimally invasive alternative to routine axillary lymph node dissection, with few long-term side effects. Although numerous studies have demonstrated that SLN biopsy can accurately determine the axillary nodal status, the sensitivity of the procedure for detection of nodal metastases has been variable (see reviews in[4-9]). The most critical factor is the false-negative rate (the proportion of patients with axillary nodal metastases who are found, incorrectly, to have histologically negative SLNs). Although it has been suggested that a false-negative rate of approximately 5% is acceptable, false-negative rates from 10% to 19% have been reported in several series.[4-9] Because of the variable false-negative rates and the fact that most of the published studies involve institutions and individuals specializing in breast cancer, there has been skepticism about the ability to disseminate this technology into widespread surgical practice.

A significant issue has been the lack of standardized methodology for the procedure. SLN biopsy is performed

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Submitted October 25, 1999; accepted March 8, 2000.

Supported by the Center for Advanced Surgical Technology of Norton Hospital, Louisville, KY.

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0732-183X/00/1813-2560

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by mapping the lymphatic drainage after injection of a vital blue dye, radioactive colloid, or both around the breast tumor. The optimal technique is a subject of some controversy, and advocates of various techniques are divided roughly into three camps, comprising those who advocate the use of blue dye alone, radioactive colloid alone, or the combination of blue dye and radioactive colloid. The only previous large multi-institutional study, using radioactive colloid as a single agent, reported an 11.4% false-negative rate.[8] The results of the present study indicate that, when applied in a multi-institutional setting, SLN biopsy using injection of both blue dye and radioactive colloid produces optimal results. The acceptable SLN identification and false-negative rates associated with the dual-agent injection technique indicate that this procedure is a suitable alternative to routine axillary dissection across a wide spectrum of surgical practice and hospital environments.

PATIENTS AND METHODS

Study Design

The primary end points of the University of Louisville Breast Cancer Sentinel Lymph Node Study were the sensitivity, specificity, negative predictive value, overall accuracy, and false-negative rate of SLN biopsy for breast cancer using single-agent injection (blue dye alone or radioactive colloid alone) versus dual-agent injection (blue dye plus radioactive colloid). The influence of patient and tumor characteristics as well as surgeon experience on the SLN identification rate and false-negative rate were examined. The study was approved by the institutional review board of each institution, and informed consent was obtained in writing from all patients after discussion of risks and benefits with the operating surgeon. Patients with biopsy-proven, clinically node-negative invasive breast cancer (T1/2, N0) were eligible. Twenty-one patients with T3 tumors were included in the study because tumor size more than 5.0 cm was established after resection of the primary tumor. All patients underwent attempted SLN biopsy followed by completion level I/II axillary lymph node dissection.

SLN Biopsy

In general, surgeons were provided flexibility in performing SLN biopsy using techniques with which they had been trained. Only 16 of 99 surgeons had performed more than 10 SLN biopsies for breast cancer before the study. The vast majority of surgeons were from community general surgery practices. Recommended guidelines for performance of SLN biopsy were provided in the protocol, which included peritumoral injection of 0.5 mCi of 0.2 micron-filtered technetium-99 sulfur colloid in a volume of 6 mL at least 1 hour before operation, followed by peritumoral injection of 5 mL of isosulfan blue dye at the time of surgery. However, the decision to perform SLN biopsy using blue dye alone, radioactive colloid alone, or the combination was left to the discretion of the individual surgeon. It was not mandated that each surgeon use the same technique on all patients; some surgeons used more than one technique. An SLN was defined as any blue node, or any node that could be identified as substantially radioactive above background. A specific SLN-to-background ratio was not specified in the protocol for defining an SLN, as the background count is quite variable depending on the location of the primary tumor and the placement of the probe. After the first radioactive SLN was removed, any node that contained radioactive counts that were $\geq$ 10% or more of the ex vivo count of the hottest SLN was considered to be an additional SLN. The protocol did not mandate removal of nonaxillary (internal mammary, supraclavicular) SLNs, as the primary objective was to determine whether SLN biopsy could be used as a replacement for axillary lymph node dissection. Each SLN was examined by routine hematoxylin and eosin staining at a minimum of 2-mm intervals. In addition, immunohistochemistry using antibodies for cytokeratin was performed in some institutions. The nonsentinel axillary lymph nodes were evaluated by routine hematoxylin and eosin staining.

Statistical Analysis

Analysis of variance was used to examine the relationship of injection technique to the number of SLNs identified. Comparison of the effect of injection technique on the SLN identification rate was performed using χ^2 analysis. Because of the small number of false-negative results, Fisher's exact test was used for comparison of injection techniques on the false-negative rate. To assess the impact of other factors on the SLN identification and false-negative rates, univariate χ^2 and Fisher's exact test analysis was performed, followed by logistic regression analysis to determine the most important independent factors to outcome. Calculations for sensitivity, specificity, positive and negative predictive values, overall accuracy, and false-negative rate have been described previously.[9]

RESULTS

Between August 1997 and June 1999, 806 patients were enrolled onto the study. SLN biopsy was performed using blue dye alone, radioactive colloid alone, or both in 216, 28, and 562 patients, respectively. Patients in each group (single- or dual-agent injection) were well balanced with respect to age, tumor size, tumor location within the breast, type of biopsy of the primary tumor (fine-needle aspiration or core-needle biopsy *v* excisional biopsy), type of surgical procedure for treatment of the primary tumor (total mastectomy *v* partial mastectomy), total number of axillary lymph nodes removed, and the use of immunohistochemistry for analysis of the SLN (Table 1). Internal mammary SLNs were identified and removed in only two patients; both were negative for tumor.

Comparison of Techniques

Comparison of the results using single- or dual-agent injection is listed in Table 2. The SLN identification rate was slightly greater in the dual-agent injection group, although this difference was not statistically significant. The mean number of SLNs removed was greater in the dual-agent injection group (1.5 *v* 2.1; $P < .0001$). The false-negative rate was significantly greater for patients who underwent single-agent versus dual-agent injection (11.8% *v* 5.8%; $P < .05$). The false-negative rates were 12.3% and 9.1% for patients undergoing blue dye injection alone or

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Table 1. Clinicopathologic Characteristics of Patients Undergoing SLN Biopsy

Variable	All Patients	Single-Agent Injection*	Dual-Agent Injection†
No. of patients	806	244	562
Median age, years	63	63	63
Tumor size, %			
T1	72	73	72
T2	25	25	25
T3	3	2	3
Tumor location, %			
Upper-outer quadrant	53	52	53
Other	47	48	47
Biopsy type, %			
FNA or core needle	68	71	66
Excisional	32	29	34
Mean no. of axillary nodes removed, SLN + non-SLN	15	14	16
Type of operation for primary tumor, %			
Total mastectomy	27	28	28
Partial mastectomy	73	72	72
IHC analysis of SLN performed, %	31	35	29

Abbreviations: FNA, fine-needle aspiration; IHC, immunohistochemistry.
*Blue dye or radioactive colloid alone.
†Blue dye plus radioactive colloid.

radioactive colloid injection alone, respectively. The difference in false-negative rates remains significant if the 28 patients who underwent radioactive colloid injection alone are excluded (false-negative rate of 12.3% for blue dye alone *v* 5.8% for blue dye plus radioactive colloid; $P < .05$). Seventy-two percent of SLNs from patients who underwent dual-agent injection were blue.

In 86% of cases in which radioactive colloid was used, it was injected peritumorally. Intradermal or subdermal injection of radioactive colloid was performed in 39 and 37 patients, respectively. In these cases, the SLN was identified in 75 of 76 cases. Fourteen of these patients had positive SLNs, and there were no false-negative results.

Other Factors Affecting SLN Identification and False-Negative Rates

In prior studies, patient age, type of biopsy of the primary tumor, tumor location within the breast, and surgeon experience have been implicated as important factors related to the SLN identification rate and false-negative rate.[4-11] Logistic regression analysis of these factors in the present study was performed (Table 3). Patient age greater than 50 years was associated with a decreased likelihood of successful SLN identification ($P = .03$). Upper-outer quadrant tumor location was associated with an increased probability of a false-negative result ($P < .05$).

Incidence of Positive SLNs by Tumor Size

The incidence of positive SLNs by tumor size is listed in Table 4.

DISCUSSION

There has been considerable controversy regarding the optimal technique for SLN biopsy.[4-11] Results of the present multi-institutional study indicate that injection of blue dye plus radioactive colloid injection provides more accurate nodal staging than the use of either agent alone. Although this is not a randomized study, the data support the use of the dual-agent injection as the method of choice to minimize false-negative results. These results do not, however, refute the excellent results obtained in some centers with single-agent injection, but rather suggest that when SLN biopsy is performed across a wide range of surgical practices and hospital environments, the combination of blue dye plus radioactive colloid injection produces more uniformly accurate nodal staging.

Presumably, the combination of the two techniques—visualization of the blue dye and intraoperative gamma probe detection—provides overlapping and complementary ability to discriminate SLNs. This may be most helpful to surgeons and institutions with less experience in the technique. Although 72% of the SLNs in the dual-agent group

Table 2. Results of SLN Biopsy by Injection Technique

Injection Technique	No. of Patients	No. of Surgeons	SLN Identified (%)	Mean No. of SLNs Removed	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Overall Accuracy (%)	False Negative Rate (%)
Single-agent	244	38	86	1.50	89.1	100	100	93.7	95.7	11.8
Dual-agent	562	96	90	2.10*	94.2	100	100	97.5	98.2	5.8†
All techniques	806	99‡	88	1.95	92.2	100	100	96.4	97.5	7.2

*$P < .0001$ versus single-agent injection, analysis of variance.
†$P < .05$ versus single-agent injection, Fisher's exact test.
‡Number of surgeons in each group does not equal 99 because some surgeons used both techniques.

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Table 3. Factors Affecting SLN Identification and False-Negative Rates

Variable	No. of Patients	SLN Identification Rate (%)	Odds Ratio	95% CI	*P*	False-Negative Rate (%)	Odds Ratio	95% CI	*P*
Age									
< 50 years	216	92.6	1.99	1.10-3.88	.03	5.8	1.61	0.53-6.02	.43
≥ 50 years	590	87.6				8.7			
Location of tumor									
Upper-outer quadrant	421	89.8	0.82	0.51-1.31	.40	11.2	3.10	1.09-11.09	.05
All other locations	381	87.9				3.9			
Size of primary tumor									
T1	553	87.7	0.76	0.42-1.32	.34	10.7	0.51	0.16-1.47	.39
T2 or T3	215	91.6				5.5			
Previous biopsy									
FNA or core needle	265	89.0	1.01	0.61-1.71	.98	7.0	0.60	0.19-2.01	.39
Excisional	530	88.7				10.2			
Surgeon experience*									
< 10 cases	456	87.9	0.73	0.44-1.20	.22	7.6	1.29	0.43-3.97	.65
≥ 10 cases	350	90.0				9.3			

Abbreviation: CI, confidence interval.

*Number of SLN biopsy cases performed by the surgeon before enrolling patients in the study.

were blue, the blue staining is often found only in retrospect after the radioactive node has been identified with the gamma probe. Alternatively, when a clear hot spot cannot be identified with the gamma probe, a blue lymphatic channel leading to a blue lymph node may be identified. The dual-agent injection technique was associated with a greater mean number of SLNs removed. The increased ability to identify multiple SLNs, when present, may account for the lower false-negative rate that was achieved using the dual-agent injection technique.

The number of patients with radioactive colloid injection alone was small (n = 28) and precludes direct comparison with dual-agent injection. However, the only other large multi-institutional study reported to date by Krag et al,[8] with 443 patients and 11 surgeons, used radioactive colloid as a single agent. In that study, the false-negative rate was 11.4%, leading the authors to speculate that combination injection techniques may lead to superior results. Taken together, the results of the study by Krag et al and the present study suggest that the dual-agent injection technique is the preferred method for most institutions.

Table 4. Incidence of Positive SLNs by Tumor Size

Tumor Size Category	No. of Patients	Patients With Positive SLNs	
		No.	%
T1	546	127	23
T1a	48	7	8
T1b	168	29	18
T1c	330	91	28
T2	192	100	52
T3	21	15	71

One potential concern involves the fact that the SLNs were subjected to more intensive pathologic analysis than the non-SLNs. This concern that greater pathologic scrutiny would identify occult micrometastases in the non-SLNs was addressed in an elegant study by Turner et al,[12] in which all nonsentinel axillary nodes were evaluated by the same method as the SLNs (multiple sections and immunohistochemical staining). When the SLN was negative for tumor, it was extremely unlikely that the non-SLNs contained metastatic disease (one of 1,087 nodes examined). Furthermore, routine histology of the non-SLNs has been the standard methodology for all other studies of breast cancer SLN biopsy, such that the results of the present study are comparable to other studies reported in the literature.

It is presently recommended that surgeons perform at least 20 to 30 cases of SLN biopsy for breast cancer with a documented low false-negative rate before consideration of abandoning axillary lymph node dissection.[10,11] In the present study, surgeon experience was not a significant factor associated with failure to identify SLNs or false-negative results. However, the majority of surgeons had little experience with SLN biopsy for breast cancer before entering the study. Certainly, the SLN identification rate (90%) and false-negative rate (5.8%) are within the acceptable range for considering this procedure as an alternative to routine axillary dissection for breast cancer. Although precise determination of the optimal learning phase is not possible from the available data, we believe that the use of

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dual-agent injection may shorten the learning curve. It is expected that, with increasing surgeon experience, these results will improve.

Patient age was inversely correlated with the ability to identify the SLN. This finding has been reported previously[8] and may be related to the ability of blue dye and radioactive colloid to be taken up by the lymphatic system when injected into the often fat-replaced postmenopausal breast. Although prior excisional biopsy has been shown previously to be associated with failure to identify an SLN,[8] the present study did not confirm such a correlation. However, distortion of normal lymphatic drainage after excisional breast biopsy is a potential problem, and we prefer to perform SLN biopsy, whenever possible, when there has been minimal disruption of the primary tumor site. Upper-outer quadrant tumor location was associated with a greater probability of a false-negative result, which may be related to difficulty in discriminating signal from background when peritumoral injection of radioactive colloid is performed near the axilla. Both of these problems may be obviated by dermal or subdermal injection of radioactive colloid, which seems to result in accurate and efficient localization of SLNs. Further study is necessary to document the validity of this approach.

SLN biopsy allows us to identify, using a minimally invasive procedure, patients with nonpalpable nodal metastases who may benefit from more aggressive adjuvant therapy. In fact, SLN biopsy may be more accurate than axillary dissection, because a more detailed pathologic evaluation is performed on the node(s) most likely to contain metastatic disease.[12,13] The majority of patients (SLN-negative) may be treated on an outpatient basis with lumpectomy and SLN biopsy. In this way, the morbidity of axillary dissection is avoided in most patients, recovery time is shorter, and return to normal activity is accelerated. Any potential therapeutic advantage of axillary lymph node dissection is not lost, because patients with nodal metastases identified by SLN biopsy may undergo therapeutic axillary dissection. Although no studies of the long- and short-term morbidity of SLN biopsy are yet available, it is believed that SLN biopsy is associated with fewer adverse side effects because it involves, on average, removal of only two lymph nodes.

Once it is established that SLN biopsy can be performed with acceptable SLN identification and false-negative rates, the primary argument against SLN biopsy comes from those who believe that pathologic staging of axillary lymph nodes is no longer necessary and that adjuvant therapy decisions can be made on the basis of characteristics of the primary tumor. Proponents of this view cite the lack of a demonstrable survival advantage in favor of axillary dissection, as well as the observation that all subgroups of breast cancer patients receive the same proportionate reduction in the risk of recurrence or death from systemic adjuvant therapy.[14-18] However, the lymph node status of patients with early breast cancer remains the most powerful factor for predicting disease-free and overall survival. The presence of nodal metastases decreases the 5-year survival of patients by approximately 40% compared with patients who are free of nodal disease.[19,20] Furthermore, information obtained from pathologic staging of axillary lymph nodes frequently changes the adjuvant therapy plan in women with early breast cancer.[21]

In fact, several recent developments support the contention that axillary lymph node status remains an important factor in making adjuvant therapy decisions. First, a recent study demonstrated a survival advantage for the addition of paclitaxel to the standard regimen of doxorubicin and cyclophosphamide.[22] This regimen is now being used in the community setting, and the decision to use this more aggressive adjuvant chemotherapy regimen is often based on the presence and number of positive axillary lymph nodes. Second, more postmenopausal women are being treated with chemotherapy in addition to hormonal therapy. Because of the small benefit for adding chemotherapy to tamoxifen in node-negative, estrogen receptor–positive patients,[23] the decision to use chemotherapy in addition to hormonal therapy is often based on the presence of positive axillary lymph nodes. Third, recent clinical trials have suggested that postmastectomy radiotherapy improves survival among women with axillary lymph node metastases.[24-26] Although the controversy over the impact of adjuvant radiation therapy continues, it can be expected that a greater proportion of node-positive patients will receive radiation therapy in the future. Overall, the axillary lymph node status provides important prognostic information for patients and physicians that cannot be determined from evaluation of the primary tumor alone.

The argument against routine axillary lymph node dissection has been made most strongly for patients with T1a and T1b breast cancers. It has been suggested that the incidence of nodal metastasis in patients with T1a and T1b breast cancers is sufficiently low that it is not worthwhile to subject these patients to the morbidity of axillary dissection. However, these patients are ideal candidates for SLN biopsy. Numerous studies have documented that approximately 10% to 20% of women with T1a and T1b tumors have positive axillary lymph nodes.[11,27-31] In the present study, the incidence of positive lymph nodes was 16%. Although this may seem to be a small fraction of patients, it must be recognized that an increasing number of breast cancers are detected early because of routine mammographic screening, such that T1a and T1b cancers may now account for almost 30% of all invasive breast cancers.[32] Failure to perform pathologic staging of axillary nodes in

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this patient population would thus result in failure to administer proper adjuvant therapy to as many as 3% to 6% of all patients with invasive breast cancer.

It is also important to recognize that patients with T1a/b, clinically node-negative tumors represent a group for which adjuvant chemotherapy and/or hormonal therapy are not routinely recommended. Therefore, the finding of a positive lymph node makes a drastic difference in adjuvant therapy decisions (treatment *v* no treatment).[9] In the longstanding debate regarding the value of axillary lymph node dissection, the important distinction between axillary lymph node staging and axillary lymph node dissection must be kept in mind. Most of the arguments have been made against axillary dissection, not against axillary nodal staging. When the morbidity of axillary dissection is weighed against the benefit in terms of adjuvant therapy decisions and potential therapeutic value, some physicians might reasonably conclude that the risk of axillary dissection exceeds the benefit for patients with early breast cancer. However, if axillary nodal staging can be performed with a minimally invasive lymph node biopsy, the analysis of risks and benefits shifts in favor of SLN biopsy for most patients. In fact, it is quite difficult to make a persuasive argument that it is in the best interest of all patients to accept less-detailed staging information, especially when that information can be obtained with a procedure that carries the morbidity of a lymph node biopsy.

In conclusion, the present study demonstrates that SLN biopsy can be performed with acceptable identification and false-negative rates across a wide variety of surgical practice and hospital environments if the combination of blue dye and radioactive colloid injection is used. Patient age and tumor location are important factors to take into account when discussing the possibilities of failure to identify the SLN or a false-negative SLN biopsy with patients. SLN biopsy is an acceptable alternative to axillary lymph node dissection for clinically node-negative breast cancer, provided that the surgeon and his or her hospital team demonstrate a low false-negative rate. Participation in ongoing clinical trials is strongly encouraged.

ACKNOWLEDGMENT

We thank Diana Simpson, RN; Vicki Viar, RN, MSN; Carla Shelton; and Sherri Matthews for data management and coordination of the study.

APPENDIX

Appreciation is also expressed to the members of the University of Louisville Breast Sentinel Lymph Node Study Group for their active participation: Bruce J. Averbrook, MD; Bradford J. Barrett, MD; Richard J. Bold, MD; Edward B. Borden, MD; Michael T. Brown, MD; Michael S. Bryant, MD; Ned Z. Carp, MD; Thomas H. Chang, MD; Janet R. Chipman, MD; Peter J. Cochrane, MD; Donald D. Coker, MD; Arnold M. Conforti, MD; Leo W. Davidson, MD; David R. DeHaan, MD; Robert C. DeWeese, MD; Ronald L. Ernst, MD; Fernando P. Estrada, MD; Robert K. Finley, MD; Carl R. Fischer, III, MD; Michael B. Flynn, MD; Gerald A. Garguilo, MD; James E. Goodnight, MD; Joseph R. Gordon, MD; Thomas M. Grayson, MD; David A. Guthrie, MD; John L. Gwin, MD; Colleen A. Hagen, MD; Danny L. Harrison, MD; Robert B. Hird, MD; William P. Hoagland, MD; Stephan U. Hochuli, MD; Michael B. Hoover, MD; Joel Horowitz, MD; James E. Hurley, II, MD; Jay R. Jeffrey, MD; W. Scott Jones, MD; Gregory L. Juhl, MD; Jeffrey L. Justice, MD; Stephen J. Kelty, MD; Mary T. Legenza, MD; Phillip B. Ley, MD; John J Lukaszcyk, MD; David T. MacMillan, MD; Edward G. Mansour, MD; Marc A. Marcum, MD; Donald W. Matzelle, MD; Bruce C. McComas, MD; Terre Q. McGlothin, MD; Gerald J. Morrow, MD; Myron E. Morse, MD; Kenneth L. Nachtnebel, MD; William L. Owens, MD; Robert E. Pennington, MD; Paul A. Rafson, MD; Maurice S. Rawlings, MD; Lee B. Riley, MD, PhD; John J. Rogers, MD; Catherine Ronaghan, MD; Joseph Ronaghan, MD; Philip M. Rosenbloom, MD; Mary K. Rosenow, MD; Jack F. Rutledge, MD; Paul L. Sasser, MD; Mark E. Schadt, MD; Stephen E. Schmid, MD, PhD; Philip D. Schneider, MD; William M. Schulman, MD; Brian W. Schymik, MD; Jerry K. Seiler, MD; Thomas E. Shaver, MD; Robert E. Sheep, MD; John A. Singer, MD; Robin A. Skrine, MD; Dale A. Sloan, MD; Jean T. Stevenson, MD; Thomas J. Tachovsky, MD; Arleen K. Thom, MD; James M. Thomas, MD; Rexford, L. Thomas, MD, PhD; Erik Throop, MD; Roderick J Tompkins, MD; Thomas E. Topper, Jr, MD; Pat Toselli, DO; Santi Vibul, MD; Harold Wechsler, MD; Thomas J. Wieman, MD; Jeffrey A. Yoder, MD; and Alfred G. Ziviello, MD.

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