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The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: Beyond removal of blue nodes ☆

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ABSTRACT

Objective. To determine the false-negative rate of a surgical sentinel lymph node (SLN) mapping algorithm that incorporates more than just removing SLNs in detecting metastatic endometrial cancer.

Methods. A prospective database of all patients who underwent lymphatic mapping for endometrial cancer was reviewed. Cervical injection of blue dye was used in all cases. The surgical algorithm is as follows: 1) peritoneal and serosal evaluation and washings; 2) retroperitoneal evaluation including excision of all mapped SLNs and suspicious nodes regardless of mapping; and 3) if there is no mapping on a hemi-pelvis, a side-specific pelvic, common iliac, and interiliac lymph node dissection (LND) is performed. Paraaortic LND is performed at the attendings' discretion. The algorithm was retrospectively applied.

Results. From 9/2005 to 4/2011, 498 patients received a blue dye cervical injection for SLN mapping. At least one LN was removed in 95% of cases (474/498); at least one SLN was identified in 81% (401/498). SLN correctly diagnosed 40/47 patients with nodal metastases who had at least one SLN mapped, resulting in a 15% false-negative rate. After applying the algorithm, the false-negative rate dropped to 2%. Only one patient, whose LN spread would not have been caught by the algorithm, had an isolated positive right paraaortic LN with a negative ipsilateral SLN and pelvic LND.

Conclusions. Satisfactory SLN mapping in endometrial cancer requires adherence to a surgical SLN algorithm and goes beyond just the removal of blue SLNs. Removal of any suspicious node along with side-specific lymphadenectomy for failed mapping are an integral part of this algorithm. Further validation of the false-negative rate of this algorithm is necessary.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with approximately 46,000 new cases and 8000 deaths in 2011 [1]. The revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system continues to incorporate lymph node (LN) status as it has been shown to be diagnostic and prognostic [2,3], but there is continued controversy over the role of lymphadenectomy (LND) in endometrial cancer. The benefit of lymphadenectomy has been refuted by two recent randomized controlled trials that did not demonstrate a therapeutic benefit to lymphadenectomy itself, although the methodology of both studies has been criticized [4,5]. A Study in the Treatment of Endometrial Cancer (ASTEC) was a large multicenter study in which almost half of the patients randomized to the LND arm had ≤9 LNs removed, and in addition, many patients were secondarily randomized to postoperative radiation independent of LN status [5]. The trial by Panici et al. did require a minimum of 20 LNs removed, but adjuvant treatment was given at the discretion of the physician and was similar in the two groups [4]. Even for those who agree that LND is not therapeutic, many still argue that LN staging is essential to guide appropriate adjuvant therapy. It is not surprising then that a survey of Society of Gynecologic Oncology (SGO) members conducted in 2009 demonstrated a lack of standardized surgical practice patterns of LND in endometrial cancer staging among providers [6].

Sentinel lymph node (SLN) mapping may serve as a potential middle ground in endometrial cancer surgical staging between no evaluation of LN status and a full pelvic and paraaortic LND as a way to adequately evaluate a patient's LN status while decreasing the risk of morbidity from a full LND, and overcoming the confusion of what the standard templates for LND are in this disease. SLN is a well-

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accepted practice in the treatment of melanoma and breast cancer [7,8] and is gaining ground in vulvar cancer [9] and cervical cancer [10]. A recent prospective multi-institutional study (SENTI-ENDO), using a similar technique of cervical injection to our approach, demonstrated that SLN biopsy may be a reasonable alternative in endometrial cancer staging [11]; this study confirmed similar and previously published observations from our institution [12,13].

The key to the controversy of LND in endometrial cancer is to agree upon a clinically practical, reproducible, and reliable method of evaluating LN status to guide prognosis and adjuvant treatment while minimizing morbidity from a procedure that is probably not in and of itself therapeutic. We propose an endometrial cancer SLN algorithm that goes beyond just removal of blue nodes. The objective was to determine the effectiveness of this algorithm in detecting metastatic endometrial cancer while minimizing the need for complete LND.

Methods

We reviewed the results of all patients from September 2005 through April 2011 who underwent SLN mapping as part of their surgery for endometrial cancer at Memorial Sloan-Kettering Cancer Center (MSKCC). Surgery was performed by laparoscopy, robotically assisted laparoscopy, or laparotomy. Surgical staging included total hysterectomy, bilateral salpingo-oophorectomy, and mapping of SLNs. The extent of bilateral pelvic and paraaortic LND was left to the operating surgeon's discretion.

All patients underwent blue dye injection into the cervix at the time of exam under anesthesia. The cervix was injected at the 3 and 9 o'clock positions with 1 mL superficial (2–3 mm) and 1 mL deep (1–2 cm), for a total of 4 mL. A small number of patients in the earlier part of the study received a blue dye injection into the fundus (1 mL into the anterior mid fundus and 1 mL into the posterior mid fundus) and/or a preoperative lymphoscintigraphy following a cervical injection of technetium-99 microsulfur colloid.

Beginning in 2005 we utilized both Tc and blue dye injection in the cervix. Following completion of our initial institutional clinical trial in 75 cases, we moved more in the direction of blue dye injection only into the cervix. All patients in this study had blue dye injected into the cervix. This is the easiest and most convenient injection site and avoids the need for a preoperative nuclear medicine injection and lymphoscintigram, which is associated with additional costs and discomfort (due to injecting the cervix with Tc when the patient is awake), and in our experience did not improve the detection rates. We do not claim that cervical injection of blue dye is superior to other methods, but from the standpoint of clinical feasibility, the performance of our algorithm can be interpreted knowing that the sensitivity, negative predictive value, and false-negative rate that we report were attained based upon the simplest of mapping protocols. Although there are no prospective randomized trials comparing injection site or detection method, a recent meta-analysis did find that the use of cervical injection was significantly associated with an increased detection rate, whereas hysteroscopic injection was associated with a decreased detection rate, and subserosal injection was associated with decreased sensitivity, thereby lending further support to our approach of cervical injection for SLN mapping [16].

SLNs were detected by direct visualization of blue dye or were localized using a gamma probe to detect hot nodes. Further detail on our mapping protocol was previously reported [14]. Grossly enlarged LNs were removed and properly documented in the surgeon's operative report; although these nodes if positive for disease are equivalents of SLN, for the purposes of this analysis, they were not considered SLNs unless they contained blue dye.

Specialized gynecologic pathologists examined all specimens. The MSKCC institutional protocol for evaluation of SLNs includes initial examination by routine hematoxylin and eosin (H&E) staining, followed by ultrastaging if the initial H&E is negative. Ultrastaging consists of two adjacent 5 μm sections cut from each paraffin block at each of two levels 50 μm apart, for a total of four slides per block. At each level, one slide is stained with H&E and the other with immunohistochemistry using anti-cytokeratin AE1:AE3 (Ventana Medical Systems, Inc., Tucson, AZ). SLNs were considered positive if they demonstrated macrometastasis (defined as tumor clusters > 2 mm), micrometastasis (defined as tumor clusters between 0.2 and 2 mm), or isolated tumor cells (ITCs) (defined as single tumor cells or small tumor clusters ≤ 0.2 mm) [15]. LNs containing only isolated cytokeratin-positive cells were not considered metastatic.

In order to determine the effectiveness of a surgical SLN mapping algorithm in detecting metastatic endometrial cancer while minimizing the need for complete LND, we performed descriptive statistics for SLN mapping alone compared to our proposed SLN algorithm. Each patient, rather than each hemipelvis, was used as the unit of analysis.

The SLN detection rate was defined as the proportion of cases in which at least one SLN was identified among patients with attempted mapping. Failed mapping refers to cases in which an SLN was not detected. Cases with bilateral failed mapping with no SLNs removed were considered non-evaluable for analysis of SLN alone; cases with no LNs taken (SLN or non-SLN) were considered non-evaluable for analysis of the algorithm. A true-negative was defined as a negative SLN or algorithm in a patient with no nodal metastases. A false-negative was a negative SLN or algorithm in a patient with nodal metastases. A true-positive was defined as a positive SLN or algorithm in a patient with nodal metastases, and a false-positive was impossible by definition. Sensitivity was calculated as the number of true positives divided by all patients with LN metastases. The false-negative rate was the number of false-negatives divided by the number of patients with LN metastases. Clinically, the false-negative rate refers to the detection of LN metastasis in the completion LND when an SLN was excised and pathologically benign. The negative predictive value was determined by dividing the number of true negatives by the number of patients with a negative test (SLN alone or algorithm).

We retrospectively applied the algorithm, as shown in Fig. 1, which includes the following steps: 1. peritoneal and serosal evaluation and washings; 2. retroperitoneal evaluation including excision of all mapped SLNs and removal of all suspicious nodes regardless of mapping; and 3. If there is no mapping on a hemipelvis, a side-specific pelvic (external iliac, internal iliac, and obturator), common iliac, and interiliac LND is performed. Paraaortic LND is left to the attending's discretion. We reviewed the surgeon's intraoperative findings based on the operative report and accounted for all metastatic nodes in the pathology report.

Results

Between 9/2005 and 4/2011, 498 patients with endometrial cancer underwent SLN mapping by 10 attending surgeons. All patients received an intracervical injection of blue dye. From the earlier time period of our SLN protocol, 34 patients also had a fundal injection of blue dye, and 75 had lymphoscintigraphy with Tc injection into the cervix as well.

Demographic and clinicopathologic characteristics of the study population are summarized in Table 1. The median age was 61 years (range, 33–88), with a median body mass index of 29.1 kg/m^2 (range, 15.7–68.7). One hundred eighty-nine cases (38%) were performed by laparoscopy, 189 (38%) by robotic-assisted laparoscopy, and 120 (24%) by laparotomy. Histology was distributed as follows: endometrioid, 393 (79%); serous, 44 (9%); clear cell, 10 (2%); carcinosarcoma, 27 (5%); and other, 24 (5%). The predominant FIGO stage was stage I (392 patients [79%]).

For the entire population of 498 patients in which SLN mapping was attempted (Table 2), the median SLN count was 3 (range, 0–15), and the median total LN count was 8 (range, 0–59). At least one SLN was detected in 401 cases (81%). There was unilateral pelvic

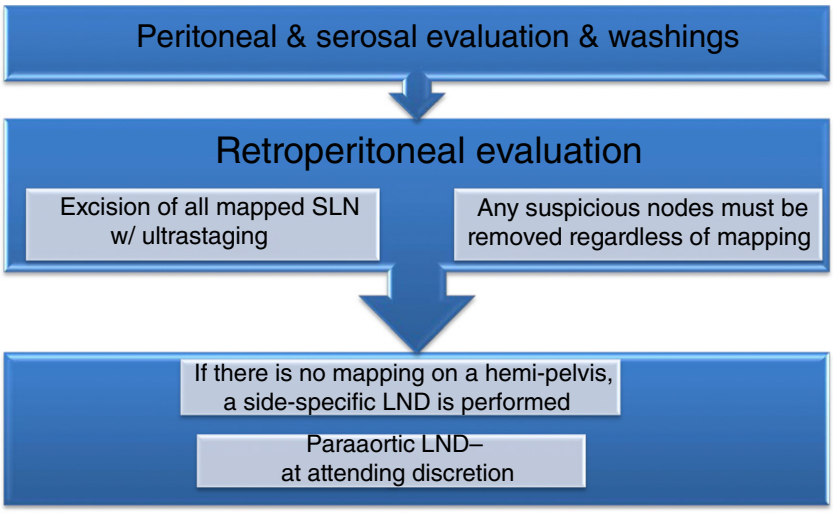

Fig. 1. Surgical algorithm for endometrial cancer.

mapping in 146/498 cases (29%), with 82/498 (17%) on the right and 64/498 (13%) on the left. Bilateral pelvic mapping was achieved in 253/498 patients (51%). Of the 401 patients with at least one SLN identified, 384 (96%) mapped only to the pelvis, 15 (4%) mapped to both the pelvis and paraaortic region, and 2 (.5%) had SLNs limited to the paraaortic region.

Table 3 summarizes the performance of SLN mapping alone compared to the implementation of our proposed endometrial cancer surgical algorithm for all patients in whom mapping was attempted. Among the 401 patients with at least one SLN identified, a positive SLN was diagnosed in 40 cases (10%), of which 9 (2%) were only detected by additional sections or IHC as part of our institutional pathology ultrastaging protocol. There were 7 false-negatives. This yielded a sensitivity of 85.1%, false-negative rate of 14.9%, and negative predictive value of 98.1%.

Among the 474 patients with at least one LN removed, the algorithm captured 53 of the patients with positive LNs, with only one false-negative still failing the algorithm. The details of the 6 false-negative cases that were captured if the algorithm was applied include the following: 4 patients failed mapping and underwent side-specific LND that detected the metastatic LN, one patient had a grossly enlarged suspicious node removed regardless of mapping, and one patient had all metastatic lesions noted on peritoneal and serosal evaluation. The one remaining false-negative after the algorithm was applied had an isolated positive right paraaortic LN with a negative right pelvic SLN and 7 negative non-sentinel pelvic LNs. The endometrial cancer surgical algorithm had an improved performance compared to SLN alone as follows: sensitivity, 98.1%; false-negative rate, 1.9%; and negative predictive value, 99.8%.

The performance of SLN mapping alone compared to the surgical algorithm was then more conservatively estimated by limiting the analysis to those patients with at least 10 LNs removed and analyzed by pathology (Table 4). Among the 180 patients with at least one SLN identified and a total of at least 10 LNs removed, a positive SLN was diagnosed in 20 cases (11%), with 6 false-negative cases. After applying the surgical algorithm to the 227 patients who had at least 10 LNs removed regardless of SLN mapping, positive LN metastases were detected in 31 patients (14%), with one false-negative case—the same patient with an isolated positive paraaortic LN described above.

For patients with at least 10 LNs removed, the endometrial cancer surgical algorithm again performed better than SLN alone on multiple measures: sensitivity, 96.9% vs. 76.9%; negative predictive value, 99.5% vs. 96.3%; and false-negative rate, 3.1% vs. 23.1%, respectively.

Table 1
Demographic and clinicopathologic characteristics, N = 498.

Characteristic	Number of Patients
Age, years	
Median (range)	61 (33–88)
Body mass index, kg/m^2	
Median (range)	29.1 (15.7–68.7)
Surgical approach	
Laparoscopy	189 (38%)
Robotic-assisted laparoscopy	189 (38%)
Laparotomy	120 (24%)
Tumor diameter, cm	
Median (range)	2.5 (0–11)
Histology	
Endometrioid	393 (79%)
Serous	44 (9%)
Clear cell	10 (2%)
Carcinosarcoma	27 (5%)
Other	24 (5%)
FIGO 1988 stage	
Stage I	392 (79%)
Stage II	12 (2%)
Stage III	85 (17%)
Stage IV	9 (2%)

FIGO = International Federation of Gynecology and Obstetrics.

Discussion

Our results are based on the largest (498 patients) prospective single-institution cohort published on SLN in endometrial cancer. These data suggest that implementation of an endometrial cancer SLN mapping algorithm after cervical injection of blue dye performs better than SLN mapping and biopsy alone and is a potential middle ground in the current controversy of endometrial cancer staging. It

Table 2
Sentinel lymph node mapping.

	Number	Calculation	%
Patients w/ cervical injection	498		
Overall SLN detection rate	401	401/498	81
Pelvic SLN detection rate	399	399/498	80
Pelvic SLN mapping			
Unilateral R pelvic mapping	82	82/498	17
Unilateral L pelvic mapping	64	64/498	13
Bilateral pelvic mapping	253	253/498	51
SLN location			
Pelvic only mapping	384	384/401	96
Pelvic and PA mapping	15	15/401	4
PA only mapping	2	2/401	0.5

SLN = sentinel lymph node, R = right, L = left, PA = paraaortic.

Table 3
Performance of SLN alone compared to the algorithm for all patients.

	LN positive	LN negative		SLN alone	Calculation	Result
SLN positive	40	0	40	Sensitivity	40/47	85.1
SLN negative	7	354	361	Negative predictive value	354/361	98.1
	47	354	401	False-negative rate	7/47	14.9
	LN positive	LN negative		Algorithm	Calculation	Result
Algorithm positive	53	0	53	Sensitivity	53/54	98.1
Algorithm negative	1	420	421	Negative predictive value	420/421	99.8
	54	420	474	False-negative rate	1/54	1.9

SLN = sentinel lymph node.

would eliminate the need for complete bilateral LND in the majority of patients and provides an acceptably low false-negative rate.

The utility of lymphatic mapping is to identify the SLNs that would be the first node(s) in a regional lymphatic basin to receive lymph flow from the primary tumor; therefore, the histologic status of the SLN would accurately reflect the status of the entire regional basin. Khoury-Collado et al. recently demonstrated that after using a cervical injection for SLN mapping, metastatic LNs were three times as likely to be detected in SLNs compared to non-sentinel nodes, supporting the practice of adding SLN mapping in endometrial cancer staging [13]. In addition, the additional pathologic ultrastaging of SLNs may be the only evidence of LN metastases in the form of micrometastasis.

Three surgical approaches were utilized over the study period: laparotomy, laparoscopy, and robotics. The selection of the approach was based on the attending's discretion. The same cervical injection techniques with blue dye were utilized in all approaches. A comparison of the efficacy of SLN mapping in these different surgical approaches is not the subject of this study and will be addressed in future publications.

In our entire cohort, the overall SLN detection rate was 81%, with "optimal" bilateral mapping in 51%. This is on par with the literature as illustrated by a recent meta-analysis of 26 endometrial cancer SLN studies including 1101 SLN procedures, which reported a detection rate of 78% (95% confidence interval [CI], 73–84%) [16]. The meta-analysis further reported an overall sensitivity of 93% (95% CI, 87–100%). Our proposed algorithm performed very well in comparison, as demonstrated by a high sensitivity of 98.1%, excellent negative predictive value of 99.8%, and a clinically acceptably low false-negative rate of 1.9%. This also compares favorably to the prospective multi-institution SENTI-ENDO study, which utilized cervical dual injection with technetium and patent blue followed by a systematic pelvic LND, and reported a sensitivity of 84%, negative predictive value of 97%, and false-negative rate of 16%.

Table 4
Performance of SLN alone compared to the algorithm for patients with at least 10 lymph nodes removed.

	LN positive	LN negative		SLN alone	Calculation	Result
SLN positive	20	0	20	Sensitivity	20/26	76.9
SLN negative	6	154	160	Negative predictive value	154/160	96.3
	26	154	180	False-negative rate	6/26	23.1
	LN positive	LN negative		Algorithm	Calculation	Result
Algorithm positive	31	0	31	Sensitivity	31/32	96.9
Algorithm negative	1	195	196	Negative predictive value	195/196	99.5
	32	195	227	False-negative rate	1/32	3.1

SLN, sentinel lymph node.

In an attempt to more conservatively and accurately estimate the performance of our algorithm, we also limited the analysis to patients who had at least 10 LNs removed. It is unclear how many LNs are considered adequate for endometrial cancer staging, but we chose 10 LNs as a cutoff based on a recent analysis from our group in which the removal of 10 or more nodes appeared to assign patients to the correct surgical stage and influence survival in select patients [17]. In addition, as a reflection of actual practice patterns, a study of over 11,000 patients who underwent LND for endometrial cancer staging reported a median of 9 LNs removed [18]. From the perspective of morbidity associated with LND, Abu-Rustum et al. showed that patients who had 10 or more regional LNs removed at initial surgery were at higher risk for developing symptomatic leg lymphedema [19]. After limiting our analysis to patients with at least 10 LNs removed, the endometrial cancer SLN algorithm still performed well, with a sensitivity of 96.9%, negative predictive value of 99.5%, and false-negative rate of 3.1%. Whether SLN mapping truly reduces the morbidity of surgical staging in endometrial cancer particularly as it relates to avoidance of complete lymphadenectomy is a very important clinical question but was not the main objective of this review. Clearly, more research into the overall complication rates of women undergoing SLN is needed; furthermore, whether the suggested algorithm may reduce the surgical complication rates from lymphadenectomy remains to be determined. The authors plan to review and address the important question of complications in future investigations.

In order for any SLN protocol to become well accepted, it needs to be clinically practical. The cervical injection of blue dye that was used for all patients in this study is the easiest and most convenient injection site and avoids the need for a preoperative nuclear medicine injection and lymphoscintigram. Perhaps the most important obstacle to the establishment of SLN mapping in endometrial cancer is demonstrating its reliability in detecting LN metastases, highlighting the importance of applying a well-defined SLN mapping algorithm that goes beyond just removal of blue nodes and ignoring pelvic sidewalls that do not map (a hazard for missing potential nodal metastasis). It cannot be stressed enough that a non-mapping pelvic sidewall is not a pathologically negative sidewall. Unilateral non-mapping should be immediately followed by side-specific lymphadenectomy. The sensitivity, negative predictive value, and false-negative rate were all improved after implementing the proposed algorithm when compared to SLN mapping alone (Tables 3 and 4). Notably, the false-negative rate when considering all patients in the cohort decreased from 14.9% when using SLN mapping alone to 1.9% after applying the algorithm. Therefore, satisfactory SLN mapping in endometrial cancer requires adherence to a surgical SLN algorithm and goes beyond just the removal of blue SLNs. Removal of any suspicious node along with side-specific lymphadenectomy for failed mapping is an integral part of this algorithm for endometrial cancer. Likewise, a recent cervical cancer publication by Cormier et al. underlined the importance of establishing an SLN algorithm to improve comprehensive detection of patients with nodal disease in the treatment of early cervical cancer [10].

There are, of course, several limitations to our study and proposed algorithm. Although this is the largest cohort of endometrial cancer SLN procedures published to date, this is a retrospective application of the algorithm. Further, some may argue that additional sites of injection or detection methods might increase the detection rate, but as already mentioned, this is unclear in the literature, and cervical injection of blue dye is simple and reproducible. The detection rate may also have been impacted by the inherent learning curve of any procedure. Ten surgeons with varying levels of SLN experience treated the patients in our cohort, and it has been suggested that performing at least 30 cases is associated with increased detection rates [20]. With regard to accurate reporting of our algorithm's performance and

false-negative rate, it can be argued that the analysis of all patients may be an underestimation of the false-negative rate if a complete LND was not performed. As we acknowledge this limitation, our nodal counts of non-SLNs probably reflect current clinical practice in the United States. When we limited our analysis to patients with at least 10 LNs removed, our algorithm continued to perform well, with an acceptably low false-negative rate of 3.1%. It is important to emphasize that although we are unable to report a true false-negative rate in this retrospective study in which a full backup LND was not required for all patients, the observed false-negative rate as the best available estimate is dramatically improved through implementation of the SLN algorithm when compared to removal of SLNs alone.

Our algorithm leaves paraaortic nodes to physician discretion, which we believe was a reasonable compromise at a time when the spectrum of LND in endometrial cancer spans from no dissection to a full pelvic and paraaortic LND. Paraaortic LND in endometrial cancer remains one of the most non-standardized procedures, with no well-defined templates, and is clearly one area in which gynecologic oncologists have failed to reach consensus on the extent and limits of this procedure. Admittedly, we know from numerous previous publications that our algorithm may be subject to missing about 1–3% of patients who would have isolated positive paraaortic nodes with negative pelvic nodes [3]; however, we have no reason to believe that this rate will be any higher, particularly if bilateral optimal SLN mapping is achieved with experience and ultrastaging is performed on these SLNs. This was in fact the case with the one false-negative that our algorithm was unable to detect.

The debate continues on the extent of LND needed for endometrial cancer staging. Two randomized controlled trials suggest that there is no therapeutic benefit to LND itself, though both studies are subject to significant methodological criticism [4,5]. Even if we accept that LND is not therapeutic, many oncologists continue to argue that it is crucial to determine LN status because it impacts prognosis and would guide adjuvant therapy. This leaves us asking: How do we assess LN status and standardize our approach, while limiting the morbidity associated with full LND?

The proposed endometrial cancer SLN mapping algorithm utilizes a simple cervical injection of blue dye but goes beyond mere identification of blue nodes to serve as a potential middle ground in the controversy of endometrial cancer surgical staging by providing a reasonably low false-negative rate, while sparing complete bilateral LND in the majority of cases. Isolated paraaortic lymphatic spread remains a known but small risk in the majority of patients.

Conflict of interest statement

Joyce N. Barlin: none.
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Dennis S Chi: Nycomed, consulting.
Yukio Sonoda: none.
Kaled Alektiar: none.
Deborah F DeLair: none.
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