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## INSIDE



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*Clinical Oncology Alert*'s Editor, William Ershler, MD, is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Peer reviewer V.R. Veerapallli, MD reports no financial relationship to this field of study.

# Deficiencies in AJCC Staging System for Prostate Cancer

ABSTRACT & COMMENTARY

***By William B. Ershler, MD, Editor***

***Synopsis:*** *AJCC staging for prostate cancer does not discriminate between regional node and distant metastases. In a review of more than 4000 patients treated at M.D. Anderson for 2 decades, survival data would indicate that such distinction would be of value.*

**Source:** Taylor SH, et al. Inadequacies of the current American Joint Committee on Cancer staging system for prostate cancer. *Cancer*. 2006;106:559-565.

THE WORLD HEALTH ORGANIZATION FIRST INTRODUCED THE concept of staging for cancer in 1929 in an attempt to create a standardized format for comparative purposes in assessing treatment outcomes from different locales.[1] Since then, the importance of accurate staging has become widely recognized. For clinicians, assessment of tumor stage prior to initial treatment is of great value in selection of the approach to be undertaken. For clinical investigators, accurate staging allows more reliable comparisons when assessing one treatment vs another.

Typically, for solid tumors, established staging systems have evolved to incorporate the extent of disease locally and to determine whether regional or distant metastases are apparent. Although quite reliable for most tumors, Taylor and colleagues have called to question the current widely used system for prostate cancer. Most clinicians treating prostate cancer rely on the American Joint Committee on Cancer (AJCC) staging which curiously does not distinguish between regional node involvement and distant metastases—patients with either are considered Stage IV.

To examine this argument, a retrospective review of 2 decades' experience of prostate cancer patients evaluated and treated at Taylor et al's institution was undertaken. Staging by the AJCC criteria was compared to the more expansive system recommended by the Surveillance, Epidemiology, and End Results (SEER) program (National Cancer Institute). The SEER staging system employed

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typically by tumor registries and for epidemiological studies (but not generally by practicing urologists and medical oncologists) describes the extent of spread from the point of origin with specific notation for site of metastases (ie, which node groups and which organs).

During the years 1982 through 2001 there were 4141 patients staged and treated. Descriptive analyses of demographic and disease variables were undertaken and survival and Cox proportional hazards regression analyses were performed.

Using the AJCC system the median survival for patients with Stage IV disease (which includes those with regional nodes only as well as those with distant metastases) was 86 months. However, the median survival for those with regional (but not distant) metastases was 134 months compared to 42 months for those who had distant metastases. When compared to patients with localized disease, patients with positive regional lymph nodes were 2.5 times more likely to die whereas those with distant metastases, the mortality risk was 10.1 times greater.

Thus, this analysis demonstrated a substantial difference in prognosis between those with regional lymph node spread compared to those with distant metastasis and the authors propose that the current AJCC classification be considered for modification.

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## COMMENTARY

Medical oncologists understand and appreciate the value of staging and use it to some degree in the formulation of treatment plans on practically every cancer patient under their care. The current report highlights a seeming error in the current system and likely the AJCC will review and consider revision. However, although the current system does not distinguish Stage IV (regional nodes) from Stage IV (distant metastases), it is interesting to note that in the current series those with regional disease were treated differently (more surgery and radiation) and those with distant disease, more systemic (hormonal) treatment. Thus, the current AJCC system does not serve one of its intended purposes: to guide therapy. The concept of staging is embedded in the oncologist's brain and despite the system, the mindset remains local/regional/distant, and this information, coupled with PSA level and rate of rise, Gleason score and histological features form the root of the treatment plan. ■

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# No Increase in Recurrent DVT Despite Thrombophilic Risk Factors

ABSTRACT & COMMENTARY

***By Andrew S. Artz, MD***

*Section of Hematology/Oncology, University of Chicago*

*Dr. Artz reports no financial relationship to this field of study.*

***Synopsis:*** *The impact of prothrombotic abnormalities on the risk of recurrent venous thromboembolism and bleeding in patients receiving long-term anticoagulation remains unclear.*

**Source:** Wahlander K, et al. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. *Br J Haematol*. 2006;133:68-77.

THIS STUDY REPRESENTS A REANALYSIS OF A LARGE randomized trial comparing ximelagatran to placebo to reduce recurrence of venous thromboembolism

(VTE) following 6 months of standard anticoagulation following after an initial VTE. Six common prothrombotic risk factors were ascertained by laboratory testing (factor V Leiden, prothrombin gene mutation, protein C, protein S, antithrombin, and anticardiolipin antibodies). At least one risk factor was identified in 41% of patients and 2 or more in 8% (21% of all subjects showed a factor V Leiden mutation). The reanalysis continued to show fewer VTE recurrences with extended anticoagulation using ximelagatran. However, prothrombotic risk factors had no impact on recurrence or bleeding in either arm compared to those without these risk factors. Thus, the common laboratory identified prothrombotic risk factors for VTE did not indicate subgroups for the risks or benefits of therapy might differ. Further research is warranted to better stratify recurrence risk after a standard course of 6 months of anticoagulation for VTE.

VTE is a common disorder with significant morbidity. At least one third will harbor a thrombophilic defect on routine laboratory testing. Anticoagulation remains standard therapy but the efficacy of prolonged anticoagulation compared to standard duration anticoagulation (usually 6 months), raises the question of optimal anticoagulation duration.[1,2] Previously, the authors reported the Thrombin Inhibitor in Venous Thromboembolism (THRIVE) III trial showing increased efficacy of an additional 18 months of ximelagatran, an oral direct thrombin inhibitor, compared to placebo for reducing recurrent VTE after a 6-month course of standard anticoagulation ($P < 0.001$).[3] In this study, the authors explore whether the presence of a laboratory identified thrombophilic risk factors increases VTE recurrence over those without risk factors from the THRIVE III trial.

In this updated analysis, they identified prothrombotic risk factors (eg, heterozygosity for factor V Leiden or prothrombin gene G20210A mutation, deficiencies of protein C, S or anti-thrombin, presence of anticardiolipin antibodies). Among the 1223 patients across 142 centers, 559 were in the ximelagatran arm and 540 in the placebo arm. Prothrombotic risk factors occurred in 41% of patients, among whom 8% had 2 or more risk factors, equally distributed between treatment arms. Factor V Leiden and prothrombin gene mutations occurred in 21% and 5% of patients, respectively. Investigators were not made aware of the thrombophilia screening results.

The updated analysis continued to show prolonged anticoagulation with ximelagatran reduced VTE recurrence over placebo and was not impacted by prothrombotic risk factors. Within the placebo group, VTE recurrence was not impacted prothrombotic risk factors. Similar results were seen in the treatment arm except for a small subset with low protein C where an VTE recurrence occurred more often. Bleeding risk was not altered by the presence of a prothrombotic risk factor (one might hypothesize a lower bleeding risk in the presence of a prothrombotic risk factor) in either the treatment or placebo group.

## COMMENTARY

Determining the optimal duration of anticoagulation after a VTE remains elusive. While randomized studies have shown fewer recurrences with prolonged anticoagulation, the inconvenience, costs, and risks of prolonged therapy can not be minimized, especially absent improved overall survival. Identifying patients at higher risk of VTE recurrence who might derive a larger relative risk reduction from prolonged anticoagulation would have enormous clinical value and also help guide clinical testing.

The findings of this study are consistent with most other data that the common laboratory defined prothrombotic risk factors may not appreciable impact recurrence risk. Despite the general notion that common mutations such as factor V Leiden or the prothrombin gene mutation place patients at very high risk of thrombosis, this study again supports the concept that heterozygosity for factor V Leiden or the prothrombin gene mutation did not increase recurrence risk over patients without a risk factor. Considering multiple effects, both genetic and environmental alike, probably combine to predispose to VTE, finding a single defect that accurately predicts recurrence risk for the majority of patients seems improbable. It is important to note that inferences are limited among subgroups of patients often considered at very high risk, such as antiphospholipid antibody syndrome (only anticardiolipin antibodies on a single test were performed) or homozygous factor V Leiden (small number).

In summary, common prothrombotic risk factors do not strongly influence VTE recurrence over patients without laboratory evidence of a risk factor. Future studies designed at better defining subsets with different VTE recurrence risks are sorely needed to tailor therapy towards individual risk. ■

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# Randomized Trial Comparing Axillary Clearance vs No Axillary Clearance in Older Patients With Breast Cancer

ABSTRACT & COMMENTARY

***By Stuart M. Lichtman, MD***

*Associate Attending, Memorial Sloan-Kettering Cancer Center, Commack, NY*

*Dr. Lichtman reports no financial relationship to this field of study.*

***Synopsis:*** *Avoiding axillary clearance for women 60 years of age and older who have clinically node-negative disease and receive Tam for endocrine-responsive disease yields similar efficacy with better early QoL.*

**Source:** International Breast Cancer Study Group. Randomized Trial Comparing Axillary Clearance Versus No Axillary Clearance in Older Patients with Breast Cancer: First Results of International Breast Cancer Study Group Trial 10-93. *J Clin Oncol*. 2006;24:337-344.

THE INCIDENCE OF BREAST CANCER INCREASES WITH age and breast cancer is the most common cancer in women older than 70 years old. In Western countries, approximately 50% of women with breast cancer are older than 65 years old. Given that populations are aging, increasing numbers of breast cancer occurrences can be expected among older women. Comorbid conditions also increase with age. Because these conditions may limit the duration and extent of a surgical procedure, there is a potential advantage to avoiding axillary surgery if it does not compromise tumor control. Avoiding axillary surgery might also reduce postoperative effects on arm pain, mobility, and lymphedema.

Recent data suggest that there is an association between increasing age at diagnosis and the presence of more favorable biologic characteristics of the tumor, such as greater expression of steroid hormone receptors, lower proliferative rates, diploidy, normal p53 expression, and the absence of overexpression of epidermal growth factor receptor and c-erbB-2. This trial investigated whether older patients with clinically node-negative and primarily endocrine-responsive early breast cancer might benefit from a change to the surgical approach that eliminates axillary lymph node dissection. This surgery usually represents the main cause of morbidity after a breast cancer resection, especially because such patients would receive adjuvant treatment with tamoxifen. Their study compares older patients undergoing breast surgery treated with axillary surgery versus patients who received no axillary surgery to determine the effect of axillary surgery on quality of life (QoL), disease-free survival (DFS), and overall survival (OS).

From May 1993 through December 2002, the study randomized 473 postmenopausal patients 60 years or older with clinically node-negative operable breast cancer were randomly assigned preoperatively to receive breast surgery with axillary clearance followed by tamoxifen (20 mg) for 5 years or breast surgery without axillary clearance followed by tamoxifen (20 mg) for 5 years. At the time of random assignment, estrogen receptor (ER) status and pathologic nodal status were unknown. In August 2002, the International Breast Cancer Study Group (IBCSG) Scientific Committee made a recommendation to discontinue tamoxifen for patients with endocrine-nonresponsive tumors. Surgery to remove the primary tumor was either a total mastectomy or breast-conserving surgery. On April 15, 1999, the original protocol was amended to allow institutions to perform sentinel node biopsy (SNB) in patients who had been randomly assigned to surgery, provided they then proceed to axillary clearance. However, only 2 patients used this option. Radiotherapy using 2 tangential fields was recommended after breast-conserving surgery.

There were 473 patients who were equally balanced according to randomly assigned treatment arm. The median age was 74 years and 22% of the patients had received prior hormone replacement therapy and 80% of the patients had primary tumors classified as ER positive. Twenty-eight percent of the patients who had axillary clearance were found to have involved nodes. The median number of examined lymph nodes was 13. Forty-five percent of the patients were treated with mastectomy, 33% had breast-conserving surgery with radiotherapy, and 23% had breast-conserving surgery without radiotherapy. Physicians were asked whether the patient experienced restricted ipsilateral arm movement and whether the patient experienced arm pain. For both end points, we found a statistically significant increase in physician-reported adverse effects in the first postoperative period for patients who had an axillary clearance. However, after the immediate postoperative period, the percentage of patients for whom the physicians reported

restricted arm movement approached the preoperative values in both groups. Similar results were observed for physician-reported arm pain. This difference between treatments was no longer statistically significant at later follow-up assessments. The proportion of patients that developed lymphedema, defined as a 5% or greater increase in arm circumference from baseline, was also not significantly different between treatments. Overall, the 2 treatment groups were similar with respect to both DFS and overall survival. Within the ER-positive cohort the 2 treatment groups were similar with respect to both DFS and OS. Similarly, no treatment difference was observed for the ER-negative cohort for DFS and OS without axillary clearance. Sites of first event were similar between the 2 treatment groups. A 2% incidence of axillary recurrence overall (as first event) and no statistically significant difference between the 2 treatment options. One patient, who did not receive an axillary clearance, experienced a subsequent axillary recurrence. All of the patients who had an axillary recurrence received a late axillary clearance after recurrence. Seventeen percent of the patients experienced a breast cancer-related recurrence, whereas 21% experienced a nonbreast second primary cancer or death without recurrence.

## COMMENTARY

The morbidity of axillary dissection has led some investigators to question its necessity, whereas others have studied alternatives such as axillary radiation therapy and sentinel node biopsy. This randomized study examined the option of avoiding axillary surgery altogether and shows that in older women with clinically negative axillary examination, this transiently improves QoL apparently without compromising DFS or OS results. The median age of the patients enrolled into IBCSG Trial 10-93 was 74 years, which is substantially older than the median age in most adjuvant therapy trials conducted for postmenopausal patients. QoL measurements by both physician and patient showed significantly inferior arm-related QoL scores after axillary surgery. The authors concluded that axillary clearance does not contribute greatly to DFS or OS. Regional recurrence or reappearance of disease in the axilla was observed for only 2% of the patients overall (3% without axillary clearance and 1% with axillary clearance).

Given the postoperative morbidity and the decrease in QoL associated with axillary surgery, especially for this elderly population, the trial results provide important evidence to support the option of avoiding axillary clearance. A recent randomized study conducted by the Cancer and Leukemia Group B (CALGB)[1] evaluated the role of radiotherapy in older women with clinical stage I (T1, N0, M0) and ER-positive breast carcinoma treated with lumpectomy and tamoxifen for 5 years. In the CALGB trial, the axillary node dissection was allowed but discouraged, confirming our hypothesis that this approach is common in clinical practice in populations of women older than 70 years. In the CALGB trial, only 2 isolated axillary recurrences were found in women treated with lumpectomy and tamoxifen. Conversely, avoiding axillary clearance for older women with ER-negative tumors may not be as safe, as suggested by the overall outcomes reported in the IBCSG study. It may be argued that axillary surgery might still be worthwhile to determine whether to offer chemotherapy to these patients.

Although knowing the axillary nodal status may be necessary to choose the best adjuvant systemic therapy, it is less relevant in an elderly population at low risk and with a potentially shorter life expectancy. Thus, the recent trend to substitute sentinel node biopsy can also be called into question, given that this present results seem to support avoidance of axillary dissection. This line of reasoning is based on the prior supposition that chemotherapy should be used for older patients with node-positive disease, but not for patients with node-negative disease.

More recently, the endocrine responsiveness of the primary tumor, not the nodal status, is the relevant feature used for guidance in the decision whether to use chemotherapy. Data for the 50- to 69-year age group from the Early Breast Cancer Trialists' Collaborative Group Overview demonstrate that for patients with endocrine-responsive disease, endocrine therapy (specifically tamoxifen) provides the majority of the advantage associated with adjuvant treatments.[2] Thus, because nodal status is less relevant for determining whether chemotherapy is indicated, there may be no need to perform even SNB procedures for an older woman with endocrine-responsive and clinically node negative disease. For older women who do require axillary dissection either because of clinical node involvement or because of a positive SNB, the results of this study are reassuring, demonstrating that for most of these women, there is little effect from this surgery on their long-term daily functioning or their QoL. IBCSG Trial 10-93 has demonstrated that avoiding axillary clearance for older women with clinically node-negative breast cancer who receive adjuvant tamoxifen seems safe and results in early improved QoL for this older population of patients. These results apply primarily for patients with endocrine-responsive disease in whom the use of tamoxifen is associated with substantial benefit in terms of dis-

ease control. For older women with endocrine-nonresponsive disease, the tailored use of adjuvant systemic chemotherapy is being investigated in a ongoing randomized clinical trials.

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# Diagnostic Open Laparoscopy in the Management of Advanced Ovarian Cancer

ABSTRACT & COMMENTARY


***By Robert L. Coleman, MD***

*Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston*

*Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.*



***Synopsis:*** *Diagnostic open laparoscopy (DOL) could be considered a valid diagnostic tool in evaluating the extent of disease in advanced ovarian cancer (AOC). These data suggest that the use of DOL leads to a decrease in the rate of primary cytoreductive surgery for AOC; on the other hand, a higher optimal debulking rate (no residual tumor) at primary surgery is achieved.*



**Source:** Angioli R, et al. Diagnostic open laparoscopy in the management of advanced ovarian cancer. *Gynecol Oncol*. 2006;100:455-461.


Optimal surgical cytoreduction is a recognized staple of initial advanced ovarian cancer care. However, within the spectrum of patients who undergo this surgery are those in whom complete resection is either impossible or unwarranted in the face of certain unacceptable morbidity. Identifying these patients before laparotomy is generally relegated to preoperative imaging and biomarkers—with limited success. Angioli and colleagues report their experience with laparoscopic evaluation of intraperitoneal disease to make this decision. Over the 50-month accrual period, 87 patients were consecutively evaluated. All were to have suspected metastatic disease (stage IIIC-IV) and were evaluated for the outcome of no post-operative tumor residual.

Those deemed unresectable were treated with neoadjuvant standard combination chemotherapy. Those in this latter group who did not progress during 3 cycles of chemotherapy were taken to cytoreduction. The primary end point of this observational study was to quantify their success in predicting cytoreduction in these patients. Overall, 53 (61%) were deemed appropriate surgical candidates at laparoscopy, in whom 51 (96%) were cytoreduced to no visible residual. Among the 34 in whom surgery was deferred, 25 (74%) were ultimately operated upon; 20 (80%) were similarly optimal at interval cytoreduction. Overall survival was best in those in whom surgery could be done initially; those undergoing surgery after chemotherapy had a significantly worse survival but was substantially better than those in whom chemoresistance was documented. Similar survival outcomes were observed for those patients who completed both surgery and chemotherapy, regardless of the sequence. Complication rates were also low in both surgical cohorts. The authors concluded that the open laparoscopy is a valuable tool to evaluate the extent of disease at presentation and may select patients in whom complete cytoreduction can be achieved at initial surgery.

## COMMENTARY

The standard clinical approach to newly diagnosed ovarian cancer is primary surgical cytoreduction followed by combination chemotherapy for patients with high-risk or advanced-stage disease. Several studies have suggested that better cytoreduction is important to response to chemotherapy and overall survival.[1] However, approximately 50% of patients who undergo attempt at cytoreduction are left with macroscopic disease—in some cases bulky macroscopic disease, in whom poorer response to treatment (and overall survival) is observed. Since previously unexposed ovarian cancer is largely sensitive to chemotherapy, an alternative treatment approach for patients with bulky intraperitoneal disease is to administer chemotherapy ahead of surgery. This not only identifies patients with chemoresistant disease (by progression on therapy) but also can substantially reduce the volume of tumor to be resected, thereby increasing the rate of optimal cytoreduction and reducing the morbidity of surgery.

To date, there have been 3 randomized trials that have been performed to evaluate the benefit of interval cytoreduction in this manner.[2-4] The 3 studies span the decades of platinum and, most recently taxane use in the primary management of ovarian cancer. Each of these trials identified patients largely through a failed (suboptimal) cytoreduction attempt and randomized their care to either standard chemotherapy or interval surgery after an abbreviated treatment course. Two of the trials, including one utilizing a regimen considered a current standard of care combination did not identify a benefit by interval (or in this case, secondary) surgical attempt. One trial, using a non-taxane combination, did suggest improved progression-free and overall survival for those undergoing an interval surgery. However, a significant fraction of women enrolled in this trial did not have an aggressive first attempt and essentially underwent a neoadjuvant program. A randomized trial of each surgical approach (neoadjuvant, interval cytoreduction and standard cytoreduction) is underway.

The current trial is unique in that the bar set for cytoreduction is high (no visible disease). Althoughvarious definitions of "optimal" have been used over the years, none have specifically used this degree of resection as a primary goal. As listed in the authors procedures, the extent of radical resection in order to achieve this outcome is greater than that generally reported in studies conducted in the multi-institutional setting. Nonetheless, it is a desired result if one accepts the relationship between tumor volume residual and survival. The current study demonstrates that laparoscopy (better than clinical or radiographic measures) may be helpful in selecting patients in whom a radical approach is warranted. There are several unknowns that still require elucidation: what percent of patients deemed as poor candidates for cytoreduction could indeed by cytoreduced? What are the implications on survival for purposefully waiting to cytoreduce in these patients? What is the impact on survival for port site metastases seen in the delayed surgical cohort? Can a lower cytoreduction bar achieve the same result? Finally, is this strategy reproducible in the multi-institutional setting? These questions will need to be formally addressed before such an approach can be globally recommended. However, the bar for complete resection should be embraced as we approach primary surgical management. ■

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# Randomized Double-Blind Trial of Estrogen Replacement Therapy vs Placebo in Stage I or II Endometrial Cancer

ABSTRACT & COMMENTARY

***By Robert L. Coleman, MD***


***Synopsis:*** *Although this incomplete study cannot conclusively refute or support the safety of exogenous estrogen with regard to risk of endometrial recurrence, it is noteworthy that the absolute recurrence rate (2.1%) and the incidence of new malignancy were low.*



**Source:** Barakat RR, et al. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2006;24:587-592.


THE ASSOCIATION BETWEEN EXOGENOUS ESTROGEN use and endometrial cancer development has been well documented. Nonetheless, the hazard of estrogen replacement therapy in women with a personal history of endometrial cancer has not been well studied and, despite anecdotal evidence of its safety, is largely discouraged among clinicians. In this regard, Barakat and colleagues from the Gynecologic Oncology Group (GOG) set out to quantify the risk/benefit of estrogen replacement in women with early stage endometrial cancer. Women undergoing primary extirpative surgery for stage IA-IIB (occult) endometrial cancer were randomized to either estrogen (premarin 0.625 mg) or to placebo. All women were to have an indication for estrogen therapy including vasomotor symptoms, vaginal atrophy, increased risk for

cardiovascular disease or an increased risk for osteoporosis. The intent of therapy was 3 years administration. Strata were considered for stage based on differing survival factors. The primary end point was time to recurrence with all cause survival a secondary objective.

Based on anticipated rates of recurrence and loss to crossover, 2108 women were to be recruited. Over 66 months, 1236 women were randomized to the trial. Effects on accrual following the announcement of data from the Women's Health Initiative (WHI) caused the GOG to terminate the study early. Half of the cohort were randomized to each treatment group. Just 41% of patients on ERT and 50% on placebo remained compliant over the course of 3 years. Recurrence was lower than expected at 2.1%, which was countered by the GOG through closure to Stage IA patients. Nonetheless, just 9 of the 45 deaths observed on the trial were from endometrial cancer (0.7% of total population). There was no observed difference in recurrence or all-cause death between the treatment arms but the trial did not meet its accrual goals in order to infer this result in this population. New malignancy rates were low (1.3% for ERT, 1.6% for placebo) in both cohorts.

## COMMENTARY

Endometrial cancer is the most common gynecologic malignancy diagnosed in the United States. Fortunately, most are confined to the uterus at presentation, which generally translates into a favorable survival profile compared to other malignancies of the genital tract. While the median age of diagnosis is older than 60, a sizeable fraction of patients are perimenopausal at diagnosis and suffer from significant estrogen deprivation following primary surgical management. Since estrogen use has been linked with the development of this disease, clinicians have been reticent to use ERT even in symptomatic women with a personal history of endometrial cancer based on the theoretical risk of "activating" dormant cells leading to recurrence. Retrospective studies have failed to confirm this suspicion.[1-3] However, the issue of ERT use is relevant as the likelihood for long-term, cancer-free survival for these women is high and their exposure to other life-threatening factors related to estrogen deprivation is significant.

Data from the WHI caused a dramatic effect in the worldwide use of ERT. While the initial reports detailed outcomes based on the use of combined estrogen and progestin, the reduction in popularity heavily influenced the trial's accrual necessitating early termination. Subsequently, data from WHI with estrogen alone regimens have been published which confirmed increased risks of thromboembolic events but no increase in cardiovascular disease or breast cancer. Protection of osteoporosis was confirmed but no specific evaluation of the influence of this therapy on quality of life was detailed. Arguably, this is of primary importance in the population being studied. While the current trial cannot be used to support or refute the use of ERT in women with endometrial cancer, the data provided do suggest that recurrence in this setting is low; but the compliance with therapy is also low. Short-term use for symptomatic patients does not appear to be associated with a dramatic acceleration of recurrence although safety cannot be definitively inferred. Similar to the discussion of ERT use in women without cancer, it would be prudent for symptomatic women with an endometrial cancer history desiring ERT to carefully counsel them to the known risks/benefits of ERT use and limit usage to the shortest practical period. ■

## CME Objectives

The objectives of *Clinical Oncology Alert* are:

- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

## CME Questions

**9. In the AJCC staging system for prostate cancer, patients with regional lymph node involvement are classified as:**

a. Stage II
b. Stage IIIa
c. Stage IIIb
d. Stage IV

**10. What best describes recurrence of VTE after 6 months of standard anticoagulation?**

a. Heterozygosity for factor V Leiden significantly increases recurrence over other patients with VTE and no known risk factor
b. Heterozygosity for the prothrombin gene G20210A mutation significantly increases recurrence over other patients with VTE and no known risk factor
c. 18 months of ximelagatran reduces recurrence over placebo
d. All of the above

Answers: 9 (d); 10 (c)

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# Can Calcium and Vitamin D Prevent Hip Fractures?

It has been a tough few months for marketers of vitamins and herbal products. Calcium plus vitamin D, saw palmetto, and glucosamine/chondroitin have all been the subject of studies that have questioned their efficacy. The calcium plus vitamin D results are possibly the most disappointing. In further data from the Women's Health Initiative study, 36,282 postmenopausal women ages 50 to 79 were randomly assigned to receive 1000 milligrams of elemental calcium with 400 IU of vitamin D3 or placebo, with the end point being prevention of hip and other fractures. After 7 years of follow-up, bone density was slightly higher, but there was no reduction in hip fractures in women who took calcium plus vitamin D (hazard ratio, 0.88 for hip fracture [95% CI, 0.72 to 1.08]). There was also no reduction in clinical spine fractures (HR, 0.90 [0.74 to 1.10]) or total fractures (HR, 0.96 [0.91 to 1.02]). Calcium plus vitamin D did result in a higher risk of kidney stones (HR, 1.17 [1.02 to 1.34]).

The authors conclude that among healthy postmenopausal women, calcium plus vitamin D supplementation did not significantly reduce hip fractures or reduce risks of kidney stones (*N Engl J Med*. 2006;354:669-683). In an accompanying editorial, Joel Finkelstein, MD, points out that many women who take calcium plus vitamin D "believe that they are completely protected against the development of osteoporosis. This study should help correct this important misconception and allow more women to receive optimal therapy for bone health." He also points out that women should not abandon calcium and vitamin D, neither should they rely on it alone as prevention against osteoporotic fractures (*N Engl J Med*. 2006;354:750-752 [correction published *N Engl J Med*. 2006;354:1102]).

### *Treatment of Benign Prostatic Hyperplasia*

Saw palmetto is used by over 2 million men to treat symptoms of benign prostatic hyperplasia (BPH). Now, a new study suggests that it is ineffective. The study, funded by the National Institutes of Health and the National Center for Complementary and Alternative Medicine, looked at 225 men over the age of 49 with moderate-to-severe symptoms of BPH who were randomized to one year of saw palmetto extract 160 mg twice a day or placebo. The primary outcomes were changes in American Urological Association Symptom Index and maximal urinary flow rates. Prostate size, the residual urinary volume after voiding, quality of life, laboratory values, and adverse effects were also measured. After one year, there were no significant differences between patients treated with saw palmetto or placebo in any of the outcomes. There was also no difference in adverse effects. The authors conclude that saw palmetto does not improve symptoms or objective measures of BPH (*N Engl J Med*. 2006;354:557-566). An accompanying editorial welcomes the scientific rigor of placebo-controlled trials applied to dietary supplements, which are generally not held to standards of safety and efficacy. The authors call for similar studies for other

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commonly used herbal products (*N Engl J Med*. 2006;354:632-634).

### Treatment of Osteoarthritis of the Knee

Glucosamine and chondroitin sulfate is used by millions to treat osteoarthritis. In another study supported by the NCCAM, along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1583 patients with osteoarthritis of the knee were randomized to 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, combination of glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Acetaminophen was allowed as rescue analgesia. The primary outcome was a 20% decrease in the pain from baseline at week 24. Glucosamine and conference sulfate were no better than placebo in reducing the pain by 20%, except for combined therapy (glucosamine plus chondroitin) in patients with moderate-to-severe pain at baseline (79.2% response vs 54.3% response placebo, $P = 0.002$). Adverse events were no different in all groups. The authors conclude that overall glucosamine chondroitin did not reduce pain effectively in patients with osteoarthritis of the knee, except in the subgroup of patients with moderate-to-severe knee pain (*N Engl J Med*. 2006;354:795-808). An accompanying editorial recommends telling patients that neither glucosamine nor chondroid alone has been shown to be more effective than placebo in treating knee pain. They suggest that glucosamine sulfate plus chondroitin sulfate may be tried in patients with moderate-to-severe knee pain, but should be discontinued after 3 months if there is no benefit (*N Engl J Med*. 2006;354:858-860).

### Refractory Asthma and TNF—Connection?

Refractory asthma is a condition with a high mortality rate and limited treatment options. A new study suggests that the tumor necrosis factor (TNF) axis is up-regulated in refractory asthma, creating the possibility of treating refractory asthma with TNF inhibitors. Researchers from the United Kingdom measured markers of TNF alpha activity in 10 patients with refractory asthma, 10 patients with mild/moderate asthma, and 10 controls subjects. Patients with refractory asthma increased expression of TNF alpha markers compared to those with mild-to-moderate asthma and controls. Study subjects with refractory asthma were subsequently randomized to receive the TNF alpha receptor etanercept 25 mg twice weekly in a placebo-controlled, double-blind, crossover pilot study. Ten weeks of treatment with etanercept was associated with a significant increase in concentration of methacholine required to provoke a 20% decrease in FEV1 ($P = 0.05$), an improvement in asthma related quality-of-life score ($P = 0$ .02), and a 0.32 liter increase in post bronchodilator FEV1 ($P = 0.01$) compared to placebo. The authors suggest that the TNF alpha axis is upregulated in refractory asthma, and that etanercept may be beneficial in these patients (*N Engl J Med*. 2006; 354:697-708). An accompanying editorial reports that several studies of TNF inhibitors in patients with refractory asthma are ongoing, suggesting that we soon should have an answer as to whether these agents are effective for treating this difficult clinical entity (*N Engl J Med*. 2006;354:754-758).

### FDA Actions

The FDA has approved anidulafungin, Pfizer's new anti-fungal for the treatment of candidemia. The drug is a new molecular entity that is given intravenously. It is approved for a variety of Candida infections including esophagitis, sepsis, abdominal abscesses, and peritonitis. It will be marketed by Pfizer as Eraxis.

The FDA has approved lubiprostone for the treatment of chronic idiopathic constipation in adults. The drug is a selective chloride channel activator that increases intestinal fluid secretion and motility. The drug will be marketed by Sucampo Pharmaceuticals as Amitiza.

CV Therapeutics has received approval to market ranolazine, the first of a new class of agents for the treatment of chronic angina. The drug is an orally available extended-release anti-anginal drug that acts without reducing heart rate or blood pressure. The drug's mechanism of action has not been fully characterized, but it is felt that it works by affecting changes in cardiac metabolism. Because ranolazine prolongs QT interval, it should be reserved for patients who have not achieved adequate response with other anti-anginal drugs, and should be used in combinations with amlodipine, beta-blockers, or nitrates. CV Therapeutics will market ranolazine as Ranexa.

The FDA has approved an oral vaccine for the prevention of rotavirus gastroenteritis in infants and children. The oral vaccine should be initiated in infants 6 to 12 weeks old, with 2 subsequent doses of 4 to 10 week intervals. The vaccine should be completed before the child reaches 32 weeks of age. Based on clinical trials, the vaccine appears to be 98% effective for preventing gastritis caused by targeted rotavirus serotypes, and 74% effective at preventing gastroenteritis of any severity. Rotavirus vaccine will be marketed by Merck as RotaTeq. ■