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Extreme Drug Resistance Assay and Response to Chemotherapy in Patients with Epithelial Ovarian Cancer

ABSTRACT & COMMENTARY

Eltabbakh and colleagues have recently reported a study of the extreme drug resistance (EDR) assay, the purpose of which was to correlate the results of the EDR assay to response to first-line paclitaxel/cisplatin chemotherapy among patients with epithelial ovarian cancer. Seventy-five patients for whom the assay was performed on tissue from primary surgery and who were then treated with paclitaxel/cisplatin chemotherapy were the principal focus of this study. The prevalence of EDR to paclitaxel was 20% (n = 15) and to cisplatin it was 2.7% (n = 2). Only one patient exhibited EDR to both paclitaxel and cisplatin. Neither the overall response rate (86.4% vs 81.3%) nor the surgical response rate (25.4% vs 12.5%) differed significantly between patients whose tumors demonstrated no EDR to either paclitaxel or cisplatin and those whose tumors demonstrated EDR to at least one of these two drugs. The single patient whose tumor exhibited EDR to both paclitaxel and cisplatin had tumor progression. The sensitivity, specificity, positive predictive value, and negative predictive value of the EDR assay were 79.6%, 27.0%, 86.0%, and 19.0%, respectively. Eltabbakh et al conclude that EDR to paclitaxel does not preclude response to the combination of paclitaxel and cisplatin as primary therapy for patients with epithelial ovarian cancer, and that the role of the EDR assay in the primary management of patients with this cancer remains to be determined. (Eltabbakh GH, et al. *Gynecol Oncol* 1998;70:392-397.)

COMMENT BY DAVID M. GERSHENSON, MD

The oncology community longs for a reliable in vitro test that predicts response (or lack of response) to chemotherapy. Such a test would allow us to better select patients for chemotherapy who would benefit. In addition, it would avoid unnecessary, expensive, potentially toxic treatment for a large number of patients. Several different assays have enjoyed popularity over the past two decades

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INSIDE

or so, but none has clearly emerged as the best option. Within the gynecologic oncology community today, the Oncotech assay—the one used in the present study—is the most popular. It is marketed to predict drug resistance, not drug sensitivity. Unfortunately, in my opinion, there is not sufficient evidence to support its routine use. The study, although admirable in its intent, has insufficient patient numbers to answer the question. As Eltabbakh et al note, only one patient's tumor demonstrated EDR to both paclitaxel and cisplatin, and that patient progressed on treatment. Resistance to only one of two drugs has little use in patients receiving combination chemotherapy. In addition, with limited choices for first-line therapy, one could argue that such an assay would be more useful in the refractory setting. In fact, we are initiating a multicenter trial for patients with recurrent ovarian cancer in which patients undergo fine needle aspiration of metastatic tumor. The cells are then tested using the EDR assay. Patients are then randomized into one of two arms: 1) assay-directed treatment using one of three drugs to which the tumor is least resistant; and 2) non-assay-directed treatment in which patients are simply randomized again to one of the same three drugs. Of course, any in vitro assay is potentially plagued by the phenomenon of tumor heterogeneity. ❖

Which of the following statements best describes the current status of in vitro drug sensitivity/resistance assays?

a. Chemosensitivity assays should be routinely used to select first-line chemotherapy for ovarian cancer patients.
b. Chemosensitivity assays should be routinely used to select secondary chemotherapy for patients with recurrent ovarian cancer.
c. Chemoresistance assays should be routinely used to select first-line chemotherapy for ovarian cancer patients.
d. Chemoresistance assays should be routinely used to select secondary chemotherapy for patients with recurrent ovarian cancer.
e. Further study is warranted before any test can be recommended for routine use.

Does Epidural Anesthesia Increase the Cesarean Delivery Rate?

ABSTRACT & COMMENTARY

Synopsis: *Epidural anesthesia is not associated with an increased cesarean delivery rate.*

Source: Halpern SH, et al. *JAMA* 1998;280: 2105-2110.

To evaluate the effect of epidural analgesia on the incidence of cesarean delivery, Halpern and colleagues conducted a meta-analysis of 10 prospective, randomized trials enrolling 2369 patients. Half of these investigations were conducted in the United States. The outcomes of patients randomized to receive epidural anesthesia were compared to those women receiving parenteral opioids. The narcotics used included meperidine, fentanyl, and butorphanol, dosed as needed or by patient-controlled analgesia. The total rate of cesarean delivery did not differ between patients receiving an epidural (8.2%) or parenteral opioids (5.6%), nor was there a difference when the data were analyzed by parity or in the rate of cesarean delivery for dystocia. While the rate of instrumented deliveries was significantly higher in the epidural group, no difference was noted in instrumented deliveries performed for dystocia. The first stage of labor was, on average, 42 minutes longer in patients receiving an epidural while the second stage was 14 minutes longer. More patients in the epidural group required oxytocin, had a fever higher than 38°C, and experienced hypotension. Pain relief was significantly improved during labor and patient satisfaction was significantly

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higher with epidural anesthesia. Analysis of neonatal outcomes revealed significantly fewer Apgar scores of less than 7 at one and five minutes in the epidural group. No differences were noted in the incidence of fetal distress or meconium passage. Infants whose mothers had received epidural anesthesia were less likely to require naloxone or have a low umbilical artery pH. Neither method of pain relief was associated with serious neonatal problems.

Halpern et al conclude that epidural anesthesia is not associated with an increased cesarean delivery rate. While the length of labor is prolonged in women receiving an epidural, patient satisfaction and neonatal outcome are better than with opioid analgesia.

COMMENT BY STEVEN G. GABBE, MD

This important meta-analysis demonstrates the benefits of epidural anesthesia as compared to pain relief with opioids. Of note, four of the studies included in the meta-analysis were published in 1997 and used an epidural technique combining a local anesthetic with a narcotic, a method associated with a less dense motor block. The prolongation of the first and second stages of labor in patients receiving epidural anestheia, while statistically significant, does not appear to be of great clinical importance. Nor were there more instrumented vaginal deliveries for dystocia in these patients. In summary, epidural anesthesia was associated with significantly better pain relief than opioids and better neonatal outcomes. ❖

Based on the study by Halpern et al, which of the following outcomes is increased when patients receive epidural anesthesia?

a. Cesarean delivery rate
b. Instrumented vaginal delivery for dystocia
c. Maternal fever
d. Meconium passage
e. Neonatal depression

Vaginal Ultrasound as an Initial Test in Postmenopausal Vaginal Bleeding

ABSTRACT & COMMENTARY

Synopsis: *In postmenopausal women with vaginal bleeding, vaginal ultrasound is highly sensitive, but less specific, for identifying those women with potentially serious disease.*

Source: Smith-Bindman R, et al. *JAMA* 1998;280: 1510-1517.

Postmenopausal women commonly present with vaginal bleeding, prompting many clinicians to ask whether noninvasive testing may be recommended as the first step in workup. Smith-Bindman and colleagues from the University of California, San Francisco, conducted an exhaustive meta-analysis of prospective studies that collected endovaginal measurements of endometrial thickness prior to sampling endometrial tissue in postmenopausal women with vaginal bleeding. Thirty-five studies including a total of 5892 women met the review's inclusion criteria.

When Smith-Bindman et al used 5 mm as the threshold for abnormal endometrial thickness (encompassing the width of both the anterior and posterior endometrial walls), vaginal ultrasound was found to be 96% sensitive for endometrial carcinoma (95%; CI, 94%-98%) and 92% sensitive for endometrial disease (cancer, polyp, or atypical hyperplasia; 95%; CI, 90%-93%). These sensitivities did not vary with hormone replacement status. If a postmenopausal woman with vaginal bleeding had a negative endovaginal ultrasound, her pretest probability of endometrial cancer was reduced by 90% regardless of hormone use. Ultrasound was 77% specific for women who were using hormone replacement (95%; CI, 75%-79%), and 92% specific for those who were not (95%; CI, 90%-94%).

COMMENT BY ELIZABETH MORRISON, MD, MSEd

Some postmenopausal women with vaginal bleeding cannot or do not wish to undergo endometrial sampling. In others, sampling is attempted but is nondiagnostic. This helpful meta-analysis by a multidisciplinary research team clarifies the role of endovaginal ultrasound for these women. Clinicians may choose to use ultrasound to exclude many postmenopausal women who do not require endometrial biopsy, as ultrasound is a highly sensitive screen for significant endometrial disease.

The meta-analysis used sound methods to explore this important question. Smith-Bindman et al explicitly stated their comprehensive strategy for selecting relevant prospective trials so that results could be combined appropriately. A test for homogeneity was done, and validity was assessed by two independent reviewers.

The results are compelling. As Smith-Bindman et al state, "For a postmenopausal woman with vaginal bleeding with a 10% pretest probability of endometrial cancer, her probability of cancer is 1% following a

normal endovaginal ultrasound result." This is not to say that all clinicians will wish to use ultrasound for screening all such patients. Some physicians will reasonably choose endometrial biopsy, hysteroscopy, or other invasive techniques for patients felt to be at moderate to high risk of endometrial cancer or atypia. Endometrial biopsy and ultrasound had similar costs in a recent cost analysis,[1] so cost need not be a factor in the decision.

It is interesting that in this meta-analysis, sensitivity and specificity were not improved when 4 mm rather than 5 mm was used as an endometrial stripe cut-off. Using a 3 mm cut-off yielded excellent sensitivity and specificity but would be impractical because relatively few women have an endometrium less than 3 mm thick. Using a 6 mm cut-off yielded sensitivity and specificity below 90% for endometrial disease. Future studies may further illuminate the optimal threshold value for endometrial thickness on ultrasound. Meanwhile, this meta-analysis will help gynecologists and family physicians use vaginal ultrasound more confidently in the workup of postmenopausal women with vaginal bleeding. ❖

Reference

1. Weber AM, et al. *Am J Obstet Gynecol* 1997;177: 924-929.

For a postmenopausal woman with vaginal bleeding who has a 10% pretest probability of endometrial cancer, her probability of cancer following a normal endovaginal ultrasound result is:

a. 0.1%.
b. 1%.
c. 5%.
d. 10%.

A Reduction in Cardiovascular Mortality with Postmenopausal Estrogen Therapy

ABSTRACT & COMMENTARIES

Synopsis: *Current ERT use was associated with decreased cardiovascular mortality and a decrease in sudden cardiac death. Breast cancer risk did not increase with current ERT use.*

Source: Sourander L, et al. *Lancet* 1998;352: 1965-1969.

Sourander and associates performed a community-based prospective cohort study of estrogen replacement therapy in a Finnish population by inviting all women born between 1923 and 1930 to participate in a free mammography screening program. Of the 8164 invited, 7944 women enrolled. Women were followed at two-year intervals for a total of four follow-up visits. Four hundred five women died by the last follow-up visit. The mean oral estradiol dose was 1.46 mg daily and the mean duration of use at enrollment was 8.2 years. The total follow-up consisted of 53,305 person-years. Nine hundred eighty-eight women were current users and 757 were former users. Of the current users, 514 took unopposed ERT and 139 used a progestin. Hysterectomized women were excluded from the analysis for endometrial cancer. Women were classified as never, current, or former users based on information provided at enrollment and verified. Women who began hormone use during the study were excluded from the analysis. Current users had a clear survival advantage. Only endometrial cancer increased, with a relative risk (RR) of 5.06 (confidence interval [CI], 2.47-10.41). The RR for cardiovascular mortality in current users was 0.21 (0.08-0.59) and 0.75 in former users (0.41-1.37). Current users had a reduced risk of coronary artery disease, stroke, and sudden cardiac death. The RR for breast cancer was 0.57 (0.27-1.20) in current users.

COMMENT BY SARAH L. BERGA, MD

This study is interesting for several reasons. First, the estrogen most commonly used was estradiol and the dose was relatively high. Apparently, most women received either 1 mg or 2 mg daily of oral estradiol. Nonetheless, the incidence of endometrial cancer during follow-up was only 2.1%. There is a prevailing folklore in the United States that estradiol is the "strongest" or "most risky" estrogen. While this study did not afford a direct comparison of different estrogen preparations, there is no suggestion of undue risk associated with estradiol use. Breast cancer rates did not vary by estrogen use, but women in the highest socioeconomic class had the highest rates of breast cancer. Possible factors identified by Sourander et al that might explain the increased risk of breast cancer in women in the highest social class were late menopause, early menarche, short breastfeeding, or increased alcohol intake. Smoking might be a factor, but less than 3% in all groups smoked. Diet or weight might be factors, but body mass index was comparable in all groups. Time since menopause also did not

explain rates of breast cancer in this study. The prevalence of diabetes and hypertension was highest in never users, but predicted survival curves showed the greatest benefit of ERT use accrued to those with hypertension and diabetes. The main limitation of the study was that few women used combined estrogen-progestin regimens. Also, bias must have existed with regard to which women were prescribed estrogen. Interestingly, most of the benefits of ERT use were lost when use was discontinued.

Overall, the results of this study are reassuring and supportive of the concept that extended ERT use after menopause is safe and beneficial. ERT appears to be a sound investment from both a personal and population perspective. Despite the evident benefits, however, only 10% of Finnish women were using ERT. We can speculate as to why rates of use are so low on both sides of the Atlantic, but I don't think anyone really knows. It is imperative that the barriers to HRT use be better defined. It is a truism that risk and risk perception are rarely aligned. Perhaps it is time to reimburse physicians for spending time with patients so that issues of risk perception can be addressed to the patient's rather than the insurer's satisfaction.

COMMENT BY LEON SPEROFF, MD

The conclusion of this study does not have the strength of a randomized trial, but Sourander et al, being very aware of the major criticism against observational postmenopausal hormone studies, carried out some meaningful analyses. The common and favorite critism of the observational studies is selection bias, specifically, that healthier women choose to use postmenopausal hormone therapy and, therefore, develop less coronary heart disease. Indeed, at the beginning of this follow-up study, the hormone users had less hypertension, less diabetes, and were more prevalent of smoking or previous occurrences of cardiac problems. Therefore, this study analyzed differences according to cardiovascular risk factors and socioeconomic class. The effect of estrogen therapy was the same in the lower social classes as compared with the higher social classes. When adjusted for the absence or presence of hypertension, coronary artery disease, cardiac failure, and diabetes, the protective effect of estrogen remained prominent. These results argue against a healthy user effect in observational studies, but, of course, this issue will not be settled definitively until data are available from the ongoing, long-term, randomized, clinical trials of postmenopausal hormone therapy.

Another important observation in this study is the lack of effect in former users of estrogen. It is increasingly apparent that the beneficial effect of estrogen on bone and the cardiovascular system is rapidly lost after discontinuation of treatment. For example, in the Nurses' Health Study, reduced risk of mortality (largely cardiovascular) was lost by the fifth year after discontinuing treatment.[1]

There was an observation in this study that is hard to understand. The study failed to observe a decrease in the incidence of cardiovascular disease. Sourander et al suggested that the results reflected a positive effect on existing disease but a failure to prevent diease. This, in fact, would be contrary to the HERS trial and the large number of observational studies dealing with primary prevention of coronary heart disease. The authors further suggest that their findings could represent their specific method of identifying women with coronary heart disease (in this study, patients were identified through a diagnostic registry rather than by only fatal cardiac events).

Overall, this study provides further support for the contention that postmenopausal estrogen therapy protects against cardiovascular disease, and it addresses the "healthy user" criticism as well as can be done without a randomized trial. ❖

References

1. Grodstein F, et al. *N Engl J Med* 1997;336:1769-1775.
2. Register TC, et al. *Arterioscler Thromb Vasc Biol* 1998; 18:1164-1171.

Which of the following statements is false?

a. If the relative risk of breast cancer associated with ERT use is 0.57 and the confidence interval is 0.20-0.80, this suggests that ERT use protects against breast cancer.
b. If the only risk of long-term ERT use was endometrial cancer, one way to guard against this risk would be to do a "prophylactic" hysterectomy.
c. Former users did not accrue any protection from stroke or cardiovascular disease from short-term ERT use in the present study.
d. Despite the apparent benefits of extended ERT use, rates of use are low worldwide.
e. The only way to convince patients of the benefits of ERT use is to have a physician they trust listen to their concerns and attempt to address their fears.

p53 Protein Overexpression: A Strong Prognostic Factor in Uterine Papillary Serous Carcinoma

Synopsis: *Patients with uterine papillary serous carcinoma whose tumors overexpress p53 have a worse prognosis than those whose tumors do not.*

Source: Bancher-Todesca D, et al. *Gynecol Oncol* 1998;71:59-63.

In a study from australia, bancher-todesca and colleagues investigated 23 cases of uterine papillary serous carcinoma (UPSC). P53 expression was studied in archival paraffin-embedded tissue by immunohistochemistry. Eleven tumors (47.8%) revealed p53 overexpression whereas 12 tumors (52.2%) were p53 negative. One of eight stage I/II (12.5%) and 10/15 stage III/IV (66.6%) tumors revealed p53 immunostaining (P = 0.027). The median overall survival was 43.3 months. Patients with advanced-stage (III and IV) disease had a five-year overall survival probability of 24% compared to 100% in those in stages I and II (P = 0.018). Myometrial invasion, lymphatic space invasion, and lymph node involvement did not correlate with the five-year overall survival of these patients. Patients whose tumors overexpressed p53 had a significantly shorter survival than those whose tumors did not (P = 0.033). This study confirms the influence of p53 overexpression on survival in UPSC patients.

COMMENT BY DAVID M. GERSHENSON, MD

Mutation of the tumor suppressor gene p53 is a common finding in gynecologic neoplasms. In this study, Bancer-Todesca et al found that almost 50% of UPSC had p53 overexpression, an indirect measure of p53 mutation. Another study found that 71.4% of 21 UPSC overexpressed p53.[1] This was in comparison with only 28.6% of endometrioid uterine cancers. In this same study, there was a trend toward p53 overexpression being more common in late-stage than early-stage UPSC—90% vs. 50%—but the difference was not statistically significant. In the present study, the marked difference in the incidence of p53 overexpression between late- and early-stage disease—66.6% vs. 12.5%—did achieve statistical significance. The present study represents yet another report that characterizes a specific tumor type with respect to a common molecular biomarker. As this information accumulates and is confirmed, in some instances it will allow clinicians to predict outcome of individual patients and also, eventually, plan therapy based on the findings. In addition, the specific molecular defect itself may prompt treatment with a specific agent. The current testing of p53 gene therapy is but one example of such an approach. Importantly, as Bancher-Todesca et al point out, we need a study with a much larger number of patients with whom to perform a multivariate analysis so that we can determine the independent influence of p53 overexpression in UPSC. ❖

Reference

1. Zheng W, et al. *Gynecol Oncol* 1996;61:167-174.

Studies of endometrial cancer and p53 overexpression reveal that:

a. P53 overexpression occurs more frequently in the endometrioid cell type than in the uterine papillary serous carcinoma cell type.
b. P53 overexpression occurs less frequently in the endometrioid cell type than in the uterine papillary serous carcinoma cell type.
c. P53 overexpression occurs only rarely in both cell types.
d. P53 overexpression occurs in almost all uterine papillary serous carcinomas.
e. None of the above

The Jarisch-Herxheimer Reaction and Fetal Monitoring Changes in Pregnant Women Treated for Syphilis

Synopsis: *The Jarisch-Herxheimer reaction occurs in approximately 40% of pregnant patients treated for syphilis.*

Source: Myles TD, et al. *Obstet Gynecol* 1998;92: 859-864.

The jarisch-herxheimer reaction is a poorly understood condition that occurs in approximately one-half of all individuals treated for syphilis. Some reports have found the condition to occur only with primary and secondary syphilis, whereas others have noted its occurrence also with the latent stages of syphilis.

Pregnant patients who receive penicillin therapy for syphilis are reported to have uterine contractions and, on occasion, fetal death. Because of the scattered reports, fetal heart rate (FHR) monitoring is commonly recom-

mended, even though most of the reports in the literature were written before FHR monitoring was developed.

Myles and colleagues reviewed their hospital's experience with the treatment of syphilis in women greater than 24 weeks gestation. Their protocol required FHR monitoring for a minimum of 10 minutes prior to penicillin therapy and for 24 hours afterward. Fifty patients fulfilled the study criteria, and fetal monitoring strips were available for 31. The hospital charts and FHR recordings were reviewed by Myles et al.

Forty percent of the patients experienced signs or symptoms of the Jarisch-Herxheimer reaction—primarily an increase in temperature. Forty-two percent of those patients with FHR records had uterine contractions following penicillin therapy. Interestingly, the median time from treatment to the onset of contractions was 10 hours, with a range of 2-18 hours. In all cases, the contractions resolved within 24 hours. Of those with contractions, approximately 50% developed variable decelerations for at least some period of time. Regular late decelerations were not observed. Except for one fetus born with congenital syphilis, there were ultimately no fetal abnormalities (though there were 5 premature births). Three of these occurred in women with a Jarisch-Herxheimer reaction. Overall, nearly two-thirds of the patients had the Jarisch-Herxheimer reaction, and/or uterine contractions, and/or variable decelerations.

COMMENT BY KENNETH NOLLER, MD

For several years, it has fallen to me to give the lecture to our third-year students concerning sexually transmissible diseases in pregnancy. Because I love eponyms (and, of course, the students hate them) I always mention that the treatment of syphilis in pregnancy can be associated with fetal stress due to the Jarisch-Herxheimer reaction. I stress the need for fetal monitoring when penicillin is given to a patient for the treatment of syphilis and when the fetus is of viable gestational age.

This report suggests that I might be "overselling" the effect on the fetus. This is a relatively large series, yet no significant fetal compromise was caused by the Jarisch-Herxheimer reaction. Whether fetal stress (or even demise) can be associated with the reaction cannot be determined with certainty, as it may be so infrequent that this relatively large series is still far too small to detect an increase in fetal wastage. For the present time, it is probably still a good idea to monitor patients for a relatively long period of time after they receive their initial penicillin therapy for the treatment of syphilis.

Unfortunately, Myles et al did not choose to examine the occurrence of the Jarisch-Herxheimer reaction in patients before 24 weeks gestation, when most syphilis is detected and treated. Although fetal monitoring at that early gestational age would not be useful, it would be interesting to know if there is a difference in the frequency of the reaction. ❖

In the article by Myles et al, the use of penicillin to treat syphilis in pregnant women was associated with which of the following conditions?

a. Uterine contractions
b. Premature onset of labor
c. Premature rupture of membranes
d. Fetal death

Effect of Hospital Volume on Operative Mortality for Major Cancer Surgery

ABSTRACT & COMMENTARY

Synopsis: *Major cancer surgery appears to be safer at hospitals that perform a high volume of cases.*

Source: Begg CB, et al. *JAMA* 1998;280:1747-1751.

Various studies in the past have indicated that hospitals that perform complex surgical procedures for cancer, but perform only a small volume of these procedures, have poorer outcomes than hospitals that treat more cases. One of the major limitations to these past studies has been the fact that they have used hospital mortality and/or days of hospitalization as their end points. Because discharge practices vary greatly, these studies might miss deaths that are clearly related to surgery but occurred after discharge.

Begg and colleagues attempted to circumvent the problem of using hospital discharge diagnoses by using the Surveillance Epidemiology and End Results (SEER)-Medicare database. By using this source of information, they were able to examine mortality occurring within 30 days following hospital admission. The major weakness of their study was the fact that all cases were 65 years of age or older.

Begg et al restricted their analyses to five procedures: Pancreatectomy, esophagectomy, pneumonectomy, hepatectomy, and pelvic exenteration. They used appropriate coding procedures using the ICD-9-CM classification system. Appropriate statistical analyses were performed. The time period of interest was 1984-1993.

The results were largely consistent with previously published studies. Specifically, Begg et al found that hospitals performing a larger volume of these complicated procedures had lower mortalities. The only exception was pneumonectomy where the difference between mortality at the low- and high-volume hospitals did not meet the criterion for statistical significance.

A co-morbidity case mix study did not identify this as a reason for the observed difference, though Begg et al found co-morbidity to be a difficult subject to study.

COMMENT BY KENNETH NOLLER, MD

I believe this is an important paper (and, apparently, the *JAMA* editorial board also had the same thought since an editorial accompanies the article). Yet, the results are so "common sense" it almost seems ridiculous to study it. Why wouldn't surgeons at a hospital that performs several pelvic exenterations a year be better and have less mortality than a hospital that performed only one such procedure in a decade? Nonetheless, 112 hospitals did exactly that (i.e., performed 1 pelvic exenteration during the entire study decade).

Few would argue with the conclusion of this study since it dealt with complex procedures. However, I think it is important for each of us to constantly evaluate our own abilities and limitations. Clearly, there are many conditions we were familiar with during our days in resident training that we now only see rarely, if at all. Referral to an appropriate subspecialist—at a facility that performs a large volume of the evaluation/procedures—is clearly desirable. ❖

In the study by Begg et al, hospitals that performed a high volume of cancer surgery had clearly superior results for each of the following procedures *except*:

a. pancreatectomy.
b. esophagectomy.
c. hepatectomy.
d. pneumonectomy.
e. pelvic exenteration.

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Postmenopausal Hormone Therapy and Hypertension