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Three-Dimensional Conformal Radiation Therapy in Early Stage Prostate Cancer

ABSTRACT & COMMENTARY

Source: Hanks GE, et al. *Cancer J Sci Am* 1999;5:152-158.

Prostate cancer is often detected on the basis of an abnormal serum prostate-specific antigen (PSA) level. Recent studies have provided some guidance regarding which of these asymptomatic cancers may represent a threat to life. Albertsen and colleagues[1] have shown that the histology of the tumor, graded by the Gleason score, can identify the level of risk of dying from prostate cancer. The 15-year probability of dying from prostate cancer was 4-7% for an untreated patient with Gleason score 2-4, 18-30% for an untreated patient with Gleason score of 6, and 60-87% for an untreated patient with Gleason score 8-10.

In patients who opt for treatment, the majority of patients today undergo radical prostatectomy. While this is a highly effective management approach, the majority of individuals who undergo radical prostatectomy become impotent, and a significant fraction develop incontinence. Radiation therapy is an alternative approach to treatment. Standard external-beam radiation therapy can be effective in experienced hands; however, like surgery, radiation therapy may be associated with unpleasant treatment side effects such as radiation proctitis (diarrhea) and radiation cystitis (dysuria and frequency). The argument continues regarding the efficacy of radiation therapy; most radiation therapists believe radiation therapy is equal to surgery in the control of the cancer, while urologists usually claim that surgery is superior to radiation therapy.

The efficacy of local therapy depends on the extent of disease. In patients with locally advanced cancers, radiation therapy is often used as primary therapy. A recent clinical trial suggested that the use of hormonal therapy (goserelin), used concomitantly with the external-beam radiation therapy, resulted in improved survival compared to external-beam radiation therapy alone in patients with T2 and T3 tumors without node involvement.[2]

With standard treatment planning, it is difficult to deliver more than 70 Gy to the prostate bed without an unacceptable level of toxi-

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city to the bladder and rectum. In recent years, several new techniques have been developed to deliver radiation therapy more effectively into the prostate with higher doses to the tumor bed and lower doses to the adjacent normal structures. These methods include ultrasound-guided transperineal prostate implant (IMP), intensity-modulated external-beam radiation therapy (IMRT), and three-dimensional conformal external-beam radiation therapy (3D-CRT). Data relating outcome to treatment dose in prostate cancer are limited and no prospective randomized studies with dose as the main variable have been reported. Furthermore, the new techniques for delivering higher doses of radiation therapy have not been compared to one another or to standard techniques in prospective randomized studies. However, a considerable body of data on 3D-CRT has been collected and Hanks and colleagues at Fox Chase Cancer Center have endeavored to conduct a retrospective analysis on the question of dose effects.

Hanks et al compared outcomes in two groups of patients. Group I consisted of 296 patients treated by 3D-CRT technique with doses greater than 74 Gy, and 296 patients treated by conventional or 3D-CRT techniques with doses less than 74 Gy, patients matched for stage (based on palpation), histologic grade, and PSA level (< 10 ng/mL, 10-19.9 ng/mL, ≥ 20 ng/mL). Group II consisted of 357 patients treated with doses greater than 74 Gy, and 357 treated with doses less than 74 Gy matched on stage and grade, but not on PSA levels. Four outcome variables were assessed—freedom from PSA relapse, freedom from distant metastasis, cause-specific survival, and overall survival.

In group I, the high-dose group had significantly improved freedom from PSA relapse at five years (73% vs 55%), freedom from distant metastases at five years (97% vs 91%), and cause-specific survival at five years (100% vs 97%) than the low-dose group, but overall survival was not different. For group II patients, all four outcome variables were superior in the high dose group; freedom from PSA relapse at five years was 71% for high dose and 56% for low dose, freedom from distant metastases at five years was 97% for high dose and 88% for low dose, cause-specific survival at five years was 99% for high dose and 94% for low dose, and overall survival at five years was 88% for high dose and 79% for low dose. When subset analysis was performed, patients with stage T2c and T3 appeared to benefit from the higher dose radiation therapy as did those with low Gleason grade (2-6). However, patients with T1/T2ab lesions or Gleason grade 7-10 did not seem to have a better outcome with higher doses of radiation therapy.

Hanks et al interpret the data as supporting the existence of a dose-response curve to radiation therapy in prostate cancer and showing that doses greater than 74 Gy, which cannot be safely given by standard approaches, are associated with a superior outcome, including better survival, when delivered by 3D-CRT.

COMMENTARY

3D-CRT appears to permit the safe delivery of higher and more effective doses of radiation therapy to patients with prostate cancer. Although the differences seen between groups of patients, relatively well matched retrospectively who received different doses of radiation therapy, appear to support this idea, it is important to note that the study was not a prospective randomized trial. The fact that the numbers of patients in each group were identical indicates that some sort of selection of cases from a larger pool was undertaken. The basis for deciding which patients would get higher doses and which would get lower doses is not discussed and the basis for omitting patients from groups, if it happened, is not mentioned. However, other experiences with 3D-CRT are consistent with this report.

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Zelefsky and colleagues from Memorial Sloan-Kettering conducted a phase I study in 743 patients with prostate cancer in which the tumor target dose was increased from 64.8 Gy to 81 Gy in 5.4 Gy increments.[3] The induction of a clinical response (defined as a PSA nadir ≤ 1 ng/mL) was dose-dependent; 90% in those receiving 75.6-81 Gy, 76% for those treated with 70.2 Gy and, 56% for those treated with 64.8 Gy. Five-year freedom from PSA relapse was influenced by the presence or absence of poor prognostic factors. Favorable factors were stage T1-2, PSA levels less than 10 ng/mL, and Gleason score 6 or lower. Patients with all favorable factors were considered good prognosis, those with two of these features were considered intermediate prognosis, and those with one or none of these features were considered unfavorable. Patients with intermediate or unfavorable prognosis had a significantly better freedom from PSA relapse if they received 75.6 Gy or more radiation therapy. Patients underwent surveillance sextant prostate biopsies at least 2.5 years after treatment. A positive biopsy was observed in only 1 of 15 (7%) patients who received 81 Gy. Positive biopsies were obtained from 48% of those receiving 75.6 Gy, 45% of those receiving 70.2 Gy, and 57% of those receiving 64.8 Gy. Thus, these data would argue that 81 Gy is the most effective dose of radiation therapy delivered by 3D-CRT.

How does 3D-CRT compare to the other novel methods of delivering radiation therapy to the prostate? Unfortunately, we can only make rough estimates because appropriate studies have not yet been conducted. Peschel and colleagues at Yale have studied IMP in 120 patients with prostate cancer.[4] Four-year freedom from PSA relapse was 80% for the favorable subset of patients, 66% for the intermediate subset, and 57% for the unfavorable subset. Those numbers are similar to the results obtained at Memorial Sloan Kettering with 3D-CRT (85% for the favorable group, 79% for the intermediate group, and 55% for the unfavorable group). However, these comparisons are crude. Insufficient numbers of patients were treated at the most effective doses of 3D-CRT to make valid comparisons to optimally delivered implant radiation therapy.

Even if the data permitted us to declare 3D-CRT the winner, it would be difficult to obtain the benefits of this approach for our patients. Hanks et al cite a personal communication with Jean Owen, who participated in a national Patterns of Care Study surveying the practice of radiation therapy in 1500 radiation oncology facilities in the United States. Data from that study dealt with patients treated in 1994. Only 19% of the facilities used 3D-CRT and among those facilities, only 27% of treated patients received more than 70 Gy and only 1.2% received as much as the 74 Gy that the Hanks data suggested was superior. Thus, despite the apparent dose-related advantages of 3D-CRT delivery, only a very small number of centers have translated these results to practice.

It would appear that improvements in techniques have resulted in the ability to safely deliver larger and more effective doses of radiation therapy to the prostate. Doses greater than 74 Gy and perhaps as high as 80 Gy are associated with excellent local control, improved freedom from PSA relapse, lower rates of metastasis, and a modest, but significant overall survival advantage. Critics might suggest that these findings require replication in the setting of a prospective randomized trial. Such a trial should be undertaken. The challenge now is to find a place where these benefits might be obtained for our patients who may not be eligible for a study due to intercurrent illness or other problems. Fox Chase Cancer Center and Memorial Sloan-Kettering Cancer Center appear to be two places where state-of-the-art practice is ongoing. Do your radiation oncology colleagues use 3D-CRT to deliver 74-80 Gy to the prostate? If they don't, it might be instructive to learn why not. ❖

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More on Pregnancy in Breast Cancer Survivors

ABSTRACT & COMMENTARY

Synopsis: *Premenopausal women diagnosed with invasive breast cancer between 1983-1992 were interviewed or responded to a questionnaire. By establishing appropriate controls, investigators concluded that the risk of death from breast cancer was not adversely affected by pregnancy. However, spontaneous abortions were more frequent in breast cancer survivors than in age-matched controls who had not had breast cancer.*

Sources: Velentgas P, et al. *Cancer* 1999;85: 2424-2432; Averette HE, et al. *Cancer* 1999;85: 2301-2304.

We have previously discussed the apparent safety of pregnancy among women with a prior

diagnosis of breast cancer. However, much of the existing data had certain flaws. A recent retrospective review has generated additional reassurance. With the success of primary breast cancer treatment, there has been, and will continue to be, increasing numbers of premenopausal women alive and well years after treatment. This, coupled with the trend to have children at later ages, has heightened the concern for the safety of women with regard to reactivation of breast cancer. Although this question has been studied previously, outcomes with regard to the influence of pregnancy on breast cancer survival have been difficult to interpret because of methodological difficulties.

In a recent report from the University of Washington, this question was carefully examined. Women diagnosed with invasive breast cancer between 1983 and 1992 who previously had participated in a population-based case-control study or, if deceased, proxy respondents were queried about subsequent pregnancies using self-administered questionnaire or telephone interview. Information regarding breast cancer recurrence was obtained by questionnaire and from cancer registry abstracts. Women who became pregnant after a diagnosis of breast cancer were matched with women without subsequent pregnancies based on stage of disease at diagnosis and recurrence-free survival time.

Almost 70% of women who became pregnant after being diagnosed with breast cancer delivered one or more live-born infants. However, miscarriages occurred in 24% of the patients who became pregnant compared to 18% of age-matched controls who had no history of breast cancer. Of the 53 women who became pregnant after breast cancer, five died of recurrent breast cancer. The age-adjusted relative risk of death associated with any subsequent pregnancy was 0.8 (95% confidence interval, 0.3-2.3). Thus, the findings of this survey do not suggest that pregnancy after a diagnosis of breast cancer has an adverse effect on survival.

COMMENTARY

In a recent review of previous epidemiologic studies, the conclusion was made that pregnancy did not increase the risk of recurrent breast cancer.[1] However, Collichio and colleagues point out a significant form of bias that could explain the lack of effect. After all, the development and progression of breast cancer is known to be highly influenced by hormones. Thus, it is difficult to believe that the fluctuations of hormonal milieu created by pregnancy would not alter latent or residual microscopic breast cancer likely to exist in a certain fraction of those treated. The major potential bias in the prior epidemiologic studies may relate to what Sankila and colleagues[2] have termed "the healthy mother effect." Women who become pregnant after breast cancer may be more likely to be free of disease at the time of pregnancy than similar breast cancer patients who do not have a subsequent pregnancy, even if selected prognostic factors measured at diagnosis are equivalent and the comparison group survives at least as long as the time from diagnosis to pregnancy. Without consideration of disease status at the time of pregnancy, this bias could obscure a countering harmful effect of pregnancy upon survival.

In this report, Velentgas and colleagues carefully gathered data to describe pregnancies occurring in a population-based sample of women diagnosed with breast cancer by age 40. They attempted to determine whether pregnancy after breast cancer was associated with disease recurrence or shortened survival. By taking into account recurrence after initial diagnosis, the effect of differences in health at the time of pregnancy for those who became pregnant vs. those that did not, "healthy mother effect" bias was minimized. Indeed the provision of carefully selected controls and rigorous statistical detail set forth by Velentgas et al allows confidence in the data analysis and interpretations provided.

However, it remains difficult to generalize these observations, especially because there was a relatively small number of individuals surveyed in this study who became pregnant, and there were only five total deaths in women who became pregnant after breast cancer.

One problem with a retrospective study such as this and others that have been published [3-5], is that it often depends on remote memory for those providing the care for the patients who had died. Pregnancies, particularly those that did not result in live births, may not have been accurately recorded and those patients might not have been included in the study group. The data from this study would suggest a higher rate of spontaneous abortions in patients with a prior history of breast cancer. This certainly is similar to the spontaneous abortion rate increase published for other human malignancies, and may reflect the effects of prior treatment.

In the editorial accompanying this report, Averette and colleagues have consolidated the findings from this report with those previously published. They provide six key conclusions. First, pregnancy does not appear to affect adversely the prognosis of patients with stage I or II breast cancer. Second, the decision to conceive should be influenced by the prognosis of the particular patient but should discount the effects of pregnancy on survival (as repeated studies have failed to demonstrate an effect of pregnancy on survival in this situation). Third, women with advanced stage breast cancer should be advised to avoid pregnancy for several years after treat-

ment. Fourth, chemotherapy-induced ovarian failure may lead to infertility. Fifth, chemotherapy may also result in a higher rate of spontaneous abortion. And sixth, the decision to conceive is far more complicated than just these medical and physical factors but relates as well to psychological and social issues. Thus, counseling by physicians, other health providers, family and friends may be of critical importance. The data and discussion in this report (and accompanying editorial) should prove valuable in this regard. ❖

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Management of Poor Prognosis Germ-Cell Tumors

ABSTRACT & COMMENTARY

Synopsis: *The Spanish Germ-Cell Cancer Group has used intensive alternating drug combinations in poor-prognosis metastatic germ-cell cancer. Bleomycin, vincristine, methotrexate, and cisplatin (BOMP) is alternated with etoposide, ifosfamide and cisplatin (EPI). Actuarial two-year overall survival was 64%, which may be superior to the 48% expected based on the International Germ-Cell Consensus Classification Group experience.*

Source: Germa-Lluch JR, et al. *Ann Oncol* 1999;10: 289-293.

Germ-cell tumors are curable in about 80% of cases thanks to the introduction of cisplatin-based combination chemotherapy regimens. However, the spectrum of disease presentations is quite wide. The major problem under investigation for the patients with good prognosis tumors is how little therapy is enough. The major problem under investigation for the patients with poor prognosis tumors is can any amount of therapy be enough.

The field achieved a major organizational advance when an international group of investigators got together in 1996 and developed a set of consensus criteria for distinguishing prognosis in patients with metastatic germ-cell tumors.[1] Patients with poor prognosis germ-cell tumors are now agreed to be those with mediastinal primary or non pulmonary visceral metastases or any of the following poor prognosis markers: alpha-fetoprotein levels greater than 10,000 ng/mL, beta-human chorionic gonadotrophin levels greater than 50,000 iu/L (10,000 ng/mL), or lactate dehydrogenase levels more than 10 times the upper limit of normal. About 16% of patients with nonseminomatous germ-cell tumors fall into this category (no patients with seminoma have a poor prognosis) and the five-year survival is about 48%.

The Spanish Germ-Cell Cancer Group has developed and tested an intensive six-drug combination chemotherapy program for patients with poor prognosis germ-cell tumors consisting of alternating combinations of drugs. Methotrexate is given on day 1 as a 100 mg/m^2 intravenous bolus followed by 200 mg/m^2 by continuous infusion over 12 hours. Vincristine 2 mg is given intravenously after the methotrexate infusion. Bleomycin 30 mg is delivered as a 12-hour or 24-hour continuous infusion on day 2. Cisplatin 100 mg/m^2 iv is given on day 3. Bleomycin 30 mg is also given on days 8, 22, and 29 of the 35-day cycle. On days 15-18, etoposide 120 mg/m^2, ifosfamide 1300 mg/m^2, and cisplatin 25 mg/m^2 are given. Cycles were repeated until the patient achieved a complete response, stable residual radiographic abnormalities were noted, or disease progressed. Bleomycin was stopped after 12 weekly injections.

Thirty-eight patients were entered on the study from 13 centers (i.e., around 3 patients/center). Eighteen (47%) achieved a complete response to chemotherapy alone; four additional patients (10.5%) had residual disease resected; and another four patients (10.5%) had marker-negative stable residual masses. Thus, 58% achieved a complete response to therapy and another 10.5% may have achieved a significant response. After a median follow-up of 41 months, two-year overall survival is 64%. Toxicity was mainly hematopoietic; 70% of patients experienced grade IV granulocytopenia. It is possible that this treatment is more effective than standard bleomycin, etoposide, and cisplatin (BEP) in poor-prognosis patients.

COMMENTARY

A number of different approaches have been taken to try to improve the treatment outcome for patients with poor prognosis germ-cell cancer. The agreement about what constitutes poor prognosis disease is a recent development; therefore, much of the literature is confusing because of inclusion of patients who may not actually have poor prognosis features. Nevertheless, a review of the experiences to date in trying to improve therapy in this disease may be instructive.

Doubling the dose of cisplatin in BEP from 100 to 200 mg/m^2 showed greater toxicity, but no increase in response rate or disease-free survival. Induction regimens using weekly cycles of bleomycin, vincristine, and cisplatin (BOP) followed by consolidation with a distinct drug combination has shown some promise,[2] but randomized studies have not been conducted. Horwich and colleagues modified BOP by substituting carboplatin on weeks 2 and 4 and consolidating treatment with three cycles of BEP. This C-BOP/BEP regimen appeared active in pilot studies and is being tested in a nonrandomized phase II study by EORTC. Kaye and colleagues conducted a randomized study comparing three cycles of BOP given every 10 days followed by three cycles of etoposide, ifosfamide, cisplatin, and bleomycin (VIP-B) against four cycles of BEP followed by two cycles of EP without the bleomycin.[3] The more intense arm was more toxic but not more effective.

Alternating combinations have also been tested in a number of centers. Alternating BEP with cisplatin, vinblastine, and bleomycin (PVB), which entails alternating use of etoposide and vinblastine in different cycles, did not improve survival.[4] Bower and colleagues at Charing Cross Hospital have been using an alternating intensive regimen called POMB/ACE (cisplatin, vincristine, methotrexate, and bleomycin alternating with actinomycin D, cyclophosphamide, and etoposide) for nearly 20 years and have achieved overall three-year survival of 75% in a group of poor prognosis patients.[5] This regimen from the Spanish Germ-Cell Cancer Cooperative Group (BOMP/EPI) is similar to POMB/ACE and also appears to achieve results better than expected with BEP. However, randomized studies are in progress to evaluate the more intensive alternating regimens against the standard regimen.

Another important approach to improving outcome in poor prognosis germ-cell tumors is the use of primary high-dose therapy with hematopoietic stem cell support. The German Testicular Cancer Study Group has developed a sequential high-dose combination regimen of cisplatin, etoposide, and ifosfamide given with granulocyte colony-stimulating factor and peripheral blood stem-cell support for four cycles every three weeks.[6] Of 141 evaluable patients, 82 (58%) achieved a complete response and 32 (23%) have achieved partial remission with marker normalization. The early death rate was 8%. The projected five-year overall survival rate is 74%. It is not completely clear if patients receiving high-dose therapy as primary treatment are better off than those receiving intensive therapy without stem-cell support.

New agents are also being introduced into the treatment of germ-cell tumors including paclitaxel and gemcitabine. Their integration into effective combination programs may represent a path to successful treatment of poor prognosis patients.

Regardless of the treatment approach to poor prognosis patients, a disturbing new prognostic factor was recently elucidated, the site of treatment. Collette and colleagues examined the outcome of patients entered into the EORTC randomized study comparing BOP/VIP-B to BEP/EP (cited previously) as a function of the number of patients treated at a particular center.[7] They found that patients of similar poor prognosis treated on the same protocol had significantly different outcomes based on whether they were treated at an experienced center or an inexperienced center. The cut point separating experienced and inexperienced was five patients. Centers entering at least five patients on the study over a four-year period achieved two-year overall survival rates of 77% while those entering less than five patients achieved two-year overall survival rates of 62% (P = 0.006). Significant differences in the dose intensity of delivered therapy were detected when the groups were compared.

This is not the first example of the impact of center experience on treatment outcome. Prior data have suggested that allogeneic transplant centers need to treat at least six patients per year in order to acheive the optimal outcome. One wonders the degree to which negative results in large cooperative group studies are related to experience. Data analysis from multi-institutional studies should probably include exploratory analysis to assess whether site of treatment influences outcome. Of course, such differences may not always be related to deviations from protocol or altered delivery of treatment. Some centers may see sicker patients. No matter what the reason, significant deviation in treatment outcome based on the treatment center should probably be a stimulus to examine the patient population and treatment practices at the center. The radiation oncologists are way ahead of the medical oncologists in the area of monitoring treatment delivery. ❖

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Screening for Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Screening for ovarian cancer remains of unproved value. In this randomized, controlled trial, Jacobs and colleagues from the United Kingdom examined the feasibility of a strategy that used serum CA-125 determination followed by pelvic ultrasonography for those with elevated marker levels. More than 10,000 women were randomized to this screening strategy that was used annually for three straight years. An equal number of women were followed without screening. Mortality from ovarian cancer was lower in the screened population.*

Source: Jacobs IJ, et al. *Lancet* 1999;353:1207-1210.

The value of screening for ovarian cancer remains to be established. In this report, a novel screening strategy was used which involved both serum determination of the tumor marker CA-125 and, in patients with high marker levels, pelvic ultrasonography and gynecology consultation.

Postmenopausal women, aged 45 years or older, were randomly assigned to a control group (n = 10,977) or screened group (n = 10,958). No other risk factors (e.g. nulliparity) were evaluated to select subjects for screening. Those in the screened group were offered three annual evaluations that included measurement of serum CA-125 and pelvic ultrasound, if the CA-125 value was 30 units/mL or more. Individuals were referred to a gynecologist if the ovarian volume was 8.8 mL or more on the ultrasound evaluation. All of the enrolled women were followed up to determine if they developed invasive epithelial cancers of the ovary or fallopian tube.

In the screened group, 468 women (4.3%) with elevated CA-125 values were identified. Twenty-nine of these women (6.2% of those with high CA-125 levels and 0.26% of all screened women) were referred for gynecologic opinion based upon their ovarian volume by ultrasound. In this group, the screening detected an indexed cancer in six patients, whereas 23 had false-positive results. Thus, the positive predictive value (i.e., the fraction of persons with a positive test who actually had the disease) was 20.7%.

During the follow-up period (7 years), 10 additional women with indexed cancers were identified in this screened group, and 20 ovarian cancers were found in the control group. The median survival for women with indexed cancers in the screened group was 72.9 months vs. 41.8 months in the control group. (P = 0.0112). The number of deaths from an indexed cancer did not differ significantly between the control and screened groups (18 in the control group vs 9 in the screened group for a relative risk of 2.0, but with 95% confidence interval 0.78-5.13). The results were interpreted as indicative of the potential value for this screening strategy for ovarian cancer. However, because there was a relatively small number of ovarian cancers in this population, it was impossible to determine absolute survival advantage. Jacobs and colleagues suggested that a larger, randomized trial would be of value to determine if the screening strategy affects mortality.

COMMENTARY

This trial from the United Kingdom provides a hopeful suggestion that screening for ovarian cancer may be of clinical value. The numbers of women screened were large, but the actual rates of ovarian cancer were too small to demonstrate a survival advantage from early detection. Nevertheless, for the women who were found to have cancer in the screened group, the median survival was significantly longer than that for the control group. Interpretation of this result must be made with great caution because of the lead time bias artifact which may have been operational. Thus, women who were found to have ovarian cancer at an earlier stage may have demonstrated longer survival, not because the screening influenced the success of therapy, but because it allowed recognition of the cancer for a longer period of time. The findings were of sufficient interest to warrant the conclusion made by Jacobs et al that the larger trial is warranted.

A positive feature of this is that the strategy used was fairly simple and logical. There seemed to be excellent compliance in the approach as the number of women who were screened for each of the three successive years fell only by a small percent. In fact, the first screen was completed by 86% of the women, the second screen was completed by 79.7%, and the third by 77.2%.

Furthermore, the positive-predictive value of this screening strategy was moderately high; 21% which was apparently quite similar to the positive-predictive value of this approach in a previous study from this group.[1] Furthermore, this approach seems to have a higher positive predictive value than other approaches such as pelvic ultrasonography alone[2] or pelvic ultrasonography with color-flow Doppler.[3]

In conclusion, this trial has provided useful informa-

tion about the feasibility of a randomized investigation of ovarian cancer screening by the introduction of sequential CA-125 determination, ultrasonography, and gynecologic consultation. Although its cost-effectiveness has not been rigorously defined, it is not an expensive undertaking and may be a reasonable approach for primary care providers who are oriented toward early detection and possible disease prevention. However, it may take a larger study in which economic factors are evaluated before insurance companies get behind this strategy. Rather than screen an unselected population, it is possible that this approach would be proven to be effective in a population at greater than normal risk, such as nulliparous women, or those with a positive family history. ❖

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CME Questions

1. Which of the following statements best describes the results of using three-dimensional conformal radiation therapy (3D-CRT) in patients with early stage prostate cancer?

a. Dose-response effects have been noted in which doses of more than 74 Gy appear more effective than those less than 74 Gy.
b. No dose-response effects have been noted in the range of doses that can be safely administered by this technique.
c. Prospective randomized studies have documented that 3D-CRT is more effective than radiation therapy delivered by implants.
d. Prospective randomized studies have documented that 3D-CRT is more effective than surgery.
e. 3D-CRT does not permit the delivery of higher doses of radiation therapy than well-designed external beam radiation therapy using four opposing fields.

2. Which one of the following statements about pregnancy that occurs after treatment of breast cancer is true?

a. Fertility has been shown not to be adversely affected by prior history of breast cancer.
b. Pregnancy has been shown to increase the rate of recurrence of breast cancer for those with Stage II disease at diagnosis.
c. An unusually high rate of birth defects has been observed in offspring of women with breast cancer.
d. Unsuccessful pregnancies (spontaneous abortions) are not more frequent in women with a prior history of breast cancer.
e. Pregnancy does not appear to influence survival in women with a prior history of breast cancer.

3. When patients with poor prognosis nonseminomatous germ-cell tumors are treated with standard bleomycin, etoposide, and cisplatin (BEP) chemotherapy, the expected five-year survival is what?

a. 22%
b. 48%
c. 64%
d. 77%
e. 92%

4. With regard to a practical approach for screening for ovarian cancer, which of the following sequences of screening tools is most logical:

a. Serum CA-125, gynecology consultation, pelvic ultrasonograpy
b. Gynecology consultation, pelvic ultrasonograpy, serum CA-125
c. Pelvic ultrasonograpy, gynecology consultation, serum CA-125
d. Serum CA-125, pelvic ultrasonograpy, gynecology consultation
e. Pelivic ultrasonography, serum CA-125, gynecology consultation

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Clinical Oncology Alert.* Send your questions to: Holland Johnson—Reader Questions, *Clinical Oncology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Clinical Oncology Alert* via the Internet by sending e-mail to holland.johnson@medec.com. You can also visit our home page at http://www.ahcpub.com. We look forward to hearing from you. ❖

In Future Issues:

Gemcitabine and Carboplatin: A Well-Tolerated Active Combination For Advanced Non Small-Cell Lung Cancer