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ABSTRACT & COMMENTARY

Effect of Prophylactic Cranial Irradiation on Survival in Elderly Patients with Limited-Stage SCLC

By Samir P. Kanani, MD

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Dr. Kanani reports no financial relationships relevant to this field of study.

SYNOPSIS: Using the SEER database, this report examined 1926 patients aged ≥ 70 years who were diagnosed with limited-stage small cell lung cancer between 1988 and 1997. Overall survival (OS) for patients who received prophylactic cranial irradiation (PCI) vs those who did not was estimated using the Kaplan-Meier method and compared with the log-rank test. A Cox proportional hazards model was fitted to estimate the effect of PCI on OS after adjusting for age, race, sex, and tumor. A total of 138 patients (7.2 %) received PCI. The 2-year and 5-year OS rates were 33.3% and 11.6%, respectively, among patients who received PCI vs 23.1% and 8.6%, respectively, among patients who did not receive PCI ($P = 0.028$). On multivariable analysis, PCI was found to be an independent predictor of OS (hazard ratio, 0.72; 95% confidence interval, 0.54-0.97; $P = 0.032$]). On subgroup analysis, PCI remained an independent predictor of OS among patients aged ≥ 75 years, but not among patients aged ≥ 80 years.

SOURCE: Eaton BR, et al. Effect of prophylactic cranial irradiation on survival in elderly patients with limited-stage small cell lung cancer. *Cancer* 2013;119:3753-3760.

Multiple prospective trials have demonstrated a significant benefit in brain metastases-free survival and a pivotal meta-analysis[1] demonstrated a significant benefit in overall survival (OS) with the use of prophylactic cranial irradiation (PCI) in patients with limited-stage small cell lung cancer (SCLC) who have a complete response to chemotherapy and radiotherapy (RT). Elderly patients represented a small minority of patients included in trials evaluating the efficacy of PCI and thus the benefit of PCI in this population has been questioned.

The authors note that the incidence of SCLC is rising in the elderly population, making this type of statistical analysis of the Surveillance, Epidemiology, and End Results (SEER) database vital. The authors from Emory University queried the SEER public use database, which represents more than 28% of the U.S. population. They looked at cases between 1988 and 1997. They found nearly 3400 cases of non-metastatic SCLC. They excluded patients with < 6 months OS and those with no information about PCI. This left 1926 patients for analysis. Patient-related and

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treatment-related characteristics including age at diagnosis, sex, race, tumor size, extent of lymph node involvement, AJCC stage of disease, receipt of brain RT (PCI), receipt of thoracic RT, and receipt of surgery were collected. Patients who received PCI and those who did not were well balanced with regard to race, sex, lymph node status, and tumor size. Patients who received PCI were younger at the time of diagnosis, were more often diagnosed with stage III vs stage I or II disease, and were more often treated with thoracic RT. The median OS for the entire population was 1.2 years. The 2-year Kaplan-Meier estimate of OS for patients who received PCI was significantly higher than for patients who did not receive PCI: 33.3% vs 23.1%. The 5-year Kaplan-Meier estimate of OS for patients who received PCI was also significantly higher than for patients who did not receive PCI: 11.6% vs 8.6%. The 2-year and 5-year Kaplan-Meier estimates of cause-specific survival (CSS) were also significantly higher for patients who received PCI compared with those who did not: 37.5% and 19.3%, respectively, vs 27% and 12.5%, respectively. In a separate analysis of patients ≥ 75 years of age, the OS advantage remained significant. The 2-year Kaplan-Meier estimate of OS for patients ≥ 75 years who received PCI was significantly higher than those for patients who did not receive PCI: 36.8% vs 10.5%. The 5-year Kaplan-Meier estimate of OS for patients ≥75 years who received PCI was also significantly higher than for patients who did not receive PCI: 10.5% vs 7.9%. The CSS in patients ≥ 75 years was improved with PCI, although the results did not reach statistical significance as the *P* value was 0.059. On multivariable analysis, receipt of PCI was found to be an independent significant predictor of both improved OS and CSS. In the last subgroup analysis of patients ≥ 80 years, the OS and CSS were also higher in patients who received PCI, but the results were not statistically significant, likely given the small numbers.

COMMENTARY

The study summarized above provides a rationale to not withhold potentially beneficial treatment to patients solely based on age. In the landmark meta-analysis by Auperin et al,[1] the relative risk of death with the use of PCI was only slightly changed after controlling for age (relative risk, 0.84 vs 0.83). The meta-analysis demonstrated a 5.4% absolute benefit in survival at 3 years from 15.3% in patients not receiving PCI and 20.7% in patients who did receive PCI. In this SEER analysis, the absolute benefit was closer to 10% at 2 years. The randomized trials contributing to the meta-analysis had limited patients > 70 years of age. The interesting part of this study was that it looked at patients > 80 years of age. In this population, there was still a benefit to adding PCI (not a detriment), although the differences were not found to be statistically significant, likely because of small sample size and insignificant power. While this study could be used to justify the use of PCI in the elderly population, clinicians should weigh the potential benefits of PCI against the potential neurocognitive effects. A number of studies have indicated declining physical function, motor function, and memory in patients who receive PCI. This can be worse with advanced age.[2] Decisions regarding the benefit of PCI should be individualized to the patient; advanced age and comorbidities should be included in the decision-making process. This SEER analysis provides justification for the use of PCI in patients ≥ 70 years and even those ≥ 80 years. ■

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Choosing Myeloma Maintenance Therapy: Patient Choice

By William B. Ershler, MD

SYNOPSIS: In a survey of consecutive myeloma patients from the Mayo Clinic on hypothetical constructs with varying expectations regarding overall survival benefit, toxicity, and financial burden, it was found that the majority of patients would not choose maintenance if toxicity was more than just mild and overall survival benefit was less than 1 year. Increasing financial burden (drug cost) also reduced the numbers that would choose maintenance therapy. Males were more likely than females to choose treatment in each of the scenarios presented.

SOURCE: Burnette BL, et al. Treatment trade-offs in myeloma. A survey of consecutive patients about contemporary maintenance strategies. *Cancer* 2013;119:4308-4315.

Treatment recommendations for patients with multiple myeloma (MM) have evolved over the past 5 decades. Novel agents and combinations have led to patients living longer, and more effective initial therapy, including high-dose chemotherapy followed by autologous stem cell reconstitution, has more than doubled life expectancy for newly diagnosed patients compared to 2 decades ago. Despite this demonstrably greater success with initial therapy, the role of maintenance therapy has remained controversial. Early efforts using primarily a continuation of alkylating agent therapy showed little, if any, benefit.[1,2] Subsequently, maintenance strategies incorporating interferon demonstrated prolongation in progression-free survival (PFS) by meta-analysis.[3,4] The more recent use of novel agents such as thalidomide, lenalidomide, and bortezimib have proven effective and with less toxicity. Two randomized trials have demonstrated improved PFS with lenalidomide maintenance after autologous transplantation for MM.[5,6] Yet, enhancement of overall survival (OS) remains to be conclusively demonstrated, and quality-of-life (QOL) data are lacking.

Although current myeloma maintenance strategies generally involve less toxic agents (lenalidomide, bortezimib) than their predecessors such as thalidomide and interferon, they are not without side effects and are very expensive. For example, a monthly supply of lenalidomide costs an estimated $10,000.

With the currently available information including effects on PFS, OS, and cost, investigators at Mayo Clinic conducted a systematic survey of MM patients regarding what constitutes a meaningful benefit that would make burdens of maintenance treatments (toxicity and cost) acceptable.

A self-administered survey was mailed to 1159 consecutive, living patients who had been evaluated at Mayo Clinic; 886 responded and 736 (66%) returned a completed questionnaire. The survey provided background information on the standard of care for MM and existing data on the effectiveness of maintenance.

Among responders, the most worrisome potential toxicity was identified as peripheral neuropathy by 27%, cytopenias by 24%, deep vein thrombosis by 20%, fatigue by 15%, nausea by 8%, and diarrhea/constipation by 7%. If treatment were to be provided free of cost, had no toxicity, and the OS benefit was ≤ 1 year, then 49% of patients indicated they would choose maintenance. In comparison, if treatment were associated with moderate toxicity, this proportion decreased to 42%. Adding a treatment cost of $25 per month decreased the proportion that would choose maintenance to 39% of patients. A moderate increase in cost to $250 per month did not affect the proportion choosing maintenance. However, with a marked increase in cost to $10,000 per month, the proportion who would choose maintenance with mild or moderate toxicity decreased to 32%. Across the different scenarios, male patients were more likely than female to choose maintenance therapy and older patients required a smaller increment in improved survival to opt for maintenance when compared to younger patients.

COMMENTARY

The current results indicated that willingness to receive maintenance treatment declined when actual benefits were provided in concrete numeric terms compared with a general statement of PFS benefit. The authors also observed that the magnitude of benefit required to consider maintenance was affected by cost and toxicity. The findings are sobering, but not all that surprising in light of the real but modest data on efficacy as honestly presented to study participants and the clear discussion of potential toxicity and costs. The findings should also be interpreted in the appropriate context. All of the patients had been evaluated at the Mayo Clinic, many of whom travelled great distances for consultation, if not treatment. Despite this common thread, responses came from patients

at all stages, including those recently diagnosed and those who were in the terminal phase of illness. Nonetheless, it is important to recognize that patient choice is an essential element in the selection of treatment, and what might be considered standard therapy could be less desirable when quality of remaining life or financial considerations are factored in. This, of course, is relevant to all aspects of the physician/patient relationship. However, in the context of choosing maintenance therapy for patients with myeloma, this report provides current and relevant parameters. Although maintenance therapy is commonly selected, future research will hopefully define those who are most likely to benefit. For example, as suggested by the authors, those patients who had experienced an excellent response to initial intervention might be just the population for whom maintenance therapy is of limited benefit and should be withheld.[7,8] ■

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ABSTRACT & COMMENTARY

Panitumumab-FOLFIRI: Effective Second-line Treatment for Metastatic Colorectal Cancer

By William B. Ershler, MD

SYNOPSIS: A previously reported, industry-sponsored phase 3 trial (Study 20050181[1]) showed improvements in progression-free survival, objective response, and a non-significant trend toward increased overall survival with panitumumab-FOLFIRI vs FOLFIRI alone for second-line wild-type KRAS metastatic colorectal cancer. The current report describes long-term outcomes from this same dataset.

SOURCE: Peeters M, et al. Final results from a randomized, Phase 3 study of FOLFIRI ± panitumumab for second-line treatment of metastatic colorectal cancer. *Ann Oncol* 2014;25:107-116.

Epidermal growth factor receptor (EGFR)-targeted agents have shown efficacy when combined with chemotherapy in first-[2,3] and second-line[1,4,5] settings and as monotherapy in chemorefractory colorectal cancer.[6,7] Tumor KRAS status predicts the efficacy of anti-EGFR agents in metastatic colorectal cancer (mCRC) patients[8,9] and is a well-established biomarker for patient selection. Panitumumab is a fully humanized monoclonal antibody that binds to the EGFR of tumor cells and inhibits downstream cell signaling with antitumor effects of inhibition of tumor growth, induction of apoptosis, and inhibition of angiogenesis.[10]

Study 20050181 was a large, internationally conducted, randomized, Phase 3 trial designed to address whether the addition of panitumumab to FOLFIRI would enhance outcomes for second-line treatment of patients with mCRC.[1] Long-term data regarding significant clinical outcomes are now available and are the subject of this current report. Patients receiving one prior mCRC treatment were randomly assigned (1:1) to panitumumab (6.0 mg/kg)-FOLFIRI vs FOLFIRI every 2 weeks. Progression-free survival (PFS) and overall survival (OS) were prospectively analyzed by tumor KRAS status.

Patients (n = 1186) were randomly assigned. In patients with wild-type (WT) KRAS tumors (n = 597), panitumumab-FOLFIRI significantly improved PFS vs FOLFIRI (median 6.7 vs 4.9 months; hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.97; $P = 0.023$). For this group, response rates improved from 10% to 36% ($P < 0.0001$) and, once again, there was a trend toward longer OS (median 14.5 vs 12.5 months; HR, 0.92; 95% CI 0.78-1.10; $P = 0.37$). From post-hoc analyses for patients who had received oxaliplatin-bevacizumab as first-line

treatment, panitumumab-FOLFIRI improved PFS (median 6.4 vs 3.7 months; HR, 0.58; 95% CI, 0.37-0.90; *P* = 0.014). PFS and OS were better for those with more skin toxicity (grade 2-4) vs those with no or minimal toxicity (0-1). Safety results were as previously reported and consistent with the known toxicities with anti-EGFR therapy. Quality-of-life data were incompletely captured (about 60% in all study groups), but did not demonstrate any statistically significant or clinically meaningful differences in changes from baseline between treatments.

COMMENTARY

These data confirm the primary efficacy and safety findings as initially reported and establish panitumumab-FOLFIRI as effective second-line treatment of WT KRAS mCRC. Of additional importance, the data indicate that panitumumab offers no added benefit for patients with mutated variants of KRAS. The updated data strengthen the association between skin toxicity and tumor response. Patients with WT KRAS tumors receiving panitumumab-FOLFIRI experiencing grade 2 or higher skin toxicity had improved PFS and OS, as well as higher overall response rates, compared with those experiencing no or mild (0-1) skin toxicity. In fact, OS and PFS appeared shorter for patients with a mild or no skin toxicity in panitumumab-treated patients compared with those receiving FOLFIRI alone, and the overall response rate was also lower in these patients. Based on these findings, a key question in the management of patients with WT KRAS mCRC is whether therapy discontinuation should be considered in patients who do not mount higher levels of skin toxicity. However, as some panitumumab-treated patients develop skin toxicity later in their treatment course (at or beyond the fourth cycle), discontinuation should be considered with caution. A final note of emphasis can be drawn from the current analysis relating to prior therapy. The panitumumab improvement in PFS was discernible for most subgroups of patients with WT KRAS including those who had received prior oxaliplatin with or without bevacizumab. Thus, panitumumab-FOLFIRI is an effective and safe second-line regimen for patients with recurrent or refractory WT KRAS mCRC. ■

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SPECIAL FEATURE

Pelvic Radiation in Endometrial Cancer: Are We Cutting Off Our Nose to Spite Our Face?

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationships relevant to this field of study.

This article originally appeared in the January 2014 issue of *OB/GYN Clinical Alert*.

SYNOPSIS: Long-term complications, particularly secondary cancers, were significantly more common in patients receiving whole pelvic radiation (vs brachytherapy alone) for early-stage endometrial cancer. No difference in overall survival was found in women receiving additional radiation therapy.

SOURCE: Onsrud M, et al. Long-term outcomes after pelvic radiation for early-stage endometrial cancer. *J Clin Oncol* 2013;31:3951-3956.

Between 1968 and 1974, 568 patients with stage 1 endometrial cancer were treated adjuvantly with vaginal brachytherapy and then randomized to either external beam whole pelvic radiation (n = 288) or no further therapy (n = 280). A trial reported in 1980 demonstrated no improvement in overall survival for the addition of pelvic radiation.[1] This current trial was conducted to examine the long-term effects of external beam radiation therapy (EBRT) in this population. Stratification was made for age given the high degree of noncancer mortality. After median 20.5 years (range, 0-43.4 years) of follow-up, no statistically significant difference was revealed in overall survival (P = 0.19) between treatment groups. However, women younger than age 60 years had significantly higher mortality rates after EBRT (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.06-1.76) than the control group. The risk of secondary cancer increased after EBRT, especially in women younger than age 60 years (HR, 2.02; 95% CI, 1.30-3.15). The HR for secondary cancer in women older than age 60 years was 0.81 (95% CI, 0.45-1.43). The median time to a secondary cancer was 15 years. The authors conclude no survival benefit of external pelvic radiation in early-stage endometrial carcinoma. In women younger than age 60 years, pelvic radiation decreased survival and increased the risk of secondary cancer. Adjuvant EBRT should be used with caution, especially in women with a long life expectancy.

COMMENTARY

It's actually quite remarkable that in the 33 years since this landmark paper was published, the role of adjuvant radiation is still not defined in women with early-stage endometrial cancer.[1] While, in some regard, the good overall prognosis of this cohort does not lend itself to be "modality evaluable," the topic of external beam pelvic radiation therapy is hotly debated, and routinely used as standard of care in many parts of the world. However, in locations where surgical staging (pelvic and para-aortic lymphadenectomy) is universally applied or patient-individualized, adjuvant treatment plans are primarily based on findings in uterine and extrauterine tissue samples. In this context, patients without metastatic disease but deemed at high risk for recurrence are increasingly being treated with systemic chemotherapy. This pattern of care has largely eliminated pelvic radiotherapy from many treatment algorithms. Thus, three principle issues can frame the debate of which adjuvant therapy is most appropriate in early-stage endometrial cancer: assessment of risk, role of lymphatic dissection (surgical staging), and the ultimate impact of therapy (survival).

Endometrial cancer is largely considered among the most "survivable" of the gynecological tumors given its predominately early stage at diagnosis and curative impact of simple organ removal. Overall, the 5-year survival for women with early stage endometrial cancer exceeds 85%. However, a small proportion of these patients will experience recurrence, despite a negative evaluation of extra-uterine disease. Patterns of recurrence are roughly one-third local, one-third distant, and one-third both local and distant in nature. Recognizing these issues and the difficulty in curing all but the most focal of recurrences, researchers have devised a series of clinical trials to evaluate adjuvant therapy in the hopes of mitigating this risk. As mentioned, the first randomized trial to do so was that of Aalders and colleagues. In this trial, women with stage I endometrial cancer were given adjuvant vaginal brachytherapy to address recurrence at the vaginal cuff and then were randomized to either whole pelvic radiation or no further therapy. The trial's accrual window was opened 45 years ago, used clinical staging (based on preoperative findings), and delivered radiation with fairly low-energy cobalt machines in a two-field (AP-PA) exposure. The results demonstrated a decrease in local recurrence with pelvic radiation therapy, but no difference in overall survival (*see Table*). Despite this remarkable trial's conclusions, each of the variables mentioned (old staging criteria, lack of lymphadenectomy, and radiation technique) were criticisms to widespread adoption of the practice. Also, since vaginal brachytherapy was given to all patients, its contribution to the findings was questioned.

In 1987, the Gynecologic Oncology Group (GOG) launched a trial to evaluate pelvic radiation vs no further therapy in women undergoing formal surgical staging with stage IB, grade 2-3, or IC grade 1-2 uterine cancer. Like the previous trial, local recurrence was increased in the no further therapy arm but overall survival was similar.[2] Also similar to the previous trial, long-term toxicity was increased in women receiving adjuvant pelvic radiotherapy. Review of the risk stratification from the GOG trial identified a cohort of women in which additional therapy appeared to improve long-term outcomes over no further therapy. In light of these findings, subsequent trials conceded that there were a group of low-risk patients for whom adjuvant therapy was of no benefit and could be safely eliminated. However, the argument as to whether surgical staging was necessary to identify these patients continued, and unfortunately, is still unresolved.

Since the risk of nodal metastases is not much different than the risk of recurrence (about 10%),

Table

Trial	No of Patients and Eligibility	Surgery	Randomization	Age (Mean)	Local Recurrence	Survival	Complications
Aalders[1]	540 Stage I	TAH-BSO	VBT vs VBT + Pelvic XRT	60	7% vs 2% at 5 years $P < 0.01$	89% vs 91% at 5 years P = NS	No initially reported; increased risk of secondary malignancy in Pelvic XRT at 20-year follow-up
GOG 99[2]	392 Stage IB, I, II (occult)	TAH-BSO, Pelvic LN	NAT vs Pelvic XRT	61	12% vs 3% at 2 years $P < 0.01$	86% vs 92% at 4 years P = NS	8% GI at 2 years for Pelvic XRT
PORTEC[3]	714 Stage IB grade 2-3 IC grade 1-2	TAH-BSO	NAT vs Pelvic XRT	66	14% v 4% at 5 years $P < 0.001$	85% vs 81% at 5 years P = NS	3% GI at 5 years Trend for increased secondary malignancy at 15-year follow-up
PORTEC-2[4]	427 age > 60, IB grade 3 Stage IC or IIA, grade 1-2, stage	TAH-BSO LN was optional	VBT vs Pelvic XRT	62	< 2% vs < 2% P = NS	85% vs 80% at 5 years P = NS	GI < 1% and 2% grade 3 at 5 years
ASTEC/EN.5[5]	905 Stage IA/B grade 3, Stage IC, Stage IIA, IIB	TAH-BSO part of study was lympha-denectomy randomization	NAT vs Pelvic XRT Half of patients also received VBT optional	66	15% vs 12% P = NS	85% vs 85% at 5 years P = NS	GI 3% vs 7% at 5 years

the merit of unselected adjuvant therapy is still questioned. This contention was bolstered by the PORTEC trial, which randomized 714 women with "intermediate risk" for recurrence to the same treatment arms outlined in GOG 99, but in this case, did not require lymphatic evaluation.[3] As can be seen in the Table, the recurrence risk, survival, and toxicity observations are nearly matched to GOG 99. Subsequently, several trials have been conducted to try to clarify the first two tenets of the debate: risk assessment and the need for lymphadenectomy, using variously defined factors.[4,5] These generally consider age, grade of the tumor, myometrial invasion, involvement of the lymph-vascular spaces, and tumor size/location. The bottom line is that while routine lymphadenectomy as a staging procedure accurately identifies those patients with metastatic disease, the impact on long-term outcome is limited. One response to the lack of this evaluation is increased use of pelvic radiation to "cover" the regional lymphatics for potential early metastatic (but undiagnosed) disease. As has been well covered in several meta-analyses, the practice leads to equivalent outcomes, but as was identified in the Aalders and PORTEC-1 trials, comes with a cost — the risk for secondary malignancy.[6,7]

Long-term risk from therapy is an uncommon topic in most gynecological malignancies. This is because outside of non-epithelial ovarian and early-stage cervix and endometrial cancer, expected survival is far shorter than the time frame for a second cancer to develop. However, the current trial emphasizes the importance of evaluating the cost of therapy both short- and long-term. Since many of the patients apparently cured of their primary disease received DNA damaging therapy unnecessarily (i.e., not risk stratified), the issue is of great relevance. One effort to mitigate both recurrence and toxicity risk is the use of short-term adjuvant chemotherapy added to vaginal brachytherapy. Since nearly two-thirds of recurrences will include an element of distant disease, it is hypothesized that systemic chemotherapy may be better situated to address this risk. Since vaginal brachytherapy appears to be as good as pelvic radiation in patients undergoing accurate staging, the combination of two would appear an ideal combination. However, the proof of chemotherapy efficacy is lacking despite one randomized trial that suggests its equivalence to pelvic radiation.[8] It is hoped that the strategy, currently being evaluated in a Phase 3 trial, can provide long-term benefit while lowering long-term adverse events. These will be welcomed additions if proven, because more than ever, patients are experiencing long post-diagnosis survivorships. ■

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4. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

Continuing Education Questions

1. Which of the following comments regarding prophylactic cranial irradiation (PCI) in patients ≥ 70 years of age is true?

a. PCI has no benefit in overall survival (OS) or cause-specific survival (CSS) in patients ≥ 70 years of age.
b. PCI has a benefit in improving both OS and CSS in patients ≥ 70 years of age.
c. PCI has no benefit in CSS in patients ≥ 70 years, but it does improve OS.
d. PCI improves CSS in patients ≥ 70 years, but not OS.

2. Among patients with multiple myeloma who were presented with information about expected benefit of maintenance chemotherapy in prolonging survival up to 1 year, but with anticipated moderate toxicity and a cost of $10,000 per month, the percent inclined to pursue treatment as defined by the Mayo Clinic survey was approximately:

a. 5%.
b. 15%.
c. 32%.
d. 49%.

3. Panitumumab-FOLFIRI when compared to FOLFIRI alone in the second-line treatment of metastatic colorectal cancer has been associated with:

a. significantly improved progression-free survival (PFS), response rates, and overall survival (OS) for those with wild-type (WT) KRAS.
b. significantly improved PFS and response rates for patients with both WT and mutated KRAS.
c. significantly improved PFS and response rates for patients with WT KRAS but not mutated KRAS.
d. significantly improved response rates but diminished quality of life for treated patients with WT KRAS.

4. Which of the following statements accurately represents the findings in the trial of pelvic radiation for early-stage endometrial cancer?

a. Overall survival was statistically improved in women receiving pelvic radiation after surgery for early-stage endometrial cancer.
b. In women younger than age 60 years, mortality was increased with pelvic radiation therapy.
c. Locoregional recurrence risk was improved with vaginal brachytherapy.
d. Secondary malignancy was statistically increased among women age 60 and older.

[IN FUTURE ISSUES]

Cancer-reducing effect of OCPs in BRCA1/BRCA2 carriers