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INSIDE

Preserving Ovarian Function in Cancer Survivors

ABSTRACT & COMMENTARY

Synopsis: *There are increasing numbers of women who have been cured of cancer but have residual endocrine and reproductive ovarian failure. In the current report, a novel approach for reconstituting ovarian function in selected patients is presented. Laparoscopically obtained ovarian tissue was cryopreserved and then thawed. Frozen/thawed samples were comparable to fresh samples in several histological and immunohistochemical analyses. Thus, either orthotopic or heterotopic ovarian transplant may eventually be possible for women cured by radiation, chemotherapy, or the combination thereof.*

Source: Fabbri R, et al. *Gynecol Oncol*. 2003;89:259-266.

Currently, there are increasing numbers of young women cancer survivors who have been exposed to chemotherapy and/or radiation therapy. These treatments may have had a deleterious effect on ovarian function, and fertility issues may compromise overall quality of life. In the current report, a new strategy for ovarian tissue cryopreservation is evaluated.

Ovarian tissue was obtained by laparoscopy from 22 patients with different malignant conditions. The specimens were frozen under a strict cryopreservation protocol. For analysis, both fresh and frozen thawed tissues were examined by histological and immunohistochemical analyses. Fabbri and colleagues found good stromal and follicular morphology in both the fresh and frozen thawed tissue. Importantly, there was no significant difference found in follicular density, distribution, and diameters in fresh vs frozen thawed tissue. The follicle immunohistochemical analysis showed a high percentage of negative staining for both estrogen receptor and progesterone receptor. Additionally, Ki67 protein and Bcl2 protein had comparable patterns in fresh and frozen thawed specimens. Fabbri et al concluded that human ovarian tissue morphology, antigenicity, cellular proliferation, and anti-apoptotic index were well preserved by the cryopreservation technique used.

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COMMENT BY WILLIAM B. ERSHLER, MD

Ovarian damage can occur either from ionizing radiation or from certain types of chemotherapy treatments (most notably alkylating agents, antimetabolites, and vinca alkaloids).[1,2] Cryopreservation of ovarian tissue represents an attractive strategy for conserving both steroidogenic and gametogenic functions for women at risk for losing ovarian function from cancer treatment. It is apparent that ovarian tissue collection and storage may have significant advantages over egg or embryo storage. Although oocytes can be collected following gonadotropin stimulation, embryo cryopreservation is only relatively efficient. In contrast, primordial follicles, available in large numbers in ovarian tissue, are better suited for cryopreservation because they are small, lack the zona pellucida, and are metabolically quiescent and undifferentiated.[3] Fabbri et al suggest that after thawing of the frozen ovarian tissue it could be grafted into its normal site (orthotopic) or into a site other than its normal position (heterotopic). The advantage of an orthotopic placement would be that the engraftment itself would allow the possibility of pregnancy without further medical assistance, whereas the heterotopic engraftment would require in vitro fertilization to obtain pregnancy.

This is a new and very exciting strategy for the preservation of ovarian function after cancer therapy. The results presented herein suggest that ovarian tissue morphology, antigenicity, cellular proliferation, and antiapoptotic index are preserved by the cryopreservation technique used. There remains a tremendous amount of research to be accomplished before this approach will have widespread clinical application. ■

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Meta-Analysis Indicates Value of Neoadjuvant Chemotherapy for Invasive Bladder Cancer

ABSTRACT & COMMENTARY

Synopsis: *The value of neoadjuvant chemotherapy for invasive bladder cancer had not been definitively established, possibly because clinical trials have been of insufficient size to demonstrate efficacy. In a well-constructed meta-analysis of 10 completed clinical trials, investigators found a significant, albeit modest, improvement in overall survival for those who were treated with platinum-based combinations. The research highlights the value of meta-analysis for the evaluation of repeated clinical investigations.*

Source: Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Lancet*. 2003;361:1927-1934.

THERE CONTINUES TO BE SOME CONTROVERSY WITH regard to the efficacy of neoadjuvant chemotherapy for patients with invasive bladder carcinoma. The question persists despite several reports involving more than 3000 patients. The Advanced Bladder Cancer (ABC) meta-analysis collaboration was undertaken by a group under the direction of the British Medical Research Council (MRC), which funded the collaborative effort of a large number of investigators. They identified 14 randomized trials that used neoadjuvant strategies. However, 4 of the selected trials were eliminated

because of confounding variables (n = 3) or inability to retrieve the complete data set (n = 1). Thus, data for 2688 individual patients from 10 available randomized trials were reviewed.

Platinum-based combination chemotherapy showed a significant benefit to overall survival (combined hazard ratio [HR], 0.87 [95% CI, 0.78-0.98; *P* = .016]); 13% reduction in risk of death; 5% absolute benefit at 5 years; and increased overall survival from 45% to 50%. The effect was observed regardless of the type of local treatment (surgery, radiation, or combined surgery and radiation). The hazard ratio for all trials, including those using single-agent cisplatin, tended to favor neoadjuvant chemotherapy, although this tendency was not significant (*P* = .084). Thus, although platinum-based combination chemotherapy was beneficial, there was no evidence to support the use of single-agent platinum. The data were interpreted to demonstrate a clear, albeit modest, improvement in survival with the use of platinum-based combination chemotherapy for patients with invasive bladder cancer.

COMMENT BY WILLIAM B. ERSHLER, MD

The advanced bladder cancer meta-analysis collaboration has provided definitive evidence for the use of neoadjuvant chemotherapy for invasive bladder cancer. The analysis clears up considerable confusion introduced because of conflicting reports from small studies. The strength of this report lies in the methodology used. Importantly, the ABC investigators obtained primary data from each individual study rather than depending on the summaries of these studies that were published in the literature. They also sought data from completed but unpublished studies, thereby minimizing any bias created by the tendency to publish only positive reports.

Although the findings indicate the value of neoadjuvant combination chemotherapy, the findings must be tempered with the realization that the added benefit in absolute survival at 5 years is only 5%. However, the result for disease-free survival, locoregional disease-free survival, and metastases-free survival lend support to the evidence of survival benefits associated with combination chemotherapy. Nonetheless, the added benefit needs to be countered with the potential for toxicity with combined chemotherapy and its effect on quality of life.

The neoadjuvant strategy has, therefore, once again been demonstrated to be beneficial as it has under certain circumstances with other tumor types, such as lung, breast, and colorectal carcinoma. Although the demonstrated benefit is modest, the treatment strategy appears sound. Now, as more effective chemotherapeutic agents and combinations are developed and shown to be active in the setting of metastatic disease, these approaches may very reasonably be applied to the neoadjuvant setting and compared to platinum-based combinations.

Adjuvant Bestatin Provides Survival Benefit for Stage I Squamous Cell Lung Cancer

ABSTRACT & COMMENTARY

Synopsis: *In a multicenter trial from Japan, Bestatin, an aminopeptidase inhibitor, was shown to enhance survival in patients with stage I sqaumous cell carcinoma of the lung. This well-constructed trial will most certainly foster enthusiasm for exploring Bestatin in this role (adjuvant, postresection for low-stage squamous cell carcinoma) as well as in others, such as in combination with various chemotherapeutic or biologic agents.*

Source: Ichinose Y, et al. *J Natl Cancer Inst*. 2003; 95:605-610.

Bestatin is a potent aminopeptidase inhibitor with immunostimulatory and antitumor activity. Ichinose and collaborators throughout Japan performed a prospective, randomized, double-blind, placebo-controlled trial to determine whether postoperative adjuvant treatment with Bestatin could prolong the survival of patients with completely resected stage I squamous cell carcinoma. For this, patients with resected stage I lung cancer were randomly assigned to either Bestatin (30 mg) or placebo daily by mouth for 2 years. Between the years 1992 and 1995, 400 patients were entered in the study—202 were treated with Bestatin and 198 with placebo. The median follow-up for surviving patients was 76 months (range, 58-92 months). The 5-year overall survival was 81% in the Bestatin group and 74% in the placebo group for a difference of 7% (95% confidence interval [CI]; -1.4% to 15%). The 5-year cancer-free survival was 71% in the Bestatin group and 62% in the placebo group for a difference of 9% (95% CI, -.7% to 17.8%). Overall survival (*P* = .033, log-ranked test) and cancer-free survival (*P* = .017, log-ranked test) were significantly different by Kaplan-Meier analysis. Few adverse events were observed in either group. Ichinose and colleagues conclude that survival was significantly enhanced for patients with completely resected stage I squamous cell carcinoma

who received Bestatin as a postoperative adjuvant therapy when compared to those who received placebo. Ichinose et al conclude that these findings need to be confirmed in additional, large-scale clinical trials.

COMMENT BY WILLIAM B. ERSHLER, MD

Despite having localized disease at the time of presentation, patients with stage I lung cancer have a high relapse rate, and many will die of recurrent disease. Bestatin is a potent inhibitor of some, but not all, aminopeptidases.[1] In preclinical studies, Bestatin has been shown to inhibit the invasion of metastatic tumor cells[2] and induce apoptosis in non-small-cell lung cancer cell lines.[3] Furthermore, in tumor-bearing mice, Bestatin inhibits metastases and tumor growth, as well as prolonging survival.[4] In the clinical setting, Bestatin has been shown to prolong survival of patients with adult, nonlymphocytic leukemia when used with chemotherapy.[5] In a single-institution study examining the role of Bestatin as an adjuvant for non-small-cell lung cancer, a subset (those with completely resected stage I squamous cell lung cancer) showed survival benefit.[6] This survival benefit was not demonstrable when examined across other histologic types or stages. The current study, which represents a rather homogenous group of patients, all with squamous cell carcinoma and stage I (T1-2N0) who were treated with a single, daily oral dose of Bestatin, had significantly better survival than placebo controls. The finding is remarkable because it indicates another oral biological therapy with promise for the treatment of at least 1 subset of lung cancer patients, those with squamous cell carcinoma.

The precise role for Bestatin needs to be further defined. Its role as an adjunct to chemotherapy for patients with squamous cell or other forms of non-small-cell lung cancer needs to be evaluated, and certainly the current finding of enhanced survival in stage I squamous cell cancer should be confirmed. If this transpires, Bestatin will be a welcome addition to our arsenal of anticancer agents.

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Surgery vs Radiotherapy for Solitary Brain Metastases

ABSTRACT & COMMENTARY

Synopsis: *There have been no randomized trials comparing surgery and radiotherapy for solitary brain metastases, nor are there well-defined guidelines for the management of these patients. This study from the Mayo Clinic performed a retrospective analysis of the institutional experience comparing outcomes in patients treated with both approaches and concluded that the type of therapy selected was not prognostic in terms of survival but was a statistically significant factor regarding local control.*

Source: O'Neill BP, et al. *Int J Radiat Oncol Biol Phys*. 2003;55:1169-1176.

Approximately half of the 200,000 patients diagnosed with brain metastases annually have solitary lesions. The number of patients with solitary brain metastases (SBM) is expected to rise as systemic therapies improve, given that the brain is considered to be a sanctuary site. While surgery and stereotactic radiosurgery (SRS) are believed to offer local control benefits over whole-brain radiotherapy alone, there are few data comparing surgery and SRS and their respective impact on local control. Though the surgical option is not available to half of SBM patients because of comorbid conditions, the other half may be treated with either modality.

In order to compare local control and survival results for the 2 types of therapy, O'Neill and associates at the Mayo Clinic retrospectively reviewed their experience with 97 SBM patients treated from 1991-1999. All patients underwent an MRI with contrast to confirm that their metastases were solitary, and all were felt to have been eligible for either therapy in retrospect (ie, tumors were < 35 mm, not deep-seated or located in the brainstem, and patients were free of ventricular obstruction). There were 74 patients treated surgically (76%) and 23 treated with SRS (24%). Among the surgically treated patients, 82% received whole-brain radiotherapy, and among the SRS patients, 96% received it (P = NS). There were no significant differences in the baseline demographic characteristics in the 2 treatment groups, although the SRS patients had "a less favorable mix of prognostic factors." Median age for the surgery patients was 66 years (range, 51-71 years) and 63 years for the SRS patients (range, 55-70 years). Metastases were

symptomatic in 89% of the surgery patients and 74% of the SRS patients (P = NS). All SRS patients were treated with a Gamma Knife radiosurgery system.

Median follow-up was 20 months for surviving patients (range, 0-106 months). According to O'Neill et al, survival was measured from the date of the procedure. A propensity score for therapy assignment was derived for each patient as a means of accounting for confounding and selection biases, covering 25 covariates. One-year actuarial survival was almost identical between the 2 treatment groups, though surgery patients lived longer in year 2 (P = .15). There were no significant differences in complication rates, either short-term or long-term, between treatment groups. There was a trend for symptomatic patients to do worse than asymptomatic patients (P = .07). SRS patients with left-sided lesions did significantly worse than their surgery counterparts (P = .001). Fifty-nine percent of surgery patients died of systemic disease compared to 48% of SRS patients (P = NS). Thirty percent of surgery patients (19/74) developed recurrences in the brain, as did 29% (6/23) of SRS patients (P = NS). Significantly, while there were no SRS patients who experienced local failures at the site of their SBM, 11/19 (58%) of the surgery patients with relapsed disease in the brain had the disease recur at the site of original brain lesion (P = .02). Despite this, more SRS patients died of CNS tumor (29%) than did surgery patients (11%, P = .36). Multivariate analysis indicated that 2 factors were independently associated with survival: ECOG performance status and lack of systemic disease. Most notably, type of therapy was not found to be a prognostic factor for survival, even after adjustments for propensity score (P = .60).

O'Neill et al concluded that neither SRS nor surgery was superior for patients with small-to-moderate sized SBMs among their group of highly selected patients. They are in favor of a randomized trial in order to minimize confounding variables and selection bias and alerted the reader that such a trial is being planned under the auspices of the American College of Surgeons. O'Neill et al suggested that a quality-of-life assessment tool be included in this type of trial.

COMMENT BY EDWARD J. KAPLAN, MD

The Mayo Clinic paper was especially interesting because the results of the study offer a unique perspective for clinicians who see SBM patients, particularly those patients who are candidates for either therapy. Although the causes of death did not differ significantly between the 2 patient groups, I was surprised that local control of SBMs was markedly better in the SRS patients. In the long run, this did not seem to matter because the overall number of brain recurrences was about the same in both groups. It is unclear why the SRS patients must have had a higher number of recurrences elsewhere in the brain compared with the surgery patients. Perhaps it was related to the use of whole-brain RT, or the doses used. The whole-brain dose and fractionation schedules were not mentioned, and we are not told whether the SRS patients received their radiosurgery before or after their whole-brain RT. Survival was measured "from the date of the procedure," which likely meant either resection or SRS. Similarly, SRS dose and prescription information was lacking.

Simonova and colleagues from Prague reported their results with Gamma Knife radiosurgery for 237 patients with SBMs. They reported a local control rate of 95% with doses > 20 Gy.[1] Jyothirmayi and colleagues from the Royal Marsden published their experience with 96 SBM patients treated with 20 Gy in 2 fractions, and they found that outcomes were comparable to surgical excision.[2] The findings in both of these studies seem to be consistent with those of O'Neill et al.

In my opinion, given 2 options for the same problem, I would opt for the least invasive technique if outcomes are similar. As the authors pointed out, the number of SBM patients is expected to increase as systemic therapy improves, and thus the results of a randomized trial comparing SRS and surgery should offer us important information in terms of clinical recommendations in the future. It is unclear whether the use of temozolomide may enhance the results in SBM patients treated by noninvasive means. ■

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Hormonal Contraception and Cervical Cancer

ABSTRACT & COMMENTARY

Synopsis: *An increased risk of cervical cancer is associated with long durations of use of hormonal contraceptives.*

Source: Smith JS, et al. *Lancet*. 2003;361:1159-1167.

A TEAM OF EPIDEMIOLOGISTS PERFORMED A META-analysis of 28 studies examining the relation-

ship between invasive and in situ cervical cancer and hormonal contraception. The analysis included 12,531 women with cervical cancer in 4 cohort and 24 case-control studies. Hormonal contraceptive use was grouped into categories: short duration (less than 5 years), medium duration (5-9 years), and long duration (10 or more years). Overall, the relative risk of cervical cancer increased with increasing duration of use, from 1.1 (CI, 1.1-1.2) with short-duration use to 2.2 (1.9-2.4) with long-duration use. The risk declined gradually after discontinuation. When the analysis was confined to the 3000 cases that tested positively for human papillomavirus (HPV), the relative risks for short, medium, and long duration of use were: 0.9 (0.7-1.2), 1.3 (1.0-1.9), and 2.5 (1.6-3.9), respectively. The results were less marked in HPV-negative women; indeed, a slight increase did reach statistical significance. The relationship was observed for in situ and invasive cancer and both squamous cancer and adenocarcinoma.[1]

COMMENT BY LEON SPEROFF, MD

Cancer of the uterine cervix is now believed to be significantly caused by persistent infection with certain types of the sexually transmitted HPV. The medical literature suggests that the use of hormonal contraceptives can influence whether HPV leads to cervical cancer. This meta-analysis supports this conclusion, finding an increasing risk with increasing duration of hormonal contraceptive use, persisting after adjustments for sexual partners, smoking, and use of barrier methods of contraception. The data largely reflect the use of combined estrogen-progestin oral contraceptives. Although the data with injectable contraceptives (largely progestin only) were limited, Smith and associates report a slight increase with this method, as well. All methods of hormonal contraception were lumped together; therefore, results according to specific types and doses are unavailable.

I have a slide that I have frequently used for more than 5 years. It reads: "Meta-Analysis is to Analysis like Meta-Physics is to Physics." The technique of meta-analysis dates back to the late 1970s when it was initiated as a method to bring together small, randomized trials in order to increase statistical power. In the 1980s and 1990s, meta-analysis was rapidly extended to case-control and cohort studies. Clinicians soon came to give great weight to conclusions from meta-analyses, believing that the sophistication of the method provided reliable conclusions.

The technique of meta-analysis contains an important element of subjectivity. A group of individuals makes judgments regarding published studies, decisions about how good or bad each study is, and whether the conclusions should be incorporated into their own decision-making. Meta-analysis cannot correct confounding problems and biases in the original studies, and the conclusion of a meta-analysis can be misleading. An excellent example is the 1996 meta-analysis concluding that induced abortion increased the risk of breast cancer.[1] Subsequently it was discovered that case-control studies of this subject contained a major problem of recall bias (the healthy women in the control groups were reluctant to tell the truth about induced abortions). Appropriately designed studies (avoiding personal interviews) do not find an association between induced abortions and the risk of breast cancer.[2,3]

Cancer of the cervix is affected by many risk factors. Is it possible to lump 28 studies together and adequately control for confounding influences? Even Smith et al point out in their discussion that not a single one of the original studies adjusted for all confounding factors, and it would require uniform definitions and adjustments in each individual study to improve the reliability of the data. An excellent study from the Centers for Disease Control and Prevention (CDC) concluded that there is no increased risk of invasive cervical cancer in users of oral contraception, and an apparent increase in situ cancer is due to enhanced detection because of more frequent Pap smears.[4] However, the World Health Organization Study found an increased risk of in situ cancer even when Pap smear frequency was adjusted.[5] Very concerning is the rising incidence of adenocarcinoma of the cervix in young women over the last 20 years and impressive agreement among case-control studies that the risk of cervical adenocarcinoma increases with increasing duration of oral contraceptive use.

Fortunately, Pap smear surveillance is very effective for cervical cancer. The new methods incorporating HPV identification will be even better. This is another good argument against making hormonal contraception available over the counter. This meta-analysis of hormonal contraception and cervical cancer shouldn't change clinical practice because evaluation for cervical cancer is already part of the routine care for these women. It makes sense to me to perform cervical cancer screening every 6 months in women using hormonal contraception for longer than 5 years, especially if they are at higher risk because of their sexual behavior. ■

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Drug Treatments to Prevent Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *Only tamoxifen has enough evidence to recommend it for the prevention of breast cancer, and its use is limited to very high-risk women with a low risk of side effects.*

Source: Cuzick J, et al. *Lancet*. 2003;361:296-300.

Epidemiologists from England, Italy, and Australia reviewed the combined results of breast cancer prevention trials and added updated results. Reports are now available on 4 trials using tamoxifen, 20 mg daily for 5 years, for prophylaxis against breast cancer. In addition, data are available on the effect of raloxifene, derived from the trial investigating raloxifene prophylaxis against fractures in women with osteoporosis.

The combined data indicated a 48% reduction in estrogen receptor-positive cancers and no effect on the incidence of estrogen receptor-negative cancers. The overall relative risk of endometrial cancer with tamoxifen was increased to 2.4, and the relative risk of venous thromboembolic events was 1.9. The length of follow-up and patient numbers do not allow data regarding breast cancer mortality. Cuzick and colleagues estimated the effect of 5 years of tamoxifen treatment, given appropriate survival rates, and concluded that 1000 high-risk women would demonstrate an 18% reduction in mortality within 10 years of diagnosis.

COMMENT BY LEON SPEROFF, MD

Cuzick et al concluded that the evidence supports tamoxifen reduction of the risk for estrogen receptor-positive breast cancer. But at the same time, they believe that tamoxifen should not be recommended as a preventive agent, except for women at very high risk. This conclusion is based upon the degree of reduction in risk compared with the incidence of side effects. The data are too limited to support the use of raloxifene as prophylactic treatment, and a stronger position awaits the outcome of the STAR trial comparing tamoxifen with raloxifene. The Medical Research Council of the United Kingdom and the National Cancer Institute of the United States have reached similar conclusions.

The evaluation by the National Cancer Institute is very helpful.[1] This report is the result of a workshop directed to the development of a program to select the best candidates for tamoxifen treatment. Because the risks associated with tamoxifen (endometrial cancer, stroke, pulmonary embolism, and deep-vein thromboembolism) increase with age, balancing the risks and benefits indicates that tamoxifen is best for younger women with an elevated risk of breast cancer (an increased relative risk of approximately 1.7). A similar conclusion was reached by a working group of the American Society of Clinical Oncology.[2] This means that only a relatively small number of women will qualify because 85% of women who develop breast cancer do not have an identifiable risk factor.

I am still concerned that the favorable conclusion regarding tamoxifen for prevention is influenced by the American results. The other 3 trials did not achieve statistical significance, results that are usually dismissed on the basis of trial size—the American trial accounted for 47% of the treated women. The recent international trial results achieved statistical significance only when ductal carcinoma in situ cases were included.[3] Nevertheless, experts and organizations in the breast cancer world have agreed that tamoxifen reduces the incidence of estrogen receptor-positive cancers in high-risk women.

Women being treated with tamoxifen for prevention of breast cancer should receive appropriate antithrombotic measures, especially during and after major surgery, and during immobility. I disagree with the National Cancer Institute's position regarding monitoring for endometrial changes, which is to simply refer the patient to a gynecologist for evaluation when the patient bleeds. Endometrial cancer is not the only side effect of tamoxifen. Women on tamoxifen treatment should be examined every 6 months to detect the emergence of endometriosis, ovarian cysts, and uterine enlargement. I believe annual measurement of endome-

trial thickness by transvaginal ultrasonography is indicated, recognizing that interpretation is difficult and often requires saline instillation (sonohysterography) in order to make accurate measurements. The use of the levonorgestrel-releasing IUD is highly recommended as prophylactic treatment. Interestingly, at the San Antonio Breast Cancer Symposium in December 2002, a study was presented finding no effect of postmenopausal hormone therapy against tamoxifen-induced hot flushing, when the 2 treatments were administered concomitantly. Hot flushing on tamoxifen is best treated with a serotonin uptake inhibitor.

Important questions remain unanswered. Will long-term follow-up reveal an incidence of tamoxifen-resistant cancers—cancers that are actually stimulated by tamoxifen? Will the incidence of estrogen receptor-negative cancers increase over time? What is the effect of tamoxifen treatment on quality of life and cognition (including the risk of Alzheimer's disease)? ■

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CME Questions

1. **Which of the following is true regarding the O'Neill brain metastasis study?**
   a. All patients received whole-brain radiotherapy as part of their treatment.
   b. Local control was better in the radiosurgery group.
   c. Local control was better in the surgery group.
   d. Local control was the same in both treatment groups.

2. **Which of the following statements is best supported by data from the brain metastasis study?**
   a. Complications from therapy were similar in both treatment groups.
   b. CNS recurrences tended to be beyond the RT target area in SRS patients.
   c. Control of systemic disease was a significant prognostic factor in both treatment groups on multivariate analysis.
   d. All of the above

3. **Which of the following statements regarding the status of the strategy to enhance ovarian function in women who have received chemotherapy and/or radiotherapy involving pre-treatment ovarian biopsy, cryopreservation, and post-treatment orthotopic engraftment is most accurate?**
   a. Ovarian tissue from cancer patients has been frozen and thawed and shown to be in many ways comparable to fresh tissue.
   b. Ovarian tissue from cancer patients obtained prior to chemotherapy has been frozen and later successfully implanted orthotopically.
   c. Ovarian tissue from cancer patients obtained prior to chemotherapy has been frozen and later successfully implanted orthotopically, and ovulation from the engrafted tissue has been demonstrated.
   d. Ovarian tissue from cancer patients obtained prior to chemotherapy has been frozen and later successfully implanted heterotopically with demonstrable cyclical secretion of both estrogen and progesterone.

4. **Bestatin, administered orally once daily, was shown to prolong survival in which subset of lung cancer patients?**
   a. Those with extended-stage small-cell carcinoma
   b. Those with limited-stage small-cell carcinoma
   c. Those with stages I and II adenocarcinoma
   d. Those with stage I squamous-cell carcinoma

Answers: 1(b); 2(d); 3(a); 4(d)

In Future Issues: **Chemotherapy for Stage I and II Lung Cancer**