

## Radiation Oncology

**Alan Pollack, M.D., Ph.D.,** *Senior Member, Chairman*  
**Gary M. Freedman, M.D.,** *Member, Training Program Director*  
**Eric M. Horwitz, M.D.,** *Member, Clinical Director*  
**Andre A. Konski, M.D.,** *Member, Clinical Research Director*  
**Nicos Nicolaou, M.D.,** *Member*  
**Penny R. Anderson, M.D.,** *Associate Member*  
**Deborah Watkins Bruner, R.N., Ph.D.,** *Associate Member,  
Director, Prostate Risk Assessment Program*  
**Mark K. Buyyounouski, M.D.,** *Associate Member*  
**Steven Feigenberg, M.D.,** *Associate Member*  
**Alexander Kirichenko, M.D.,** *Fellow*  
**Matthew Abramowitz, M.D.,** *Resident*  
**Stephen Andrews,\* D.O.,** *Resident*  
**David D'Ambrosio, M.D.,** *Resident*  
**Shelly Hayes, M.D.,** *Resident*  
**Peter Morgan, M.D.,** *Resident*  
**Khanh Nguyen,\* M.D.,** *Resident*  
**Niraj Pahlajani, M.D.,** *Resident*  
**Alice Tsai, M.D.,** *Resident*  
**Kathleen MacDonald, R.N., B.S.N., O.C.N.,** *Nursing Coordinator*  
**Cindy Briola, R.N., O.C.N.,** *Primary Care Nurse*  
**Jean Holland, R.N., M.S.N., A.O.C.N.,** *Primary Care Nurse*  
**Ruth Krieger, L.P.N.,** *Primary Care Nurse*  
**Eileen McGarrity, L.P.N.,** *Primary Care Nurse*  
**Joanne McGarvey, R.N., B.S.N., O.C.N.,** *Primary Care Nurse*  
**Mariellen Smith, R.N., B.S.N., O.C.N.,** *Primary Care Nurse*  
**Carole Sweeney, R.N., M.S.N., A.O.C.N.,** *Primary Care Nurse*  
**Barbara Devlin, L.P.N.,** *Staff Nurse*  
**Bette Tumir, L.P.N.,** *Staff Nurse*  
**Zhaomei Mu, M.D.,** *Staff Scientist*  
**Thirupandiyur S. Udayakumar, Ph.D.,** *Research Associate*  
**Li-Yan Khor, M.D.,** *Postdoctoral Associate*  
**Radka Stoyanova, Ph.D.,** *Senior Scientific Associate*  
**Paul Hachem, B.S.,** *Scientific Assistant*  
**Hae Won Kwon,** *Scientific Technician*  
**Sharyn M. Shill,** *Administrative Manager*



The clinical Radiation Oncology department includes physician staff, nurses, fellows and residents who are committed to delivering the highest quality care to patients. Our mission is to combine clinical research, the latest technology from the fields of radiation physics and biology, and compassionate care for the treatment of cancer with radiation. In 2005, our staff members achieved academic excellence by contribution to clinical and basic science research, participation in national cooperative group and Fox Chase Cancer Center (FCCC) research protocols, publication in peer-reviewed medical journals, and presentation at scientific medical society meetings.

### FCCC Institutional Programs

**Prostate Cancer:** The prostate cancer program is directed by A. Pollack, and staffed by E. Horwitz, A. Konski, S. Feigenberg and M. Buyyounouski. All patients with prostate cancer are treated with state-of-the-art intensity modulated radiation therapy (IMRT). This

highly technological program includes routine MRI and CT simulation, daily prostate ultrasound, and multileaf collimation of the radiation beams. Accrual is nearly completed on a phase III randomized trial of hypofractionated radiation therapy. For this trial, 300 men with

prostate cancer are randomly assigned to receive higher doses every day to finish in five weeks instead of the standard eight weeks. The study will determine if this program has improved efficacy and convenience without increasing side effects. In another innovative study, CT-on-rails technology entered clinical use for men with prostate and other cancers. A CT scanner was installed with one of the linear accelerators so that patients can have daily CT scans to pinpoint their tumor location right before every treatment for the greatest possible accuracy. The brachytherapy program continued to treat selected candidates with low dose rate seeds or high dose rate prostate implants planned with advanced ultrasound and MRI techniques.

Horwitz collaborated on four studies, Fox Chase with 8 other U.S. institutions, of 4,839 patients with prostate cancer treated by external beam radiation alone between 1986 and 1995 (1–4). Important findings were that: 1) radiation doses  $\geq 72$  Gy were associated with improved biochemical disease control even controlling for other prognostic factors such as pretreatment PSA and grade; and 2) different definitions used for prostate specific antigen (PSA) biochemical failure can make results of treatment seem to vary significantly from 15%–72% five years after radiation so that they must be correlated with clinical outcomes to determine which is most appropriate for clinical and comparative research use. Feigenberg reported a study that determined, prior to treatment, which patients with locally advanced prostate cancer will have a high risk of recurrence with radiation therapy alone (5). This study demonstrated using recursive partitioning methodology that a cutpoint of PSA 30 ng/ml delineated patients into intermediate versus high-risk subgroups. The study excluded patients with proven high risk features such as Gleason score 8 to 10 and T3 disease, in which cases hormonal therapy is already indicated.

Feigenberg found that a pretreatment PSA  $>30$  ng/ml also predicted a high risk of recurrence, the five-year freedom from recurrence was only 20% when treated with radiation alone; so he recommended they also be treated with adjuvant hormonal therapy to improve upon these results. Feigenberg also published a comparison of the late side effects after prostate radiation for patients who had androgen deprivation

with those who did not (6). The use of any long-term androgen deprivation was the only independent predictor of developing grade 2 and 3 genitourinary (GU) side effects on multivariate analysis. The five-year risk was 14% compared with 8% in those having no or only short-term hormone therapy. Long-term hormone use also predicted an increased risk of grade 2 and 3 gastrointestinal (GI) side effects. These risks of hormones need to be considered before offering them routinely to patients.

Konski published a cost-effectiveness analysis of IMRT for prostate cancer (7). He used a Markov Model to compare IMRT to 3D conformal radiation using cost data for the initial treatments as well as follow-up care including salvage therapies for patients with recurrence. He found that IMRT was cost-effective for good and intermediate risk early stage disease despite the higher initial cost. This was due to reduced recurrence rates and lower salvage therapy costs improving overall quality adjusted survival. He found that a longer time frame for analysis of cost and younger age at time of treatment further improved the cost effectiveness ratio for IMRT.

Buyyounouski reported a descriptive analysis of serum PSA kinetics in men following radiotherapy for prostate cancer (8). He found that post treatment PSA kinetics differed between men treated with radiotherapy alone and radiotherapy with androgen deprivation therapy. The consequence of this was that the standard American Society of Therapeutic Radiation Oncology (ASTRO) definition for biochemical failure overestimated biochemical failure more often with combination therapy than with radiotherapy alone (20–30% vs. 5%). Buyyounouski then compared three definitions of biochemical failure, including the ASTRO definition, to determine which was best (9). In his study, the PSA nadir plus 2 ng/mL definition was superior to the standard ASTRO definition, defined as three consecutive rises in PSA backdated midway between the nadir and first rise. The nadir + 2 ng/mL definition resulted in a smaller misclassification rate, a higher correlation with clinical outcome, and a shorter interval to diagnosis. Furthermore, the nadir plus 2 ng/mL definition was insensitive to the addition of androgen deprivation therapy and length of follow-up. Pollack and Horwitz published review articles on the use of androgen

suppression plus radiation for prostate cancer (10–11), and Horwitz co-authored a paper on the difficulties in determining whether or not a patient has recurred after prostate cancer treatment using only serum PSA levels (12).

The department radiobiology laboratory has focused on: 1) the identification of biomarkers in pretreatment diagnostic tissue from men with prostate cancer who were treated with radiotherapy with or without androgen deprivation; and 2) the use of novel biologic/small molecule methods to sensitize prostate and pancreatic cancers. The expression of other markers, particularly key proteins in the apoptotic pathway, are being examined as potential correlates of radiation response and tumor spread. Related to the effort to maximize the cell killing effect of treatment, three antisense molecules have been found to enhance the response of prostate cancer cells to radiation. Antisense molecules were chosen to reduce the expression of selected proteins in the apoptotic pathway that protect cells from such killing. Since androgen deprivation and radiation are often combined together in men with high-risk prostate cancer with no evidence of metastases, this strategy has promise for being applied clinically.

Our department was well represented at the 87<sup>th</sup> meeting of the American Radium Society in Barcelona, Spain, April 30–May 4, 2005. Pollack reported that race and family history are not predictive factors for outcome after radiation therapy for prostate cancer. While they have been previously shown to be associated with differences in stage at presentation or risk for prostate cancer development, he found that there was no correlation with biochemical failure, clinical failure, or survival endpoints on multivariate analysis controlling for dose, PSA, stage and grade. Konski presented a study of age and outcomes for men with early stage prostate cancer treated with radiation. Eighty-four men were matched for important prognostic factors of stage, grade, and pretreatment PSA. There was no statistically significant difference between men <55 years, 60–69 years, or >70 years of age in overall survival, biochemical disease control, or rate of distant metastases. He concluded that young men (<55 years) remain appropriate candidates for radiation even with early stage disease. Feigenberg presented the meaning of a transient

rise or bounce in the patterns of PSA values after external beam radiation therapy. He defined a bounce as a rise in PSA of 0.4 ng/ml or more over a six-month period followed by a subsequent decrease. A bounce was found in one-quarter of patients after treatment, making this a common phenomenon. He found that a bounce of 1.5 ng/ml or more was associated with a higher risk for future biochemical recurrence, distant metastases and death from prostate cancer. He recommended that patients with a bounce in PSA be monitored closely and considered for additional therapy sooner than commonly done now in clinical practice. Buyyounouski compared three methods of estimating tumor volume from prostate biopsy specimens as a prognostic factor following radiotherapy (reported at 2005 ASTRO meeting, Denver, CO). Earlier studies showed that the percentage of positive biopsy cores was an independent pretreatment prognostic factor following radiotherapy. The results of his comparison, performed on a modern series with higher radiation doses, showed that the percentage of positive tissue, a more precise estimate of tumor volume that corrects for oversampling of involved regions and variations in the length of each core involved, was superior to the percentage positive cores. His study suggests that simply determining the ratio of positive cores (or regions) to the total number of cores (or regions) obtained is not sufficiently accurate for estimating tumor volume. Men with more than 25% involvement of the biopsy specimen with tumor had a significantly worse biochemical outcome.

Buyyounouski was also awarded an ASTRO Travel Grant to attend the NCI Radiation Research Program (RRP)/Radiation Oncology Sciences Program (ROSP) Young Investigators Workshop for Radiation Oncology in Bethesda, Maryland. The residents and fellows in the department of radiation oncology were also active in our prostate cancer research effort, publishing manuscripts during 2005 (see *Medical Education* section below). R. Jacob (fellow completed 2004) reported the importance of radiation dose in prostate cancer (13). The study looked at 420 patients selected because of a combination of pretreatment PSA, grade and T-stage that predict for a 15% or higher risk of pelvic lymph node metastases. Radiation dose > 77Gy was the most important

prognostic factor, not short-term hormones or field size. Patients receiving doses > 77 Gy had the highest five-year biochemical control rate of 74%, compared with 64% for 73–76.9 Gy and 48% for < 73 Gy.

**Breast Cancer.** G. Freedman P. Anderson

The department completed a phase I/II clinical trial using IMRT, hypofractionation and an incorporated breast boost to shorten treatment time for postlumpectomy radiation from the traditional 6–7 weeks to 4 weeks. IMRT is a further advance in the way radiation is delivered for an individual patient; it uses 3-D determination of the lumpectomy site and breast target volumes, dose planning with Monte Carlo dose calculations, and multileaf collimation. IMRT improves the dose homogeneity across the different areas of the skin and breast tissue to reduce common side effects seen with conventional radiation during and after the treatment. Other goals are to reduce the dose of radiation given to the heart. Hypofractionation is the delivery of larger daily doses of radiation than standard to complete treatment sooner. Lastly, the trial delivers a higher daily dose to the tumor bed, or a boost, rather than extending treatment an extra 1 1/2–2 weeks for the boost as is usually done. Data is being collected on acute toxicity, tumor recurrence, cosmesis and quality of life. The department also continued participated in clinical trials studying the safety and efficacy of partial breast irradiation. In one study, patients with ductal carcinoma in situ (DCIS) are treated with the MammoSite brachytherapy system (Proxima Therapeutics) in a multi-institutional study. A phase III randomized multicenter study of whole-breast versus partial breast irradiation is also underway at FCCC sponsored by the RTOG and NSABP. This study is open to women with Stage 0–II early stage breast cancer smaller than 3 cm treated by lumpectomy. Women at FCCC randomized to partial breast irradiation will have the option of treatment by either MammoSite or 3-D conformal radiation.

Freedman published the long-term patterns of local recurrence after breast-conserving surgery and radiation (14). The study consisted of 2,730 women with Stage 0–II breast cancer, all treated with post-lumpectomy radiation. The rate of local recurrence in the same quadrant, called ‘true local’ recurrences, as the initial

tumor was 3%, 6% and 9% at 5, 10 and 15 years. The risk of recurrence in other parts of the breast was 1% and 2% at 5 and 10 years (very low as reported in by other series) but at 15 years was 7% and not significantly different from the risk of true local recurrences. This 15-year risk of elsewhere recurrence was half the 14% risk of long-term contralateral breast recurrence, which was statistically significant. This may suggest a protective effect of breast radiation on other parts of the breast. One conclusion from the study was that brachytherapy, partial breast radiation that treats just the area of the lumpectomy, needs to be studied on clinical trials with careful patient selection and long-term follow-up to see if it offers comparable local control to standard whole-breast radiation. Also, Freedman published a review article on radiation therapy for women undergoing implant reconstruction after mastectomy (Breast Cancer Online). Konski studied the cost and clinical outcome of women presenting with breast cancer in a managed care organization (15). The study analyzed data on cost and outcome with respect to method of cancer diagnosis, cancer stage and insurance product. He found that women diagnosed by mammography had earlier stage disease at diagnosis, fewer recurrences, and were less likely to receive chemotherapy than women who were self-diagnosed. Although recurrences were fewer in this group, mammographic detection did not reach statistical significance for improved disease-free and overall survival. For women with commercial insurance, there was also less cost to the insurance plan when cancers were mammographically detected. This was not seen in the Medicare population but the patient numbers were small. Cost was not higher for breast-conservation compared with mastectomy. H. Diratzouian (resident completed 2004) compared outcomes after breast-conservative surgery and radiation with or without systemic therapy for women whose cancers were evident on physical exam versus only on mammography (16). Cancers detected solely by physical exam were associated with age <40 years, larger tumor sizes, and positive axillary lymph nodes compared with tumors detectable solely on mammography. These patients were also more often treated with chemotherapy. However, despite having these worse prognostic factors, this group of women had improved 10-year

local control and overall survival. She concluded that physical examination remains important as a method of detecting breast cancer, particularly in young women in whom mammography is less sensitive, and does not necessarily confer a worse prognosis.

At ASTRO, Anderson reported the timing of tamoxifen with radiation therapy for early stage breast cancer. She compared patients treated with radiation therapy followed by tamoxifen with those in whom tamoxifen was started prior to and during radiation therapy. Some studies in the past have suggested concurrent use of tamoxifen could negatively impact on radiation sensitivity, while other studies have not shown a worse clinical outcome. After adjusting for age and other prognostic variables that were different between the two groups, the sequence of tamoxifen with radiation did not impact on disease control or survival. Concurrent tamoxifen use was associated with decrease in long-term cosmetic result of the treated breast. She recommended sequential sequencing of tamoxifen after radiation whenever possible. Freedman studied the selection of patients to start on an aromatase inhibitor after finishing five years of tamoxifen for early stage breast cancer. He included women who were free from all adverse events five years after surgery, radiation and tamoxifen. None of these patients had additional therapy, which was standard practice at the time, but studies indicate that use of an aromatase inhibitor would reduce events by 30%. For all patients, the adverse event-free survival was 93% by 10 years after treatment. He found that a clinically significant risk of contralateral breast cancer or recurrence could be potentially mitigated by the additional hormonal therapy in women aged under 60 years or those with four or more positive axillary nodes. Women older than 60 years of age had a higher mortality from other causes that would diminish the potential benefit from additional breast cancer therapy after five years.

**Lung Cancer.** S. Feigenberg, N. Nicolaou, A. Konski

Feigenberg accrued patients to a clinical trial of extracranial stereotactic radiotherapy for metastatic and primary lung tumors. This technique was previously used only for brain tumors, and involves high doses of radiation pinpointed to

small tumors in the lung using advanced planning techniques and modifications to the linear accelerators used for standard radiation. Instead of a usual course of 6–7 weeks of daily radiation, this protocol uses large single doses given once per week for only four weeks. The study aims to determine the safety and tumor response with this technique. He presented a study at ASTRO of the optimal beam margin for extracranial stereotactic radiosurgery. He studied the first five patients treated on this protocol with 40 Gy in four fractions. A margin of 2 mm was optimal for insuring target coverage while minimizing dose to nearby normal lung tissue. The department continued participating in an RTOG trial combining three-dimensional conformal radiotherapy with chemotherapy in non-small cell lung cancer. Currently, Positron Emission Tomography (PET) scans are used in the treatment planning process with CT scans for most patients with lung cancer to better delineate the areas of the lung and regional lymph nodes involved by cancer.

**Lymphoma:** N. Nicolaou administers all necessary radiation for patients with lymphomas and other hematologic malignancies. He additionally coordinates the ongoing cooperative efforts of the Fox Chase/Temple University Hospital Bone Marrow Transplantation program at Jeanes hospital. The highly specialized technique of total body irradiation (TBI) is given with high dose chemotherapy to appropriate patients followed by allogeneic (donor) bone marrow transplantation, or autologous (harvesting one's own bone marrow or peripheral stem cells) transplantation.

**Head and Neck Cancer.** N. Nicolaou, S. Feigenberg

Patients are treated with state-of-the-art three-dimensional conformal radiation therapy (3D-CRT) and intensity modulation radiation therapy (IMRT) utilizing CT and MRI simulation. The department participated in several RTOG trials testing integration of altered radiation prescriptions with concurrent chemotherapy and also IMRT, for the treatment of head and neck cancers to improve long term outcomes while minimizing treatment related toxicities. Nicolaou and Feigenberg specialize in organ preservation therapy for these patients.

N. Kramer (resident, completed 2004) published the toxicity and two-year results of phase I/II clinical trials at FCCC for patients with recurrent head and neck cancer (17). The work represents a collaborative effort between radiation oncology and the medical and surgical oncology departments. The trial treated previously radiated patients with a regimen of hyperfractionated radiation (twice per day) and chemotherapy. The overall survival was 50% and 35% at one and two years, respectively, which was considered promising and better than would be expected from chemotherapy alone given the very serious nature of these recurrences. Second recurrences occurred in more than half of patients again within the radiation fields. An important finding was that regional node irradiation was not indicated in these patients which reduces the potential for toxicity. This experience was the basis for the subsequent national study in the RTOG that has been completed but not yet reported.

**Skin Cancer.** E. Horwitz, N. Nicolaou

Our department uses radiation to treat skin cancers in patients who cannot have these cancers removed surgically for whatever reason. Results and cosmesis are excellent. Radiation is especially useful in cases where surgery would result in unacceptable cosmesis or loss of function of involved organ.

**Gynecologic Cancer.** P. Anderson

Anderson continued a clinical trial of hypofractionated radiation for endometrial cancer. This trial enrolls patients giving consent to receive either standard pelvic radiation or an innovative program of IMRT given over a shorter number of weeks. Goals are to reduce treatment time, side effects, and cost of radiation. The department also continues to treat patients with cervix cancer with high dose rate brachytherapy, which replaces a two-four day hospitalization for an implant with an outpatient regimen. Women with gynecologic malignancies also continued to be enrolled on ongoing Gynecologic Oncology Group (GOG) and RTOG protocols.

**Gastrointestinal Cancer.** A. Konski, G. Freedman

Konski reported the incorporation of functional PET scan imaging into the simulation process

for treatment of esophageal cancer (18). Twenty-five patients underwent radiation planning with CT simulation and PET scans; the PET scan images the metabolic activity of tumors, and when merged with the anatomic information from CT scanning, may improve the targeting of radiation therapy compared with CT imaging alone. Most patients underwent endoscopic ultrasound to delineate the tumor as well. His study found that the length of the tumor determined by PET scanning was closer to the endoscopic length than CT that was approximately 1.5–2 cm longer. Endoscopic ultrasound was better than PET and CT for identifying positive regional lymph nodes that should be covered in radiation portals. He recommended routine incorporation of PET and ultrasound to the radiation planning process usually done with CT alone to improve field design and target coverage. Konski also published a study in 2005 on the incorporation of functional PET scan imaging into preoperative radiation therapy for rectal cancers (19). Twenty patients underwent PET scanning before and after chemotherapy and radiation. The follow-up PET scans showed in general less metabolic activity, with a decrease in the median standard uptake value of 71%. However, although 30% of patients had no residual disease at surgery, the PET scan was not sufficiently predictive for the absence of any microscopic tumor in the resected rectal specimen to use at the present time to select which if any patients could have avoided surgery. In collaboration with medical and surgical oncology, Freedman was a co-author of a report on preoperative chemoradiation for esophageal cancer (20). The study retrospectively compared patients undergoing esophagectomy alone to those that had preoperative radiation and chemotherapy followed by surgery between 1994–2002 at FCCC. The study found that patients with a significant reduction in their tumor after chemoradiation, determined by the amount of tumor remaining at the time of surgery, had better long-term survival. Overall, survival was 33% at five years in those undergoing chemoradiation followed by surgery compared with 11% for those undergoing surgery alone; however, the patients were not randomized between the two treatments and these survival differences did not reach statistical significance. The study gives support to the

benefit in some patients from downstaging the tumor prior to surgery with chemoradiation to improve the likelihood of complete resection and possibly improve chances for survival.

Konski presented a study of cardiac PET imaging in esophageal cancer (American Radium Society, Barcelona, Spain). Twenty patients underwent Pet scans pre and post chemotherapy and radiation for esophageal cancer. The cardiac uptake by PET was found to be higher after chemoradiation, with the interval from treatment predicting the amount of change. The dose parameters of radiation to the heart volumes showed a statistical trend in predicting the increased left ventricle change in uptake. He recommended further follow-up to determine if there is a clinical effect associated with these findings.

Freedman continued his study of dose escalation for locally advanced rectal cancer. The study uses IMRT with escalating doses of radiation to the tumor bed with concurrent oral capecitabine chemotherapy prior to surgical resection. End-points of the study include toxicity, the response rate of the tumor to chemoradiation measured after surgery, and the quality of life.

**Central Nervous System (CNS).** S. Feigenberg, M. Buyyounouski

Feigenberg continued a collaborative stereotactic radiosurgery effort with the neurosurgery department of Temple University Hospital. This technology allows very high doses of radiation to be delivered with pinpoint accuracy for small tumors of the brain, even in patients who have been previously irradiated. The treatments can be given in a single large treatment called stereotactic radiosurgery, which is an alternative to surgical resection for tumors under 4 cm.

**Palliation:** Konski published a review article on the many indications for radiation therapy in the palliative care of cancer patients (21). The study summarized data for different treatment schedules and outcome for radiation of bone metastases, including recent literature on use of radionuclides alone or with external beam radiation. The article covered common problems of palliation for brain metastases and spinal cord compression, and palliation of local symptoms from tumors of the lung, gastrointestinal tract, genitourinary and head and neck cancers.

## **Radiation Therapy Oncology Group (RTOG)**

Konski serves as the chair of the economic subcommittee of the Outcomes committee and principal investigator for RTOG at Fox Chase Cancer Center. Pollack heads the Translational Research Program Section of the Genitourinary Section of the RTOG, and Dr. Bruner is a Vice-chair of RTOG and the chairperson for the RTOG Outcomes Committee.

Konski, D. Watkins-Bruner and E. Sherman,<sup>a</sup> published an economic analysis of adding hormonal therapy to radiation for locally advanced prostate cancer (22). The study used patient data from RTOG 86-10, a randomized trial of hormone therapy with long-term outcomes data. The study compared cost of treatment for radiation plus hormones, which was greater initially than radiation alone. However, the hormones satisfied criteria for cost-effectiveness because of the resulting improvement in outcomes such as disease progression and survival. Bruner and Konski were co-authors of a randomized trial investigating two fractionation schedules for palliation of bone metastases in breast and prostate cancer (23). Patients were randomized to 8 Gy in a single fraction or 30 Gy in 10 fractions. There was no difference in response rate (66%) in terms of pain and relief from narcotic use. There was a higher rate of retreatment 18% vs. 9%,  $p < 0.001$ ) for the single fraction arm. Feigenberg and Watkins-Bruner published a study of quality of life outcomes after prostate brachytherapy (24). The study examined patient-reported quality of life measures from questionnaires in 98 patients treated with prostate brachytherapy on RTOG 98-05. The study found that there was a very low risk of urinary incontinence of 1%, and 78% of men at one year continued to be sexually potent. However, compared to baseline pre-treatment scores, the men did report decreased urinary and sexual function. Pollack was a co-author of a study of MDM2 as a predictor of outcomes in RTOG 86-10, which concluded that overexpression was weakly associated with distant metastases (25). B. Movsas<sup>b</sup> and N. Nicolaou reported a randomized trial, RTOG 98-01, of amifostine added to chemotherapy and hyperfractionated radiation for locally advanced non-small cell lung cancer (26). The study showed that amifostine, a radioprotector for normal tissue used

with radiation, did not decrease toxicity for lung cancer patients as hoped for; the incidence of grade 3 esophagitis was approximately 30% in both treatment arms with and without amifostine. The quality of life analysis showed a potential for improvement in pain and swallowing function within six weeks of treatment with amifostine. In addition, it did not compromise overall survival. Further study of amifostine with radiation was recommended. Pollack and Movsas were co-authors of two other RTOG studies in 2005 (27–28).

Pollack presented a study of MDM2 expression in patients treated on RTOG 92-02 at the annual ASTRO, and the annual meeting of the American Radium Society (ARS). MDM2 is a feedback regulator of p53 and is involved in cellular apoptosis and death from radiation injury. The expression was measured in patients treated on a randomized trial of radiation and hormonal therapy for prostate cancer and correlated with clinical outcomes. Pollack found that the percentage of tumor nuclei staining positive for MDM2 protein expression correlated with biochemical failure, and the mean intensity scores or staining correlated with biochemical failure, distant metastases and mortality. The expression was a significant predictor of outcome on multivariate analysis. He recommended that MDM2 expression be used for patient stratification in future clinical trials, and further research into antisense-targeted therapy against MDM2 may be a future treatment approach.

Konski presented a study at ASTRO of treatment outcomes for unmarried male patients on RTOG 97-14. Previous head and neck studies in the RTOG have shown worse outcomes for unmarried men; it is felt that having added social support from marriage or a live-in partner could improve compliance and tolerance to treatment. He found that unmarried men had a lower retreatment rate for bone metastases that more likely reflects less social support to pursue further treatment than better response to the initial treatment. E. Horwitz presented results of RTOG 99-11, a phase II study of paclitaxel, cisplatin, and split course hyperfractionated radiation for patients with recurrent head and neck cancer. This aggressive regimen is offered to patients with a recurrence despite prior radiation who would otherwise have a

very poor prognosis and severe symptoms from their disease. Approximately 70% or more of patients were able to receive the planned chemotherapy and radiation. Toxicity was severe but expected, with 8% fatal toxicities in these heavily pretreated patients. The median survival was 12 months, with 35% of patients free from progression of their cancer after one year. This compared favorably with historical controls on prior RTOG studies, so that this approach will be the subject of a future phase III randomized trial.

**Medical Education:** G. Freedman is the director of the residency/fellowship training program. In 2005, the program received approval of certification for an additional five years by the ACGME, and permission to increase the number of residents to eight total from the current number of six.

M. Buyyounouski was awarded the RSNA Roentgen resident/fellow research award for his publications, book chapters, and presentations at scientific meetings during the past year (see *Prostate Cancer* section above). He published a case report of PET scan imaging in a patient with stomach cancer (29). The patient had a unique histologic type called signet-ring, a variety of mucinous carcinoma, that had minimal FDG accumulation than would be expected for average adenocarcinomas. He cautioned against the use of PET for staging and detecting recurrence in this subgroup of gastric cancer patients. S. Andrews reported the time between diagnosis of prostate cancer and the start of radiation (30). The median time until starting radiation of the men studied was 3.2 months. He found no significant difference in outcome of delaying radiation for four groups of patients who started treatment within 3 months, 3–6 months, 6–9 months, or >9 months. Some patients in the study received androgen deprivation during this time between diagnosis and treatment, which also did not affect the clinical outcome of these patients even when there was a long delay to radiation. S. Hayes published a review article in the *Journal of Clinical Oncology* on the role of radiation therapy for salvage of recurrent prostate cancer after initial treatment by radical prostatectomy (31). The article examined the decision-making process for management based upon prognostic factors, use of systemic hormone therapy, and outcomes after treatment.

Four presentations were given by the residents and fellow at the annual meeting (ARS) in Barcelona. K. Nguyen gave a report on E2F-1 transcription factor. He found that E2F-1 enhanced the radiation response of both p53+ and p53- prostate cancer cell lines as measured by cell survival in clonogenic assays and levels of apoptosis (32). D. D'Ambrosio presented a study on Gleason score grading and outcome after radiation therapy for prostate cancer. The percentage of high-grade 4 or 5 disease (on a scale of 1-5) was an independent predictor of distant metastases on multivariate analysis, and more predictive than the unquantified Gleason score alone. Patients having greater than 5% Gleason 4/5 had a five-year biochemical freedom from recurrence of 64%, compared to 78% if 5% ( $p=0.03$ ). Buyyounouski reported the time to failure after radiation therapy using the Nadir plus 2 ng/mL definition of PSA relapse. This method of determining relapse has been shown in previous studies from our department to be more accurate than the currently accepted ASTRO definition. He found that a time to biochemical failure  $\leq 18$  months was a stronger predictor of prostate cancer-specific mortality than PSA doubling time. He concluded that men with early relapse be considered immediately for salvage therapy. P. Alcantara<sup>c</sup> reported a study of urinary side effects at ASTRO and the ARS meeting in 1,427 patients treated with conformal radiation therapy in prostate cancer. She analyzed the relationship of dose given to specific volumes of the bladder and the incidence of long-term grade 2 or 3 toxicity. Andrews reported at ASTRO a study of time to treatment for men treated with brachytherapy for early stage prostate cancer. The median time to treatment was 4.3 months from the time of their positive prostate biopsy. There was no observed effect on treatment outcomes for patients with time to treatment longer or shorter than this median. Nguyen presented a study of type-II diabetes and outcomes after prostate cancer radiation therapy. He found no difference in disease stage, grade or pretreatment PSA levels between patients with or without diabetes. Diabetes was associated with an increased risk of mortality, due to deaths from non-prostate cancer causes,

but did not effect rates of clinical or biochemical disease control. Hayes presented an analysis of outcomes based upon marital status for patients with early stage breast cancer treated with lumpectomy and radiation. Previous studies have shown worse outcomes for unmarried men but not women with head and neck cancer, probably due to lower treatment compliance and tolerance to side effects of treatment. There were significant differences in age, method of detection, number of breast surgeries and use of systemic therapy among women who were single, married, widowed or divorced. However, on multivariate analysis correcting for these differences, there was no difference in relapse-free survival. D'Ambrosio presented a study of transurethral resection of the prostate (TURP) and its effect on prostate cancer outcomes after radiation. He found that men with a history of TURP and PSA in the range of 10-20 ng/ml had a worse outcome than without history of TURP. An explanation put forth for this is the TURP lowers the PSA at presentation by reducing the amount of normal prostate tissue, so that these patients have a tumor burden more consistent with patients having pretreatment PSA of  $>20$  ng/ml. He recommended adjuvant hormonal therapy for these patients.

### **Prostate Cancer Risk Assessment Program**

The Prostate Cancer Risk Assessment Program (PRAP) is an ongoing research effort directed by D. Bruner. A. Konski serves as clinical director with S. Feigenberg as assistant director. The program recruits men with prostate cancer and men at risk for the disease into a prostate cancer risk registry for the study of epidemiologic and genetic factors that may predispose men to the disease. The program prospectively enrolls men at risk into a multidisciplinary clinic that combines clinical screening for prostate cancer with translational research including the divisions of population sciences and tumor genetics. The long-term goals of the program include the identification of clinical, genetic, and environmental risk factors for the initiation and development of prostate cancer. The program is also prospectively collecting data on quality of life in both the men with prostate cancer and high-risk men.

## Publications

1. Horwitz, E.M., Thames, H.D., Kuban, D.A., et al. Definitions of biochemical failure that best predict clinical failure in prostate cancer patients treated with external beam radiation alone – a multi-institutional pooled analysis. *J. Urol.* **173**:797-802, 2005.
2. Kuban, D., Thames, H., Levy, L., Horwitz, E., et al. Failure definition-dependent differences in outcome following radiation for localized prostate cancer: can one size fit all? *Int. J. Radiat. Oncol. Biol. Phys.* **61**:409-414, 2005.
3. Kupelian, P., Kuban, D., Thames, H., Levy, L., Horwitz, E., et al. Improved biochemical relapse-free survival with increased external beam radiation doses in patients with localized prostate cancer: the combined experience of nine institutions in patients treated in 1994 and 1995. *Int. J. Radiat. Oncol. Biol. Phys.* **61**:415-419, 2005.
4. Kupelian, P., Thames, H., Levy, L., Horwitz, E.M., et al. Year of treatment as independent predictor of relapse-free survival in patients with localized prostate cancer treated with definitive radiotherapy in the PSA era. *Int. J. Radiat. Oncol. Biol. Phys.* **63**:795-799, 2005.
5. Feigenberg, S.J., Hanlon, A.L., Horwitz, E.M., Uzzo, R.G., Eisenberg, D.F., Pollack, A. What pretreatment PSA value warrants long-term androgen deprivation? *Int. J. Radiat. Oncol. Biol. Phys.* **61**:1003-1010, 2005.
6. Feigenberg, S.J., Hanlon, A.L., Horwitz, E.M., Uzzo, R.G., Eisenberg, D., Pollack, A. Long-term androgen deprivation increases grade 2 and higher late morbidity in prostate cancer patients treated with three-dimensional conformal radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* **62**:397-405, 2005.
7. Konski, A. Expert Rev Pharmacoeconomics Outcomes Res **5**:137-140, 2005.
8. Buyyounouski, M.K., Hanlon, A.L., Horwitz, E.M., Uzzo, R.G., Pollack, A. The temporal kinetics of Prostate Specific Antigen (PSA) following 3D-conformal radiation therapy with androgen deprivation. *Int. J. Radiat. Oncol. Biol. Phys.* **61**:1291-1298, 2005.
9. Buyyounouski, M.K., Hanlon, A.L., Eisenberg, D.F., Horwitz, E.M., Feigenberg, S.J., Uzzo, R.G., Pollack, A. Defining biochemical failure after radiation therapy with and without androgen deprivation for prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **63**:1455-1462, 2005.
10. Horwitz, E.M. Does addition of 6 months' androgen suppression to radiotherapy prolong survival of men with prostate cancer? *Nature Clin. Pract. Urol.* **2**:16-17, 2005.
11. Pollack, A., Horwitz, E.M. Is 6 months of androgen suppression therapy plus radiotherapy of benefit in patients with localized prostate cancer? *Nature Clin. Pract. Oncol.* **2**:12-13, 2005.
12. Vicini, F.A., Vargas, C., Abner, A., Kestin, L., Horwitz, E.M., Martinez, A. Limitations in the use of serum prostate specific antigen levels to monitor patients after treatment for prostate cancer. *J. Urol.* **173**:1456-1462, 2005.
13. Jacob, R., Hanlon, A.L., Horwitz, E.M., Movsas, B., Uzzo, R.G., Pollack, A. Role of prostate dose escalation in patients with greater than 15% risk of pelvic lymph node involvement. *Int. J. Radiat. Oncol. Biol. Phys.* **61**:695-701, 2005.
14. Freedman, G.M., Hanlon, A.L., Anderson, P.R., Eisenberg, D., Nicolaou, N. Pattern of local recurrence after conservative surgery and whole-breast radiation: Implications for partial breast irradiation. *Int. J. Radiat. Oncol. Biol. Phys.* **61**:1328-1336, 2005.
15. Konski, A. Clinical and economic outcomes analyses of women developing breast cancer in a managed care organization. *Am. J. Clin. Oncol.* **28**:51-57, 2005.
16. Diratzouian, H., Freedman, G.M., Hanlon, A.L., Eisenberg, D.F., Anderson, P.R. Importance of physical examination in the absence of a mammographic abnormality for the detection of early-stage breast cancer. *Clin. Breast Cancer* **6**:330-33, 2005.
17. Kramer, N.M., Horwitz, E.M., Cheng, J., Ridge, J.A., Feigenberg, S.J., Cohen, R.B., Nicolaou, N., Sherman, E.J., Babb, J.S., Damsker, J.A., Langer, C.J. Toxicity and outcome analysis of patients with recurrent head and neck cancer treated with hyperfractionated split-course reirradiation and concurrent cisplatin and paclitaxel chemotherapy from two prospective phase I and II studies. *Head Neck* **27**:406-414, 2005.
18. Konski, A., Doss, M., Milestone, B., Haluszka, O., Hanlon, A., Freedman, G., Adler, L. The integration of 18-fluoro-deoxy-glucose positron emission tomography and endoscopic ultrasound in the treatment planning process for esophageal carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.* **61**:1123-1128 2005.
19. Konski, A., Hoffman, J., Sigurdson, E., Haluszka, O., Engstrom, P., Cheng, J.D., Cohen, S.J., Watson, J.C., Eisenberg, D., McGarrity, E., Freedman, G., Meropol, N.J. Can molecular imaging predict response to preoperative chemoradiation in patients with rectal cancer? A Fox Chase Cancer Center prospective experience. *Semin. Oncol.* **32**:63-67, 2005.
20. Berger, A.C., Farma, J., Scott, W.J., Freedman, G., Weiner, L., Cheng, J.D., Wang, H., Goldberg, M. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J. Clin. Oncol.* **23**:4330-4337, 2005.

21. Konski, A., Feigenberg, S., Chow, E. Palliative radiation therapy. *Semin. Oncol.* **32**:156-164 2005.
22. Konski, A., Sherman, E., Krahn, M., Bremner, K., Beck, J.R, Watkins-Bruner, D., Pilepich, M. Economic analysis of a phase III clinical trial evaluating the addition of total androgen suppression to radiation versus radiation alone for locally advanced prostate cancer (Radiation Therapy Oncology Group protocol 86-10). *Int. J. Radiat. Oncol. Biol. Phys.* **63**:788-794, 2005.
23. Hartsell, W.F, Scott, C.B., Watkins-Bruner, D., et al. *J. Natl. Cancer Inst.* **97**:798-804; 2005.
24. Feigenberg, S.J., Lee, W.R., Desilvio, M.L., et al. *Int. J. Radiat. Oncol. Biol. Phys.* **62**:956-964, 2005.
25. Khor, L.Y., Desilvio, M., Al-Saleem, T., Hammond, M.E., Grignon, D.J., Sause, W., Pilepich, M., Okunieff, P., Sandler, H., Pollack, A., RTOG. MDM2 as a predictor of prostate carcinoma outcome: an analysis of Radiation Therapy Oncology Group protocol 86-10. *Cancer* **104**:962-967, 2005.
26. Movsas, B., Scott, C., Langer, C., Werner-Wasik, M., Nicolaou, N., Komaki, R., Machtay, M., Smith, C., Axelrod, R., Sarna, L., Wasserman, T., Byhardt, R. Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: Radiation Therapy Oncology Group trial 98-01. *J. Clin. Oncol.* **23**:2145-2154, 2005.
27. Chakravarti, A., Winter, K., Wu, C., Kaufman, D., Hammond, E., Parliament, M., Tester, W., Hagan, M., Grignon, D., Heney, N., Pollack, A., Sandler, H., Shipley, W. Expression of the epidermal growth factor receptor and her-2 are predictors of favorable outcome and reduced complete response rates, respectively, in patients with muscle-invasive bladder cancers treated by concurrent radiation and cisplatin-based chemotherapy: a report from the Radiation Therapy Oncology Group. *Int. J. Radiat. Oncol. Biol. Phys.* **62**:309-317, 2005.
28. Komaki, R., Swann, R.S., Ettinger, D.S., Glisson, B.S., Sandler, A.B., Movsas, B., Suh, J., Byhardt, R.W. Phase I study of thoracic radiation dose escalation with concurrent chemotherapy for patients with limited small-cell lung cancer: Report of Radiation Therapy Oncology Group (RTOG) protocol 97-12. *Int. J. Radiat. Oncol. Biol. Phys.* **62**:342-350, 2005.
29. Buyyounouski, M.K., Klump, W.J., Konski, A., Wu, H., Adler, L.P. FDG PET imaging of signet-ring cell adenocarcinoma of the stomach. *Clin. Nucl. Med.* **30**:118-119, 2005.
30. Andrews, S.F, Horwitz, E.M., Feigenberg, S.J., Eisenberg, D.F, Hanlon, A.L., Uzzo, R.G., Pollack, A. Does a delay in external beam radiation therapy after tissue diagnosis affect outcome for men with prostate carcinoma? *Cancer* **104**:299-304, 2005.
31. Hayes, S.B., Pollack, A. Parameters for treatment decisions for salvage radiation therapy. *J. Clin. Oncol.* **23**:8204-8211, 2005.
32. Nguyen, K.H., Hachem, P., Khor, L., Salem, N., Hunt, K.K., Calkins, P.R, Pollack, A. Adenoviral-E2F-1 radiosensitizes p53 wild-type and p53 null human prostate cancer cells. *Int. J. Radiat. Oncol. Biol. Phys.* **63**:238-246, 2005.

<sup>§</sup> Fox Chase researcher

\* Personnel left Fox Chase

<sup>a</sup> E. Sherman: Present address—UPHS, University of Pennsylvania, Philadelphia 19104

<sup>b</sup> B. Movsas: Henry Ford hospital, 2799 W. Grand Boulevard, Detroit, MI 48202

<sup>c</sup> P. Alcantara: c/Aeronave 12, 3B, 28042 Madrid, Spain