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PROSPECTS

Prostate Carcinoma: Opportunities for Translational Research

T.J. Fitzgerald,[1]* Edmund Simon,[2] and Joshua Meyer[3]

[1]Department of Radiation Oncology, Worcester, Massachusetts
[2]Department of Medicine and Cancer Biology, Worcester, Massachusetts
[3]University of Massachusetts Medical School, Worcester, Massachusetts

Abstract Adenocarcinoma of the prostate continues to be a major health concern. Although modern screening techniques have increased the number of men presenting with early stage disease, a significant population of men will present with intermediate or advanced pathological risk factors for recurrence. There are defined limitations in outcome with traditional therapies including surgery, radiation therapy, and hormone manipulation. Patients with intermediate and high-risk factors for treatment failure are candidates for protocols using translational research strategies incorporated into studies currently in development. These strategies may be able to selectively treat expression products of tumor and thus be more selective in the target for treatment. Carefully designed studies using these translational strategies have great potential in improving clinical outcome, tumor kill, and normal tissue tolerance in the care of these patients. J. Cell. Biochem. 91: 433–442, 2004. © 2003 Wiley-Liss, Inc.

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Prostate cancer continues to be a major health issue in the United States. It represents the single most common malignancy and the second most common cause of cancer death in men. In 2001, nearly 200,000 men were diagnosed with prostate cancer with 32,000-recorded deaths from the disease [Aaltomaa et al., 1999; Abdollahi et al., 2003]. Since the introduction of serum prostate specific antigen screening, there has been significant increase in identifying men with more limited stage disease. This has been referred to by many investigators as stage migration associated with PSA screening. With more men identified with early stage disease, there has been a renewed interest in establishing the possible role of chemoprevention of this disease [Aus et al., 1998]. Although PSA screening has been a clear improvement in health care for men, a significant population of men continues to present with disease with intermediate to high-risk outcome probability. These patients represent a spectrum of tumor risk factors and tumor phenotypes including varied grade, stage, and propensity for invasive behavior and metastasis [Aus et al., 1998; Aaltomaa et al., 1999; Brachman et al., 2000; Abdollahi et al., 2003; Ben-Josef, unpublished communications]. Traditional therapies have had success; however, there appear to be limitations in the overall success of surgery, radiation therapy, and hormone management. This group of patients is targeted for the need of improvement in outcome with developments in translational research.

Seminal work performed by Patrick Walsh has provided important information defining the population of patients at risk for recurrence [Ben-Josef, unpublished communications; Catalona et al., 1993; Corn et al., 1995; Bolla et al., 1997; Brachman et al., 2000; Carter and Partin, 2002; Cheing et al., 2003; Chism et al., 2003; Coleman et al., 2003; Cordes and van Beuningen, 2003]. Dr. Walsh and colleagues performed tireless work defining pathologic correlates to outcome in the patient population undergoing definitive surgery including capsule and nerve sparing procedures. Organ defined disease has an approximate 90% chance of undetectable PSA at nearly 20 years after definitive surgery.

*Correspondence to: T.J. FitzGerald, MD, Department of Radiation Oncology, University Campus, UMass Memorial Health Care, 55 Lake Avenue North, Worcester, MA 01655. E-mail: fitzgert@ummhc.org

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Patients with extra-capsular extension of disease, seminal vesicle involvement, and lymph node involvement identified at the time of surgery have an approximate 50%, 25%, and 10% of maintaining an undetectable PSA [Brachman et al., 2000]. Gleason grade likewise is an important indicator of outcome in patients undergoing definitive surgery. Epstein et al. demonstrated in men with extra capsular extension and negative lymph node and seminal vesicle involvement that patients with high-grade disease had a higher rate of progression than low-grade tumors [Catalona et al., 1993]. It is also thought that a positive surgical margin may influence the risk of recurrence in these patients [Epstein, 1990; Dent et al., 2003; Despras et al., 2003]. Investigators and practitioners vary at this time as to how they interpret these variables and provide recommendations for further treatment. Many of these patients are considered candidates for postoperative radiotherapy. Evidence exists that patients treated with postoperative radiotherapy on an adjuvant basis have an improved outcome based on PSA evaluation as opposed to those treated on a postoperative basis secondary to a rising PSA (salvage) [Hurdes et al., 1997]. These patients at risk for relapse based on surgical findings and Gleason grade provide the clinical infrastructure for translational research. Augmenting their care with agents that promote cell cycle sensitivity and synergistic cell kill during radiation management or agents that selectively kill tumor are the target concepts for translational research. The role and synergy of hormone and radiotherapy with additional translational therapies in this group of patients need further investigation.

Over the past 20 years, radiation therapy has made significant improvements in the care provided for patients with adenocarcinoma of the prostate. The development of computer tomography three-dimensional simulators and planning systems has revolutionized tumor and normal tissue target definitions and provided an electronic infrastructure to enhance dose to tumor target and better define and limit target dose to normal tissue including rectum and bladder. The Radiation Therapy Oncology Group (RTOG) has successfully completed a protocol (94-06) permitting only three-dimensional planning and external treatment execution for patients with prostate carcinoma [Folkman, 1990; Epstein et al., 1993a; Marx, 2003]. This protocol has permitted full digital transfer of information and treatment objects for quality assurance review. This process has permitted the development of a uniform treatment database for protocol review and outcome analysis. There have been $>1{,}000$ patients treated on this trial to an isocenter dose of 7,900 cGy with a very limited number of grade 3 toxicities to rectum and bladder reported to date. The significance of this study is that it is re-defining the standard of care for external radiation therapy by treating patients to a high-target dose and defining toxicities to the bladder and rectum with a dose volume histogram (DVH) analysis provided by three-dimensional planning systems. Investigators are now looking to further improve target dose definition and dose gradients to normal tissue with the use of intensity modulation radiation therapy (IMRT) uses three-dimensional target definitions as its infrastructure and applies segmented areas of targets to be treated as an individual area. IMRT provides significant improvement in target dose definition beyond three-dimensional planning and treatment by defining these subsets of treatment areas within treatment targets (beamlets) to better define dose to target [Hanks et al., 1994; Liu et al., 2000; Gupta et al., 2003; Sethi et al., 2003]. These techniques will further improve treatment dose delivery and may permit even higher doses of external radiation therapy to be delivered to tumor with further sparing of normal tissues. The use of image guided objects permit three-dimensional analysis of targets not previously evaluated by radiation oncologists. IMRT is currently permitted for use in many clinical cooperative group trials. Further improvements in patient outcome are anticipated using these techniques. For example, using images housed in this database for protocol 94-06, an extramural investigator was able to enter the database from a remote location and re-contour structures on computer tomography studies in order to establish a radiation dose volume relationship to the penile bulb and determine if that dose volume relationship influenced potency in outcome analysis [Manyak et al., 1999; Marx, 2003]. Studies such as this will further our knowledge of normal tissue tolerance and improve patient care.

Improvements in the development of transrectal ultrasound and magnetic resonance imaging have re-established the role of brachytherapy (implant therapy) in the management

of patients with adenocarcinoma of the prostate. Ultrasound has provided both improved target definition and security that radioactive seeds are being placed into the appropriate location with appropriate spacing and distribution. Anthony D'Amico and others have investigated the role of magnetic resonance imaging in this setting both in a single institution and cooperative group protocol setting [Dalkin et al., 1996; D'Amico et al., 1998, 1999; Dong et al., 2003]. Most institutions use radioactive iodine with perimeter distribution of the seeds to ensure as uniform radiation dose distribution as possible without extended dose to the urethra. Most investigators at this time feel there is no difference in failure free outcome between external radiation therapy and brachytherapy. Some investigators feel there is an improved outcome with brachytherapy with respect to incremental decrease in PSA. Because brachytherapy delivers a high-local dose to target without intentional treatment of lymph node drainage target areas, investigators use brachytherapy in patient populations who have a very low risk of pelvic lymph node involvement and may likewise be considered good candidates for definitive surgical intervention [Greenlee et al., 2001; Khan and Partin, 2003]. There is a current open protocol directed by the American College of Surgeons randomizing patients between surgery and brachytherapy in order to define if there are subgroups of patients better served by one mode of therapy or another. The strategy of combining external radiation therapy with brachytherapy for boost specifically for patients considered to have an intermediate risk for failure is currently being investigated by both the CALGB and the RTOG with rectal injury as one of the target endpoints for the study. The advantage of such a strategy is that external management can deliver X-ray target dose to the prostate and draining lymph node regions, while the implant for boost delivers a high-local dose to the gland itself. Selective institutions for implant therapy have utilized alternative brachytherapy strategies with high-dose rate afterloading devices. These devices deliver brachytherapy at a much higher dose rate as compared to permanent implants. The strategy is to use three-dimensional planning objects to develop the care plan for these patients and alter the dwell time of the high-dose rate source to accommodate for varied geometries. This technique also permits investigators to deliver accelerated X-ray doses to specific areas of target interest. For example if an advanced imaging technique can demonstrate areas of increased tumor burden or an area of radiation resistance (hypoxia, accelerated tumor burden, area of DNA synthesis, etc.), an investigator can increase dose to segmented areas of these targets by altering source dwell time. It is important to acknowledge the fact that the method of cell kill may be quite different for low- and high-dose rate radiotherapy. These forms of therapy require further study to determine if the methodology of cell kill and normal tissue tolerance is similar for these varied applied forms of radiotherapy.

Selection of patients for specific therapies is dependant on physician-patient interaction, patient choice, and co-morbid medical status. Patients with low risk of pelvic lymph node involvement and favorable PSA and Gleason grade are generally candidates for definitive surgery with pelvic lymph node staging or brachytherapy. These patients are also candidates for external radiation therapy if they have significant medical co-morbidities or have undergone a previous trans urethral resection of the prostate. Patients with elevated PSA (>10) or of intermediate to high Gleason grade (>7) are candidates for consideration of hormonal intervention with external radiation therapy. Protocols currently exist attempting to define the role of brachytherapy for these patients.

There remain several outstanding issues with respect to radiation management of adenocarcinoma of the prostate. The area of treatment with external radiation therapy varies between investigators and cooperative group studies. The debate is whether or not there is an advantage to treatment of nodal drainage regions and, if so, which regions to treat. Recent update from an RTOG (94-13) study evaluating patients with intermediate risk of relapse suggests a survival advantage to patients treated with extended fields which included all pelvic lymph nodes with supplemental radiation therapy delivered to the prostate region as a boost [Manyak et al., 1999]. Controversy remains over this point as many investigators and clinical protocols continue to advise treatment to the prostate and seminal vesicles. Those investigators who support treatment to the pelvic lymph nodes also question which specific lymph nodes should be included into the

therapy field. The RTOG study demonstrating a survival advantage treated lymph drainage areas including the common iliac chain (94-13). Other investigators have supported using a nodal drainage field with a superior border at the parallax of the inferior aspect of the sacroiliac joints in order to make certain of coverage to the internal and lower external iliac lymph nodes without intentionally extending therapy target fields to cover the common iliac system [Gaillo et al., 1998]. Investigators are exploring the option of combining external radiotherapy with brachytherapy for boost treatment. The RTOG and the CALGB both have studies underway to evaluate this point using rectal injury as an endpoint to the study. Many investigators feel that this may be the most optimal manner of radiation therapy as it delivers high dose to the prostate target and microscopic target dose to draining lymph node regions. These ideas of combining external therapy and brachytherapy may succeed as it takes advantage of two possibly separate methods of radiation cell kill to the tumor target. This strategy requires further investigation to identify the appropriate X-ray target dose to tumor target and normal tissue. The molecular mechanisms involved in tumor cell kill and the relationship of support cells and integrins in this process are to date poorly understood. An improved understanding of these mechanisms would help delineate specific target areas of developmental drug research to enhance tumor cell kill with radiation therapy as well as enhance normal cell protection.

Advances in imaging research have the potential of improving patient care. Monoclonal antibody imaging with Indium-111 capromab penditide (ProstaScint) has the potential of detecting microscopic areas of tumor [Doyle et al., 1996]. It targets prostate specific membrane antigen, which appears to be more highly expressed in both primary malignant and metastaic tissue. Besides its potential benefit as a staging tool, radiation therapy investigators are beginning to evaluate the role of increasing radiation therapy target dose to areas of ProstaScint activity within prostate tissue with the use of IMRT or increasing X-ray target dose to tumor tissue within the prostate gland with accelerated dose using non-uniform dose distributions with brachytherapy. These imaging techniques thus will hopefully permit radiation oncologists to target segments of tissue within the gland identified as tumor instead of treating the entire gland as the full dose target. Several investigators are evaluating the possible role of using such analogs as therapy for prostate cancer in combination with radiation therapy as either a monoclonal antibody or a radiolabeled treatment program.

The role of androgen ablation is very important in the management of patients with prostate cancer. Always the hallmark of management of patients with metastatic disease, several trials have supported the use of varied forms of androgen ablation with radiation therapy both in an adjuvant and in a neoadjuvant format. These trials have suggested a survival benefit to patients treated in this fashion. See et al. have published preliminary results of a trial evaluating the efficacy of bicalutamide (150 mg daily) as adjuvant therapy after radical prostetectomy or radiation therapy for patients treated for intermediate risk adenocarcinoma of the prostate [Kirschenbaum et al., 2001]. Greater than 8,000 patients were entered into this randomized placebo controlled trial. At 3 years analysis, there was a clear benefit to the group treated with bicalutamide. Further analysis of long-term data is needed to determine if the benefit is long term. Neoadjuvant hormone therapy to date has not demonstrated a survival benefit to patients undergoing radical prostatectomy; however, the RTOG has demonstrated a benefit with patients treated with 4 months of hormone therapy versus radiation alone for patients with intermediate risk factors for failure [Klotz et al., 1986; Lerner et al., 1995; Kreis et al., 1999; Lewis et al., 2002]. The data at 5 years reveal a benefit in both local control and development of distant metastasis. Adjuvant hormone therapy after radiation therapy has also been carefully evaluated by the RTOG in patients with locally advanced disease with intermediate risk factors for failure. Androgen suppression was used indefinitely in the RTOG trial with goserelin [Lewis et al., 2002]. A significant improvement in disease-free survival was seen in the group receiving combined therapy. This concept was further evaluated by the EORTC with goserelin given for 3 years on an adjuvant basis after radiation therapy [Lin et al., 1997]. There was a distinct improvement in survival for patients treated with combined therapy. Duration of hormone therapy was addressed in RTOG 92-02 trial, which compared 28 months

of hormone therapy with 4 months of therapy. There was an improvement in disease-free survival in patients treated with 28 months of therapy with no benefit in overall survival at 5 years [Liu et al., 1999]. These studies suggest that there is a benefit of combining hormone therapies with local therapy, especially for patients with intermediate to high-risk factors for failure. It remains uncertain what the appropriate sequencing of therapies should be.

However, many issues remain unresolved. There are many forms of hormone therapy and the nature of the interactions of hormone therapy and radiation therapy are poorly understood. We do not know if hormone therapy interacts with cells during or after radiation therapy to either inhibit radiation repair or alter cell cycle specificity to promote cells into a sensitive phase for radiation therapy. The interactions may be complex with hormone therapies perhaps altering tumor cell adhesion through integrin function thus decreasing their likelihood for survival [Schulman et al., 2000]. Hormone therapies may promote apoptosis of tumor as their primary function. Hormones may function through many mechanisms, likely cooperative, however possibly competitive with radiation therapy. Understanding these mechanisms is important as the mechanism may influence the timing of therapies and duration of therapies. For example, if hormone functions strictly through a mechanism of apoptosis, the timing of this therapy may not be crucial to outcome. If hormone decreases tumor cell adhesion and promotes radiation sensitivity, the hormone should be given prior or during radiation management. If hormone therapy extends the cell cycle and imposes apoptosis, then hormone therapy should come after radiation therapy. We may also elucidate cooperative roles for more than one hormone intervention in the care of the patient at concurrent or segmented time intervals [Pilepich et al., 1997; Potters et al., 2003]. Hormone therapies are used in many formats for patient care. Many investigators use neoadjuvant hormone therapy prior to brachytherapy to improve the contour of the prostate gland and decrease the size of the gland to improve the geometry for radioactive seed placement. The benefit of survival or molecular influence on radiation sensitivity is unknown, however, this technique is associated with a favorable outcome according to many investigators. Further study on this issue is needed. Studies, such as this, will likely need to be performed through the cooperative group mechanism in order to accrue enough patients to empower the study. Further understanding of the molecular relationships will need to be performed through translational research.

Chemotherapy appears to have activity in prostate carcinoma. Initial series of patients treated with chemotherapy were limited to the group of patients who had developed progressive disease in spite of hormone management. Several recent studies have demonstrated a response with PSA decrease in hormone refractory prostate patients using several agents including estramustine and docetaxel. These series demonstrate a 50% reduction in PSA and a partial response in 5 of 18 patients with measurable disease in one analysis [Michalski et al., 2003]. These data established the possible efficacy of chemotherapy and have invited further evaluation. Increasing doses of estramustine and docetaxel appear to result in an improvement of PSA-defined response. Exisulind is another agent being studied for efficacy in this group of patients. In a series of 96 patients treated with prostatectomy, exisulind had a statistically significant effect in decreasing PSA progression in all subgroups including those considered at high risk for progression [Partin et al., 1995, 1997; Pilepich et al., 1995; Oh and Kantoff, 1998; Goluboff et al., 2001; Oh et al., 2002; Okunieff and Paul, unpublished communications]. These agents are currently being investigated in combination as part of a trial directed by the CALGB. The CALGB has also initiated a trial evaluating chemohormonal therapy delivered in a neo-adjuvant fashion prior to radiotherapy in patients with localized disease at presentation with high-risk features for relapse. Interestingly, chemotherapy may also be of benefit in low doses that are not thought to be directly cytotoxic [Petrylak et al., 1999]. Low-dose taxane therapy appears to influence tumor cell cycle function. Cells treated with taxanes in tissue culture appear to limit G1 arrest and induce cells into the G2M phase, thus more sensitive to radiation therapy. Since prostate cancer cells are thought to have a prolonged cell cycle, inducing G2M phase may be of benefit during radiotherapy. Very preliminary results demonstrate a good response rate in patients with lung carcinoma using this strategy. To date this strategy is untested in patients with prostate carcinoma.

There are many areas of potential translational research that need to be performed. Angiogenesis may play an important role in future therapeutic strategies for patients with adenocarcinoma of the prostate. It has been demonstrated to play an important role in the growth of all solid tumors and metastasis (Purdy and James, unpublished communications; Roach and Mack, unpublished communications). Multiple prostate cancer cell lines produce the pro-angiogenesis agent vascular endothelial growth factor (VEGF), and this production is upregulated by cobalt chloride simulation of hypoxia at both the transcriptional and secretory levels. Interestingly, the upregulation is increasingly more profound in cell lines associated with invasion (PC-3ML > PC-3 > LNCaP).

Cyclooxygenase-2 (COX-2) transcription and expression has also been demonstrated to increase under similar hypoxic conditions in prostate cell lines PC-3 and PC-3ML. Treatment of these cell lines with NS398, a selective COX-2 inhibitor, blocks the cobalt chloride induced upregulation of VEGF mRNA and protein. Additionally, when LNCaP cells are transfected with COX-2 cDNA, these cells also increase the secretion of VEGF protein as compared to non-overexpressing controls. These data support the role of COX-2 as a regulator of VEGF in hypoxic conditions for prostate cancer cell lines. COX-2 expression appears to confer a proliferative advantage for prostate cancer as evidenced by increased cell proliferation in vitro and tumor growth in vivo seen in overexpressing LNCaP cells. Additionally, PC-3 cells treated with NS398 show a decrease in cell viability and increased rates of apoptosis in vitro. A possible role for COX enzymes in decreasing the level of ceramide—a mediator of apoptosis—has been suggested and these data are consistent with this possible role [Southwick et al., 1999; Straub et al., 2001; Ryu et al., 2002; See et al., 2002].

Many of the above findings are supported by in vivo studies. In human prostate glandular epithelium tissue samples, immunostaining for COX-2 is stronger in prostate cancer cells and within prostate intraepithelial neoplasia when compared to controls of men with benign prostatic hypertrophy. These specimens also demonstrate increased immunostaining for nitric oxide synthase-2 (NOS-2), which produces nitric oxide, a known regulator of angiogenesis that has been associated with VEGF function as well [Savarese et al., 2001]. Furthermore, in nude mice innoculated with PC-3 tumor cells, NS398 demonstrates a marked decrease in tumor growth and in the number and quality of new blood vessels formed by tumor. These data suggest a possible role for this form of therapy for patients with prostate carcinoma [Southwick et al., 1999; Straub et al., 2001; Ryu et al., 2002].

PC-3 cells show a similar VEGF upregulation in response to ionizing radiation identical to their response to cobalt chloride [Stamey et al., 1999]. In addition, these cells upregulate fibroblast growth factor (bFGF) under these conditions. Endothelial cells increase their expression of vascular endothelial growth factor receptor 2 (VEGFR2) in response to similar dose of radiation (600 cGy, high-dose rate) [Schulman et al., 2000]. VEGFR2 is considered an important receptor in tumor angiogenesis. Radiation also appears to increase the ability of PC-3 cells to attract endothelial cells in migration studies (radiation doses between 200 cGy and 1,000 cGy, high-dose rate) [Schulman et al., 2000]. This effect can be partially blocked by receptor tyrosine kinase inhibitors. These data imply that sublethal doses of radiation therapy can promote VEGF expression, thus possibly promoting tumor survival. This data is in contrast to the established fact that low-dose radiation therapy (900 cGy) appears to inhibit angiogenesis in animal models. This effect appears to be a complex model mediated through multiple mechanisms. It is important to establish the pathway of these mechanisms as understanding the sequence of events in both expression and inhibition will help define the nature of future treatments and sequence of these therapies. Since it appears that low-dose radiation therapy may upregulate angiogenesis factors, it may be most appropriate to treat these patients prior to the initiation of radiation therapy and during the initial phase of radiation management. The duration of therapy would be dependent on identifying the appropriate radiation dose that would subsequently inhibit the development of these factors. Several agents that block VEGF and PDGF activity are currently in phase I/II analysis [Purdy and James, unpublished communications; Uotila et al., 2001]. Their role with radiation therapy remains to be studied. It is crucial that these issues be studied in a parallel model using

brachytherapy as this form of low-dose rate therapy may have a very different effect on tissue and expression products than traditional external X-rays delivered at a dose rate of 250 cGy per minute.

Vaccine therapies are currently being investigated by several groups directed to both expression antigens and products of prostate cancer cells as well as activated dedritic cells used as an autologous vaccine. The timing of these treatments may be dependent upon the mechanism and timing of expression of these factors.

Epidermal growth factor receptor (EGFR) function may evolve into an important treatment pathway for prostate carcinoma. As identified in prostate carcinoma and with other tumor paradigms, epidermal growth factor receptors appear to be specifically involved with the proliferation and differentiation of epithelial and other cell lines while sharing common signaling pathways with integrins. The receptors are stimulated upon ligand binding and subsequent transducing signals are initiated along a pathway that promotes cell replicaion. An overexpression of EGFR is identified in many carcinomas including prostate carcinoma. In X-ray doses of less than 1,000 cGy, there appears to be a stimulation of this process leading to cell promotion and proliferation [Song et al., 2003]. This is, interestingly, similar to angiogenesis research. Thus in a paradoxical sense, low-dose or non-therapeutic radiation appears to promote with low dose what it ultimately kills with high doses. Radiation also appears to promote cleavage of pro-transforming growth factor alpha in the plasma membrane, thus releasing it into the surrounding media resulting in increased activation. Translational research analysis may be able to identify a selected advantage to treatment of the promotion factors early in the course of radiation management to amplify cell kill [Trachtenberg, 1987; Terris et al., 1993; Song et al., 2003; Thompson et al., 2003].

The issue is likely more complex as there are activation and inhibiting signals promoted by many cellular components that influence the development and death of prostate carcinoma. In an apparently cooperative fashion with integrins, EGFR can be stimulated and activate shared signaling pathways to defend against stress as well as possible anti-tumor therapy. The shared pathway involves Pl3K, which appears to be cytoprotective in all systems analyzed to date [Pound et al., 1997]. Radiation effects on ErbB2 appear to have an anti-apoptotic expression through this and a similar pathway modulated by Bcl-2 [Song et al., 2003]. This appears upregulated in many tumors and in prostate carcinoma, its expression can be correlated to hormone refractory disease and poor outcome. Interestingly, exisulind may function through a similar pathway by modulating Bcl-2, thus creating synergy between this treatment and radiotherapy [Pilepich et al., 1995]. In prostate cancer cell lines, low-dose radiation appears to induce a G2 arrest phase but also increase the rate of apoptosis. This group also demonstrated that administering EGF (inducing EGFR) prior to radiation increased the expression of DNA repair proteins thus increasing radiation resistance. The effect of integrins on this process is not clearly understood, however, it may be very important. One possible area of exploration is to examine the role of alpha-catenin in prostate cancer. E-cadherin is an important transmembrane protein promoting epithelial cell adhesion properties. The adhesion properties appear to convey important cell regulatory maintenance. Decreased expression of this molecule and defined abnormalities in the E-cadherin-catenin complex may lead to disease progression and help define a subgroup of patients with a high risk of relapse [Brachman et al., 2000; Fornaro et al., 2001; Fujita et al., 2002]. A recent study has demonstrated that abnormal alpha-catenin expression is associated with more advanced disease [Fornaro et al., 2001]. A better understanding of this relationship may lead to therapies targeted to promote and regulate cell adhesion. Endostatin and EMD121974 appear to function by inhibiting integrin function, thus decreasing adhesion [Uotila et al., 2001]. If adhesion imparts a level of radiation resistance to tumor through cell cycle or another mechanism, then inhibiting this function with endostain may prove to sensitize tumor to radiation therapy. There also exists paradoxical evidence suggesting that decreasing adhesion promotes resistance to radiation therapy. This requires further investigation. We do not know if radiation therapy promotes or limits integrin function, therefore understanding the synergy between these systems will help us better understand the role that inhibition of integrin function may play with the radiation treatment

of the patient. The effect of radiation therapy on integrin function and its subsequent effect on tumor cells is likewise not fully studied, thus it is not known if hormone/radiation therapy promotes or destabilizes cell adhesion. A better understanding of this relationship would influence the type of translation therapies (promotion or inhibition) and the duration of these therapies.

It appears that treating cells with antibodies blocking EGFR receptor decreases cellular ability to survive stress. Although the mechanism is not well understood, it does appear that inhibition of EGFR increases tumor cell kill to radiation therapy. This may evolve into an important area of research in order to establish both the mechanism of action and subsequent timing of intervention with therapy. Understanding how these expression products appear at low- or high-dose X-ray treatment will teach us if EGFR inhibition therapy with medicines such as ZD6474 (blocks EGF and VEGF receptor) should be integrated with radiation therapy. Another area of interest is to evaluate telomerase activity. Telomerase is a ribonucleoprotein enzyme that adds telomeric repeats onto chromosomal ends using a segment of its own RNA component as a template. This activity appears important in cell immortality. Studies have demonstrated that 90% of cancer tissue in a prostatectomy specimen exhibits telomerase activity and the level of activity correlates with pathologic grade, thus implying that it may prove to be a marker for aggressiveness of disease and a possible target for treatment [Folkman, 1990]. It also appears to correlate with surgical margins of patients with locally advanced disease in a similar fashion to ras activity in head and neck cancer. Depletion of K1N17, a DNA repair gene, appears to increase the radiation sensitivity of several human tumor cell lines [Zelefsky et al., 2003].

Another important area of translational research is in the protection of normal tissues during radiation management. The therapeutic benefit of treatment may be improved if normal tissue function can be further protected, thus perhaps increasing the dose of treatment that can be delivered to the patient. These agents are thought to influence both cells of rapid and limited self-renewal potential. The best-studied chemomodifier of radiation treatment is amifostine. Amifostine is an established agent that appears to be selectively incorporated by normal tissues through active transport and protects normal tissues from damage from radiotherapy and chemoradiotherapy. Amifostine can be delivered in an intravenous and subcutaneous format prior to each radiation treatment and has established benefit in head and neck cancer and lung cancer in limiting mucositis. Investigators are evaluating the role of amifostine in prostate cancer in limiting rectal injury and urinary discomfort. Interestingly, preliminary data applying amifostine to the rectum in a topical format appear to significantly limit acute radiation injury to the rectum with a marked decrease in telangietasia at a 3-month interval post therapy [Yacoub et al., 2003]. Other agents under current investigation include keratinocyte growth factor, nitroxides, MnSOD, antioxidants, and prostaglandin/COX-2 inhibitors. Interestingly, investigators have identified Ginsan, a polysaccharide derived from Panax ginseng, as a radio protector of normal tissue [Ziche et al., 1997].

Therapies for cancer management are about to undergo significant change under the guidance of careful translational research. In prostate carcinoma, traditional therapies such as surgery, radiation therapy, and hormone therapy are likely to continue as the cornerstones of management. However new and exciting therapies will likely mature to be valuable adjuncts in the care of the patient and may likewise redefine the role of traditional management. These newer forms of therapy will likely target tumor angiogenesis (COX-2), nitric oxide expression, cell-to-cell adhesion properties (alpha-catenin and integrin function), cell cycle manipulation (low-dose taxanes) and receptor and signaling pathways (EGFR antibodies and others). Therapies will also be designed to improve normal tissue tolerance to traditional treatment. Further research will help identify the molecular relationships between these new therapies and define how these therapies will interdigitate and be sequenced with traditional management.

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