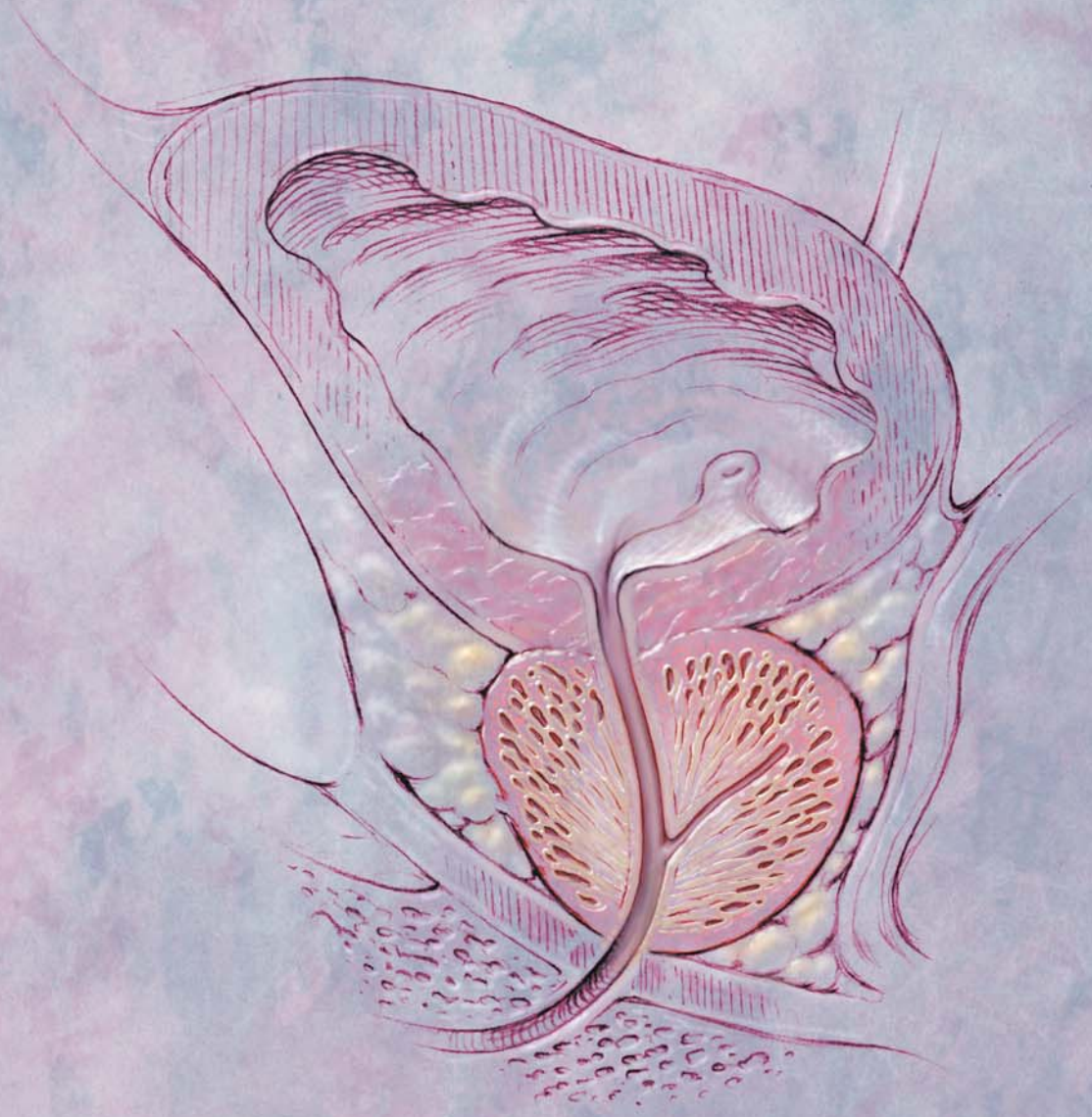
Published by the North Carolina Institute of Medicine and The Duke Endowment

North Carolina MEDICAL JOURNAL

a journal of health policy analysis and debate



Prostate Cancer: Screening, Diagnosis, Treatment, and Follow-Up **Care**

Also in this Issue
Medical Homes for Children with Special Healthcare Needs...
and Implantable Left Ventricular Devices...

www.ncmedicaljournal.com
March/April 2006, 67:2

We've joined forces to care for those close to our hearts.

In North Carolina, there are few goals more important than achieving cardiac health for our citizens.

Today, North Carolinians suffer from heart disease at one of the highest rates in the U.S. One in four experience cardiovascular disease, and it is the cause of 34 percent of all deaths in our state.

That's why East Carolina University and University Health Systems Pitt County Memorial Hospital, along with private practice physicians, are joining forces. Together, we'll offer the best of scientific research and expert clinical medicine for the highest quality patient care experience. Our recent groundbreaking was the first step in expanding both leading-edge facilities to meet this serious national healthcare need.

Working as one, we proudly announce the future of cardiac care, the East Carolina Heart Institute. Under the leadership of Dr. W. Randolph Chitwood, Jr., internationally recognized surgeon and robotic surgery pioneer, our partnership and two facilities will create a world-class cardiovascular destination.

The citizens of North Carolina will be among the first to benefit from our innovations to treat and prevent heart disease. But cardiac patients from around the world will soon appreciate the quality of care delivered by our skilled cardiovascular physicians.

Creating the East Carolina Heart Institute is just one way that we'll work together to care for people close to our hearts. Visit www.eastcarolinaheartinstitute.com.

EAST CAROLINA
HEART INSTITUTE

The Carolinas Center for Medical Excellence. We deliver.

Data driven

Quality improvement focused

Research-based

Patient-centered

After more than 20 years in the case review and quality improvement business primarily in hospitals, CCME is breaking new ground. That's why we have changed our name.

The Carolinas Center for Medical Excellence—CCME—better characterizes our work in quality improvement across the healthcare spectrum. Our logo with the archway represents our long history of improving quality of care while symbolizing our multiple strengths in the varied professional services we provide.

Hospitals. Nursing Homes.
Home Health Agencies. Physician Offices.
These are the people we serve.

A professional staff to help you deliver the right care for every person every time. A long history of quality improvement in healthcare.

CCME delivers.

The Carolinas Center *for* Medical Excellence

Formerly Medical Review of North Carolina, Inc.

100 Regency Forest Drive, Suite 200, Cary, NC 27511
800-682-2650 • www.thecarolinascenter.org

How a team of heart specialists helped Hugh McColl make the best investment of his life.

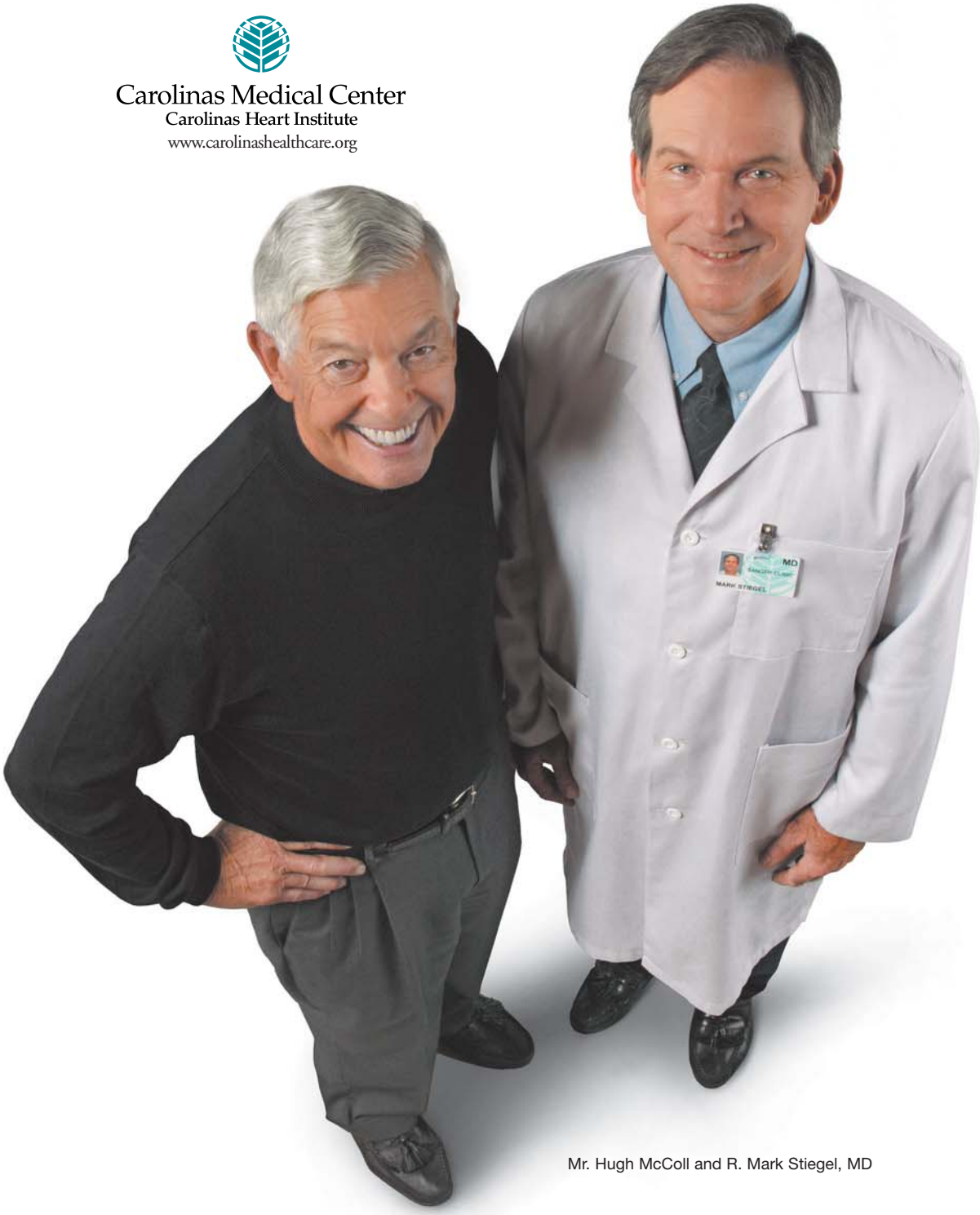
When Hugh McColl, the man who changed American banking, learned he needed heart bypass surgery, he chose the team that has outpaced all others for years. He chose the Carolinas Heart Institute at Carolinas Medical Center and the Sanger Clinic's Dr. Mark Stiegel.

Carolinas Heart Institute has a rich and storied history of groundbreaking innovations; some of the finest medical minds in America, and the latest, most advanced technology available – including the new revolutionary *64 Slice CT Scanner.*

Today, Hugh McColl is enjoying the success of his surgery with his usual zest for life. In fact, he calls his choice of care "one of the best investments I ever made."

We know Mr. McColl could have gone anywhere in the world for cardiac treatment. He chose the region's premier team.

Carolinas Medical Center
Carolinas Heart Institute
www.carolinashealthcare.org



Mr. Hugh McColl and R. Mark Stiegel, MD

North Carolina MEDICAL JOURNAL

Founded by the North Carolina Medical Society in 1849
Published by The North Carolina Institute of Medicine and The Duke Endowment
(ISSN 0029-2559)

The North Carolina Medical Journal (ISSN 0029-2559) is published by The North Carolina Institute of Medicine and The Duke Endowment under the direction of its Editorial Board. Address manuscripts and communications regarding editorial matters, subscription rates, etc., to the Managing Editor at the address below. All advertisements are accepted subject to the approval of the Journal's Editorial Board. The appearance of an advertisement in this publication does not constitute any endorsement of the subject or claims of the advertisement. This publication is listed in *Index Medicus*.

Managing Editor: Kristie Weisner Thompson, 919/401-6599, ext. 21, kristie_weisner@nciom.org. **Business Manager:** Adrienne R. Parker, 919/401-6599, ext. 28, adrienne_parker@nciom.org. **Graphic Design:** Angie Dickinson, angiedesign@tds.net. **Printing:** The Ovid Bell Press, Inc., 1201-05 Bluff St., Fulton, MO 65251, 800/835-8919. **Annual subscription (6 issues):** $40 (plus 7% NC tax = $42.80). Institutional subscriptions: $60 (plus tax = $64.20). Single copies: $5.00 (plus tax = $5.35). Periodicals postage paid at Durham NC 27713 and at additional mailing offices. Postmaster: send address changes to The North Carolina Medical Journal, 5501 Fortunes Ridge Drive, Suite E, Durham, NC 27713.

Co-Sponsors of the Journal are: The Carolinas Center for Medical Excellence, formerly Medical Review of North Carolina / North Carolina Academy of Physician Assistants / North Carolina Association of Pharmacists / North Carolina Dental Society / North Carolina Health Care Facilities Association / North Carolina Hospital Association / North Carolina Medical Society
Members of these organizations receive the Journal free of charge. Additional major funding support comes from **The Duke Endowment**.

Woodcroft Professional Center • 5501 Fortunes Ridge Drive, Suite E • Durham, NC 27713
phone: 919/401-6599 • fax: 919/401-6899 • e-mail: ncmedj@nciom.org
Internet address: http://www.ncmedicaljournal.com

Publishers of the *North Carolina Medical Journal*

The North Carolina Institute of Medicine

In 1983 the North Carolina General Assembly chartered the North Carolina Institute of Medicine as an independent, nonprofit organization to serve as a nonpolitical source of analysis and advice on issues of relevance to the health of North Carolina's population. The Institute is a convenor of persons and organizations with health-relevant expertise, a provider of carefully conducted studies of complex and often controversial health and healthcare issues, and a source of advice regarding available options for problem solution. The principal mode of addressing such issues is through the convening of task forces consisting of some of the state's leading professionals, policy makers and interest group representatives to undertake detailed analyses of the various dimensions of such issues and to identify a range of possible options for addressing them.

Members of the North Carolina Institute of Medicine are appointed for five-year terms by the Governor, and each task force convened by the Institute typically includes at least one-third of its membership from among the appointed members. Topics to be addressed through task force efforts are chosen following requests from the Governor, the General Assembly or agencies of state government. In some cases, topics are selected on the basis of requests from a number of stakeholder organizations across the state where this type of analytical process is considered to have potential value.

health policy
North Carolina Institute of Medicine

The Duke Endowment

The Duke Endowment is a private foundation established in 1924 by industrialist and philanthropist James B. Duke. The Endowment's mission is to serve the people of North Carolina and South Carolina by supporting selected programs of higher education, health care, children's welfare, and spiritual life.

The Duke Endowment

North Carolina MEDICAL JOURNAL
a journal of health policy analysis and debate

March/April 2006, Volume 67, Number 2 **Published by the North Carolina Institute of Medicine and The Duke Endowment**

ARTICLES

POLICY FORUM

Prostate Cancer: Screening, Diagnosis, Treatment, and Follow-Up Care

COMMENTARIES

SPECIAL DATA REPORT

DEPARTMENTS

"The possibility of an American man acquiring prostate cancer during his lifetime is approximately 15%."

Tarheel Footprints in Healthcare

Recognizing unusual and often unsung contributions of individual citizens who have made healthcare for North Carolinians more accessible and of higher quality

Recognizing Ann Probst, CNA, North Carolina's "Nurse Aide of the Year"

Anyone familiar with long-term care knows that the job of being a nursing assistant in a busy nursing home is both hard and demanding. Every facet of a resident's life in a skilled nursing facility is affected by the quality of care and compassion and skill of these direct care workers, who often have responsibility for as many as 20 residents at a time.

Ann Probst, CNA (left), from the Lutheran Home–Albemarle, since 1980, pictured here with one of her residents, Ms. Daisy Curlee

The North Carolina Health Care Facilities Association, the trade association for nursing homes in our state, has recognized the importance of direct care workers in the effort to provide quality health and life care to their residents. For this reason, six years ago the Association began its "Fabulous 50" program to honor ten nursing assistants in each of its five districts each year. An honoree in each district is singled out for special recognization, with one being selected statewide as the "North Carolina Nurse Aide of the Year." This year, the Association has chosen to honor Ann Probst, a 25-year veteran of nursing assistance serving the residents of Lutheran Home–Albemarle.

Many of her colleague CNAs, nurses, and family members joined together in nominating Ann Probst for this distinguished award. She has been described by those who work with her as a "transformational leader" because of the example she sets for others and for the way in which she instills the very highest level of concern for resident welfare in her everyday practice. One of the things for which she has been known is her unfailing commitment to the idea that each long-term care resident is an individual with unique gifts, if only those who serve them day-to-day can find the time and the means of unlocking those qualities of the person that define them as personalities. Her effort to know her patients as individuals have led her to use her own personal resources to decorate resident rooms for the holidays; to make her own special clothing to reflect the seasonal themes at different times of the year; to arrange for certain residents to attend church services in the facility or special crafts activities (and to arrange for their return to their rooms when these activities are over); to remind staff on different shifts to make it possible for certain residents to enjoy a televised sporting event of particular interest, to continue a hobby (e.g., coin collections or sewing), to acquire special apparel (like a jogging suit) when residents are experiencing difficulty dressing; to have activities like coloring books and games on hand for the visiting grandchildren of residents; or to be certain that patients are observed for critical signs of health and function of importance to nursing supervisors, who may not be in a position to make such detailed observations on a daily basis. It has been discovered that she anonymously paid the cable television bill of a resident whose family no longer could afford this luxury because the resident so enjoyed the experience of watching television at certain points in the day.

For Ann Probst, and the 49 other "Fabulous 50" nurse aides who have been honored this year, being a nursing assistant is a life's work offering the opportunity to serve dozens of persons at a point when they need both high quality, skilled nursing services, as well as the personal care of one who is dedicated to assuring a quality life experience when one is most vulnerable. Ann Probst's legacy is assured as both her daughter and her granddaughter have chosen to follow in her very large Tar Heel footsteps, choosing to become CNAs as well. For all these years of dedicated service to the people of this state in such a demanding role, the *North Carolina Medical Journal* is pleased to salute Ms. Ann Probst, CNA.

Medical Homes for Children with Special Healthcare Needs in North Carolina

Savithri Nageswaran, MD, MPH, Marcia S. Roth, MPH, Catherine E. Kluttz-Hile, BSN, MA, and Anita Farel, DrPH

Abstract

Background: *The American Academy of Pediatrics defines a medical home as medical care for children that is accessible, continuous, comprehensive, family-centered, coordinated, and compassionate. North Carolina uses the medical home concept as a model for providing high quality care to children with special healthcare needs (CSHCN). However, until recently, information on medical homes for CSHCN in North Carolina has not been available.*

Methods: *Using North Carolina data from the National Survey of Children with Special Health Care Needs (2000-2002), we describe the characteristics of children having a special healthcare need. We conducted bivariate analysis of socio-demographic factors with medical home and its five components (family-centered care, effective care coordination, personal doctor or nurse, usual source of care, and referrals for specialty care) and multivariate analysis to identify the predictors of having a medical home.*

Results: *Fifty-six percent of CSHCN in North Carolina have a medical home. White CSHCN are 1.7 times more likely to have a medical home compared to non-white CSHCN. CSHCN with no functional limitations are 1.6 times more likely to have a medical home compared to children with some or severe limitations of their functional status.*

Conclusions: *Current, population-based information about CSHCN and their families is essential for assessing needs and evaluating pediatric initiatives at the state level. Disparities among CSHCN due to race and functional status should be considered in organizing services for CSHCN in North Carolina.*

Background

Children with special healthcare needs (CSHCN) are those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional conditions and who also require health and related services of a type or amount beyond that required by children generally.[1] Using this definition, an estimated 9.3 million children in the United States have special healthcare needs, accounting for 13% of all children.[2]

In order to improve the quality of care for CSHCN, the Maternal and Child Health Bureau (MCHB) has adopted the "medical home" concept as a model of care for CSHCN. Increasing the proportion of children with special healthcare needs who have access to a medical home is one of the national health objectives.[3] The American Academy of Pediatrics defines medical home as medical care of infants, children, and adolescents that is accessible, continuous, comprehensive, family-centered, coordinated, compassionate, culturally effective, and delivered or directed by well-trained physicians who provide primary care and help to manage essentially all aspects of pediatric care.[4]

a The federal Maternal and Child Health Block Grant is designed to help states ensure the health of mothers and children, with a special focus on the most vulnerable populations (e.g., those who are hard-to-reach, low-income, children with special healthcare needs, and/or racial and ethnic minority populations).

Savithri Nageswaran, MD, MPH, is an Instructor in the Department of Pediatrics, Wake Forest University School of Medicine. Dr. Nageswaran can be reached at snageswa@wfubmc.edu or Medical Center Blvd, Winston-Salem, NC 27517. Telephone: 336-716-6508.

Marcia S. Roth, MPH, is the Director of Planning and Development in the Department of Maternal and Child Health, University of North Carolina at Chapel Hill, NC.

Catherine E. Kluttz-Hile, BSN, MA, is an Assistant Director of Programming for Health Services in the Division of Mental Health, Developmental Disabilities, and Substance Abuse Services, Department of Health and Human Services.

Anita Farel, DrPH, is a Clinical Professor in the Department of Maternal and Child Health,School of Public Health University of North Carolina at Chapel Hill.

There is wide variation among states in the way that services and systems of care for CSHCN are developed and implemented. Federal support through the MCHB Title V Program[a] provides an important foundation and is further shaped by state appropriations, third-party reimbursement, specific characteristics of delivery systems, and the population of CSHCN within each state. In North Carolina, services for CSHCN are organized through the Specialized Services Unit of the Children and Youth Branch in the Women and Children's Health Section of the Division of Public Health. The Medical Home Initiative for Children with Special Health Care Needs was designed by the Division of Public Health to provide a comprehensive approach to the development of medical homes for children, particularly CSHCN.[5] The Division of Public Health collaborates with the North Carolina Pediatric Society, private pediatric practices, healthcare demonstration projects (e.g., the Community Care Networks), the state Medicaid Program, parent advocacy organizations, (e.g., the Family Support Network of North Carolina, the Exceptional Children's Advocacy Center), medical schools, and specialty clinics linked to tertiary medical centers in planning and implementing programs for CSHCN.

Information on the characteristics of CSHCN and the presence of medical homes among CSHCN in North Carolina is essential for designing and implementing programs tailored to the needs of CSHCN in North Carolina. This information can also serve as a baseline for future evaluation of the state's performance. Until recently, state-level data on CSHCN and on the presence of medical homes were not available. The National Survey of Children with Special Health Care Needs provides an opportunity to obtain state-level prevalence estimates, to describe the needs of this population of children, and to identify areas that need improvement in the systems of care for CSHCN.[6]

The objectives of our study are: (1) to describe the characteristics of CSHCN in North Carolina, (2) to analyze information about the implementation of the medical home and its component parts (family-centered care, effective care coordination, personal doctor or nurse, usual source of care and referrals for specialty care) among CSHCN in North Carolina, and (3) to identify the socio-demographic factors associated with having a medical home presence in this population.

Methods

Data Source

The National Survey of Children with Special Health Care Needs was sponsored by the MCHB and conducted by the National Center for Health Statistics (NCHS) between October 2000 and April 2002. A random-digit-dial sample of households with children younger than 18 years was selected from each of the 50 states and the District of Columbia. The respondent for the survey was the parent or guardian who was most knowledgeable about the child's health. The methodology of the survey has been described elsewhere.[7] All survey data are publicly available at the NCHS website.[8] This study analyzed data about North Carolina's children with special healthcare needs collected by the National Survey. The weighted response rate for North Carolina was 63.1%.[7]

Variable Description

A child was identified as having a special healthcare need if he or she met any one of the five screening criteria listed in Table 1. Of the 5,548 children screened in North Carolina, 884 (14%) were identified as CSHCN. The CSHCN screener is a validated tool used to identify children with special healthcare needs.

The medical home is a composite outcome and a dichotomous variable (yes/no) derived from 12 questions on the survey to capture the five components of the medical home concept—namely, receipt of family-centered care and effective care coordination, presence of a personal doctor or nurse, access to a usual source of care, and absence of problems in obtaining referrals to specialists. The components, family-centered care, effective care coordination, and usual source of care were, in turn, derived from five, three, and two questions, respectively (see Table 2). If a child did not meet all of the five component

Table 1.
Proportion of Children in North Carolina with Special Healthcare Needs Identified through the CSHCN Screener Questionnaire (N = 5,548)

Screening Questionnaire Item*	Proportion of all children (%)
Child needs or uses more medical care, mental health services, or educational services than is usual for most children of the same age because of a medical, behavioral, or health condition that is expected to last 12 months or longer	7
Child needs or uses prescription medication because of a medical, behavioral, or health condition that is expected to last 12 months or longer	11
Child has a limitation in abilities to do the things that most children of the same age can do because of a medical, behavioral, or health condition that is expected to last 12 months or longer	3
Child needs or gets special therapy, such as physical, occupational, or speech therapy because of a medical, behavioral, or health condition that is expected to last 12 months or longer	2
Child has an emotional, developmental, or behavioral problem that is expected to last or has lasted for 12 months or longer for which he or she needs treatment or counseling	3

* Items not mutually exclusive

Table 2.
Criteria Used to Define a Medical Home in the National Survey of Children with Special Health Care Needs[*†]

Presence of a usual source of care
The child has a usual source for sick care
The child has a usual source for preventive care
The child has a personal physician or nurse
Experiences no difficulties in obtaining referrals to specialists when needed
Receives effective care coordination when needed
The child has professional care coordination when needed
Physicians communicate well with each other
Physicians communicate well with other programs
Receives family-centered care
Physicians spend enough time with the child
Physicians listen carefully to the family
Physicians are sensitive to family's values and customs
Physicians provide needed information
Physicians make the family feel like a partner

* Based on respondents' report

† For actual questions, please refer to the Program and Collections Procedure manual of the National Survey of Children with Special Health Care Needs[7]

criteria, then he or she was considered not to have met the criteria for having a medical home. This strategy of deriving the medical home variable was based on the method reported previously.[9,10] The questions from the survey used to derive the medical home variable are supported in the literature.[11]

Age, gender, race, functional status of the child, metropolitan status of residence, income level of the household, mother's education, and adequacy of insurance were the independent, categorical variables of interest. Income level of the household was categorized as income less than 200% of Federal Poverty Guidelines (FPG) and more than or equal to 200% FPG, because, at 200% FPG, all children in North Carolina are either eligible for Medicaid (Health Check) or the State Children's Health Insurance Plan (Health Choice).

Functional status of the child was derived from two questions and categorized into "no limitation of activities due to the child's condition" and "some or severe limitation of activities." Adequacy of insurance was derived from five variables. To be considered to have adequate health insurance, a child needed to have: (a) public or private insurance at the time of the interview, (b) no gaps in insurance coverage in the year prior to the interview, (c) insurance coverage that usually or always meets the child's needs, (d) costs not covered by insurance that are usually or always reasonable, and (e) insurance coverage that usually or always permits the child to see needed providers. If the child did not meet any one of the criteria mentioned above, insurance was considered inadequate.

Statistical Methods

Following univariate analysis, bivariate analyses were conducted to determine the association between each one of the independent variables and having a medical home and its five components. The Pearson chi-square test was used to examine the association between categorical variables. Independent variables that were statistically significant for the presence of a medical home in bivariate analysis were included in multivariate analysis. We used a logistic regression model for multivariate analysis. Some cells in these data had a small number of observations. Since estimates derived from a small number of observations are not valid population estimates, the NCHS recommends using the relative standard error (RSE) to measure an estimate's reliability. Accordingly, if an estimate had an RSE [(standard error/ estimate) x 100] of greater than or equal to 30, then the result was considered inaccurate and, hence, was not used for further analyses. In order to obtain population-level estimates, appropriate survey weights were used in the analysis. Since the study is exploratory, we did not correct for multiple comparison and considered a p value of less than 0.05 to be statistically significant. Stata Intercooled version 8.2 was used for statistical analysis. The Office of Human Research Ethics at the University of North Carolina at Chapel Hill approved this study.

Results

There are an estimated 280,770 children with special healthcare needs in North Carolina, representing 14% of all children less than 18 years of age. The proportion of children meeting the criteria for special healthcare needs is presented in Table 1.

Most of North Carolina's CSHCN are boys (61%), white (71%), and live in a metropolitan area (70%). Only 57% have adequate insurance. Forty percent live in households with incomes less than 200% FPG. Fifty-eight percent of CSHCN have some or severe functional limitations. Fifty-six percent of the mothers of CSHCN have graduated from high school. A majority of CSHCN (81%) were older than five years of age at the time of the survey.

Among CSHCN, 91% have a usual source of care, 86% have a personal doctor or nurse, 78% receive family-centered care, 48% receive effective care coordination, and 81% report no difficulty obtaining referrals. Fifty-six percent of the children have met all five components of the medical home in North Carolina, and an additional 29% have met four of the five components. Of the 29% who met four components of the medical home, more than half lacked family-centered care.

Results of bivariate analysis of the independent variables with a medical home and its five components are presented in Table 3. A higher percentage of white CSHCN (60%) compared to non-white CSHCN (45%) have a medical home (p = 0.007). Access

to a medical home is lower among CSHCN with functional limitations compared to those who do not have functional limitations (51% versus 62%, p = 0.02). While 60% of CSHCN with adequate insurance have a medical home, only 49% of CSHCN without adequate insurance have a medical home (p = 0.02). Age, gender, metropolitan residence, mother's education, and income status were not significantly associated with having a medical home based on bivariate analysis.

Differences were identified in the association of socio-demographic factors and the five components of the medical home (see Table 3). Family-centered care is associated with race, functional status, and adequacy of insurance. CSHCN who are non-white, lack adequate insurance, and have some or severe functional limitations receive family-centered care less often than their counterparts. While 11% of CSHCN with no functional limitations have difficulties obtaining referral to specialists, 24% of those with some or severe limitations have referral problems (p = 0.02). Access to a usual source of care was associated with mother's educational status: CSHCN whose mothers have a high school education or more have greater access to a usual source of care compared to CSHCN whose mothers did not have a high school education (95% versus 86%, p = 0.001). Race and household income were associated with access to a personal doctor/nurse.

Race, functional status, and adequacy of insurance were the

Table 3.
Bivariate Association of the Medical Home and Its Components with Socio-Demographic Factors among CSHCN in North Carolina*

Characteristic	Usual source of care (%)	Personal doctor/ nurse (%)	No referral problem (%)	Effective care coordination (%)	Family-centered care (%)	Medical home (%)
Age, years						
0 to 5	91	84	82	74	76	59
6 to 17	91	87	81	39	70	55
Sex						
Male	90	86	80	51	69	55
Female	92	85	84	40	74	57
Race						
Non-white	89	77‡	81	29	57†	45‡
White	92	89	81	57	76	60
Residence						
Metropolitan	91	85	81	53	70	55
Non-metropolitan	91	88	80	37	74	57
Poverty status, % FPL						
> 200	92	90§	84	50	74	59
< 200	89	81	80	52	69	53
Functional status						
No limitation	90	85	89§	70	82§	62§
Some/severe limitation	91	86	76	42	63	51
Adequacy of insurance						
Adequate	90	85	85	55	77†	60§
Not adequate	92	87	75	36	61	49
Mother's education						
More than high school	95‡	88	83	48	74	58
High school or less	86	82	79	44	68	53

* Population-level estimates. Shaded values have relative standard errors ≥ 30 and are not valid population-level estimates.
"Medical home" present if all five criteria (usual source of care, personal doctor/nurse, no referral problems, effective care coordination and family-centered care) were met.

† P < 0.001

‡ P < 0.01

§ P < 0.05

Data Source: Centers for Disease Control and Prevention, National Center for Health Statistics, State and Local Area Integrated Telephone Survey, National Survey of Children with Special Health Care Needs, 2001.

independent variables used in the logistic regression model to evaluate the association of socio-demographic factors with the presence of a medical home. None of the other variables (age, gender, residence, income status, and mother's education) confounded the relationship of the three independent variables with having a medical home.

The results of the multivariate analysis are presented in Table 4. In North Carolina, white CSHCN are 1.7 times more likely to have a medical home compared to non-white children, adjusted for functional status and adequacy of insurance. Children with no functional status limitation have 1.6 times the odds of having a medical home compared to children who have some or severe functional status limitation. After adjusting for race and functional status, adequacy of insurance was not associated with having a medical home.

Discussion

Fifty-six percent of CSHCN in North Carolina meet the operational definition of having a medical home. Children who are not white and children with functional limitations are significantly less likely to have a medical home compared to their counterparts.

Compared to national data,[10] a higher percentage of CSHCN in North Carolina have a medical home (56% versus 53%), receive family-centered care (71% versus 67%) and have effective care coordination (48% versus40%), and have no difficulty obtaining referrals (81% versus 78%). While the percentage of CSHCN in North Carolina with a usual source of care is similar to national averages, only 86% of CSHCN in North Carolina have a personal physician or nurse compared to 89% nationally. However, these differences in results between North Carolina and national data are small.

Race is an important correlate for not having a medical home in North Carolina. Previous studies have shown racial and ethnic disparities among children with special healthcare needs in access to healthcare, health-services utilization, and impact of a chronic health condition on families of CSHCN.[10,12,13] Our study provides further evidence of racial disparities in access to healthcare among children with special healthcare needs. This current information about racial disparities should be examined further.

Similar to CSHCN across the United States, severity of functional limitations was another independent predictor of not having a medical home. Disparities in healthcare of CSHCN associated with their functional status have been reported by other states.[14,15] Future studies are necessary to understand these variations in functional limitations and the causes for these disparities among children with special needs.

Although adequacy of insurance was associated with having a medical home in the bivariate analysis, the association was not significant after adjusting for functional status and race in a multivariate model. There is substantial evidence to show that being insured positively influences the healthcare experiences of CSHCN.[6,16-18] A significant difference may have emerged if insurance status were dichotomized as uninsured versus insured and the type of insurance as private versus public. Unfortunately, the sample size was too small to evaluate the association of having a medical home with insurance status or type, and we had to use adequacy of insurance as a proxy for insurance status.

The association between poverty and limited access to medical care of CSHCN is well documented in the literature.[6,10,13,17] The impact of having a child with special needs on the family is more pronounced in low-income families.[6,10,18] Although there was not an association between income and having a medical home in our study, it would be premature to conclude that level of income is not associated with access to a medical home in North Carolina. Income status was categorized into less than 200% FPG and greater than or equal to 200% FPG. The resulting smaller sample sizes did not permit analysis of multiple categories of income status in the logistic regression model. In fact, CSHCN from households with incomes less than 100% FPG had lower odds (unadjusted) of access to a medical home compared with those from households with incomes less than 400% FPG in bivariate analysis (data are not presented, but are available from the authors).

Although the results for North Carolina are better than for the nation as a whole (40%),[10] more than half of CSHCN do not receive effective care coordination in North Carolina.

Table 4.
Adjusted Odds Ratios of Socio-Demographic Factors with Medical Homes in a Logistic Regression Model[*] [†]

Characteristic (referent group)	Adjusted odds ratio (95% C.I.)	Standard error	P value
Race (All other races and multiracial)			
Non-Hispanic white	1.7 (1.1,2.7)	0.39	0.02
Adequacy of insurance (Not adequate)			
Adequate	1.5 (0.99,2.2)	0.29	0.06
Functional status (Some/severe limitation)			
No limitation	1.6 (1.1,2.3)	0.32	0.03

* Adjusted for other two variables in the model

† Population-level estimates

Data Source: Centers for Disease Control and Prevention, National Center for Health Statistics, State and Local Area Integrated Telephone Survey, National Survey of Children with Special Health Care Needs, 2001.

The American Academy of Pediatrics recognizes the importance of care coordination in the care of CSHCN and provides recommendations for care coordination for this population.[19] Policy development and program planning for CSHCN should emphasize improving care coordination for CSHCN in North Carolina. Family-centered care is another feature of access to services where North Carolina's performance should be improved. Similar to observations at the national level,[2,10] we found disparities associated with race/ethnicity and functional status of CSHCN in the receipt of family-centered care. It is possible that cultural or language differences accounted for the differences in family-centered care among racial/ethnic groups. The caregivers of CSHCN with functional status limitations report greater problems with referral to specialists. One could speculate that the referral needs of CSHCN with severe functional status limitations are much higher and likely result in problems in obtaining referrals to specialists. The association of functional status with referral problems and family-centered care needs further exploration.

It is important to note that there are differences in the association of socio-demographic factors and the five components of a medical home. For example, mother's education is an important factor in access to a source of care and not important for the other components of a medical home. Individual components of the medical home should be examined separately. The relationship between socio-demographic factors and having a medical home must be understood in order to monitor and evaluate their implementation.

Limitations

Although the National Survey of CSHCN was designed to make it possible to conduct state-level analyses, in-depth analysis could not be performed because the sample size for North Carolina was small. For this reason, specific categories among the socio-demographic factors could not be examined. Another important limitation involves the measure of having a medical home in this study. The National Survey contains information that can be used to measure the medical home concept. However, it does not fully operationalize all of its characteristics. If a different set of items were used to measure having a medical home, the results may be different. Hence, the results of this study can be compared only with other studies that use the same items to measure the medical home concept. This point is important when comparing studies across the United States and studies across different points in time. The lower response rate for the survey could have resulted in non-response bias. Since this study is exploratory in nature, multiple comparisons were made without correction, among socio-demographic factors and the components of the medical home. This could have resulted in a Type I error and in spurious associations. Hence, the associations between socio-demographic factors and the components of the medical home warrant further evaluation. Finally, because of the cross-sectional nature of this study, a causal relationship between the socio-demographic factors and the presence of medical home cannot be established.

Conclusions

Our study provides comprehensive information about the characteristics of CSHCN in North Carolina and the experience of these children and their families with a medical home. This information will be useful for North Carolina Title V needs assessment reports to the MCHB. Children with special healthcare needs belonging to specific minority groups and CSHCN whose conditions cause some or severe limitation of their activities were identified as at-risk for problems accessing a medical home. Disparities in access to a medical home should be considered in setting goals and in planning programs for CSHCN using the medical home model. The data in this study can be used to compare the health access situation for CSHCN in North Carolina with other states and to evaluate state performance in the future.

Each component of the medical home model must continue to be investigated. Since the lack of effective care coordination is the most common problem identified by families of CSHCN in North Carolina, strategies to improve performance in this area should be pursued. While efforts are made to provide certain components of a medical home, such as a usual source of care, there is a need to work toward increasing the effectiveness of care coordination and family-centered care to achieve the *Healthy People 2010* objective of providing a medical home to all CSHCN in North Carolina. **NCMedJ**

Acknowledgement: The authors thank Deborah Porterfield, MD, MPH, Department of Social Medicine, University of North Carolina at Chapel Hill, for her valuable guidance on the project and the National Research Service Award Primary Care Research Fellowship Study Group of University of North Carolina at Chapel Hill for reviewing and providing feedback on the manuscript.

REFERENCES

1 McPherson M, Arango P, Fox H, et al. A new definition of children with special health care needs. Pediatrics 1998;102(1 Pt 1):137-140.[PMID: 9714637]

2 van Dyck PC, Kogan MD, McPherson MG, Weissman GR, Newacheck PW. Prevalence and characteristics of children with special health care needs. Arch Pediatr Adolesc Med 2004;158(9):884-890.[PMID: 15351754]

3 Healthy People 2010. Available at: http://www.healthypeople.gov/Document/word/Volume2/16MICH.doc. Accessed November 2004.

4 American Academy of Pediatrics Policy statement: Organizational principles to guide and define the child health care system and/or improve the health of all children. Pediatrics 2004;113(5 Suppl):1545-1547.[PMID: 15121924]

5 Medical Homes in North Carolina [world wide web]. 10/12/2004. Available at: http://www.medicalhomeinfo.org/resources/state/north_carolina.html. Accessed November 2004.
6 van Dyck PC, McPherson M, Strickland BB, et al. The national survey of children with special health care needs. Ambul Pediatrics 2002;2(1):29-37.[PMID: 11888436]
7 Blumberg SJ, Olson L, Frankel M, et al. Design and operation of the National Survey of Children with Special Health Care Needs, 2001. Vital Health Stat 2003;(41):1-136.[PMID: 12836582]
8 National Survey of Children with Special Health Care Needs. October 25, 2004. Available at: http://www.cdc.gov/nchs/about/major/slaits/cshcn.htm. Accessed November 2004.
9 Progress Toward Implementing Community-Based Systems of Services for Children with Special Health Care Needs: Summary Tables from the National Survey of Children with Special Health Care Needs, 2001. April 2003. Available at: http://www.cdc.gov/nchs/about/major/slaits/Publications_and_Presentations.html. Accessed November 25, 2004.
10 Strickland B, McPherson M, Weissman G, van Dyck P, Huang ZJ, Newacheck P. Access to the medical home: Results of the National Survey of Children with Special Health Care Needs. Pediatrics June;113(5 Suppl):1485-1492.[PMID: 15121916]
11 Bethell CD, Read D, Brockwood K. Using existing population-based data sets to measure the American Academy of Pediatrics definition of medical home for all children and children with special health care needs. Pediatrics May 2004;113(5 Suppl): 1529-1537.[PMID: 15121922]
12 Newacheck PW, Hung YY, Wright KK. Racial and ethnic disparities in access to care for children with special health care needs. Ambul Pediatr 2002;2(4):247-254.[PMID: 12135397]
13 Weller WE, Minkovitz CS, Anderson GF. Utilization of medical and health-related services among school-age children and adolescents with special health care needs (1994 National Health Interview Survey on Disability [NHIS-D] Baseline Data). Pediatrics 2003;112(3 Pt 1):593-603.[PMID: 12949290]
14 Mulvihill BA, Wingate MS, Altarac M, et al. The association of child condition severity with family functioning and relationship with health care providers among children and youth with special health care needs in Alabama. Matern Child Health J 2005;9(2 Suppl):S87-97.[PMID: 15973483]
15 Kane DJ, Zotti ME, Rosenberg D. Factors associated with health care access for Mississippi children with special health care needs. Matern Child Health J 2005;9(2 Suppl):S23-31.[PMID: 15973475]
16 Newacheck PW, McManus M, Fox HB, Hung Y-Y, Halfon N. Access to Health Care for Children With Special Health Care Needs. Pediatrics 2000;105(4):760-766.[PMID: 10742317]
17 Mayer ML, Skinner AC, Slifkin RT. Unmet need for routine and specialty care: data from the National Survey of Children With Special Health Care Needs. Pediatrics 2004;113(2):e109-115.[PMID: 14754979]
18 Newacheck PW, Inkelas M, Kim SE. Health services use and health care expenditures for children with disabilities. Pediatrics 2004;114(1):79-85.[PMID: 15231911]
19 Care coordination in the medical home: integrating health and related systems of care for children with special health care needs. Pediatrics 2005;116(5):1238-1244.[PMID: 16264016]

Implantable Left Ventricular Assist Devices:
New Hope for Patients with End-Stage Heart Failure

Carmelo A. Milano, MD, Andrew J. Lodge, MD, Laura J. Blue, RN, Peter K. Smith, MD, G. Michael Felker, MD, Adrian F. Hernandez, MD, Paul B. Rosenberg, MD, and Joseph G. Rogers, MD

Abstract

Introduction: *Recently, the Food and Drug Administration approved implantable left ventricular assist devices (LVAD) as destination therapy (DT) for end-stage heart failure patients who are ineligible for cardiac transplantation.*

Objective and Study Design: *This is a case series that describes the early results with DT LVAD at Duke University Medical Center (DUMC). An additional objective is to provide general information to a broad group of caregivers on this LVAD therapy, which is a new and developing treatment option.*

Data Source/Collection Methods: *Pretreatment clinical condition and outcomes data were collected retrospectively on this cohort of patients through chart review. Outcomes in our patients are compared to data from prior studies and established databases.*

Principal Findings: *Since approval of this therapy two years ago, 18 patients have been treated with implantable LVAD as DT at DUMC. The primary reason for ineligibility for transplant was advanced age (median age was 66). Nearly all of the patients (89%) were confined to the hospital requiring continuous inotropic infusions or temporary mechanical support (e.g., intra-aortic balloon pump) prior to LVAD. The 30-day survival following LVAD implantation was 94.5%; one-year survival was 60%. Eighty-nine percent of patients were successfully discharged to independent living. Operative mortality is similar to that of other cardiac surgery procedures performed on patients with advanced heart failure, while duration of intensive care stay and hospitalization remain considerably longer.*

Principal Limitations: *The principal limitation of this review is the absence of a control group of patients with end-stage heart failure who received conventional therapies. For this reason, the DT LVAD outcomes are compared to prior studies and database results.*

Conclusion: *Implantable LVAD therapy provides new hope for end-stage heart failure patients who do not qualify for cardiac transplantation.*

Introduction

Heart failure (HF) remains a major public health problem in developed nations. It is estimated that five million individuals in the United States suffer from HF with over 550,000 new cases diagnosed annually.[1] Roughly 100,000 patients have end-stage HF, which is characterized by the presence of symptoms at rest, refractory to standard oral medical therapies.[2] Treatment options for these patients remain limited and include inotropic infusions and cardiac transplantation.[2] Treatment with inotropes is associated with transient improvement in symptoms, but reduced survival. In a study of patients with end-stage HF treated with continuous outpatient inotropic infusions (COSI trial), one-year survival was only 6%.[3] Heart transplant represents an effective treatment, but only about 2,000 transplants are performed annually in this country; this number does not appear to be increasing despite efforts to use marginal donor organs. Thus, while heart transplant provides tremendous rewards for a select group, it remains epidemiologically insignificant.

Given the limited options for these end-stage patients, mechanical pumps have been in development for more than three decades to replace the function of the failing heart. The total artificial heart has been the most publicized mechanical option. Unfortunately, the total artificial heart (TAH), which requires removal of the native organ and provides replacement

Carmelo A. Milano, MD, is an Associate Professor in the Department of Surgery, Duke University Medical Center. Dr. Milano can be reached at milan002@mc.duke.edu or Box 3043, Duke University Medical Center, Durham, NC 27710. Telephone: 919-684-3243.

Andrew J. Lodge, MD, is an Assistant Professor and **Peter K. Smith, MD**, is a Professor in the Department of Surgery, Duke University Medical Center.

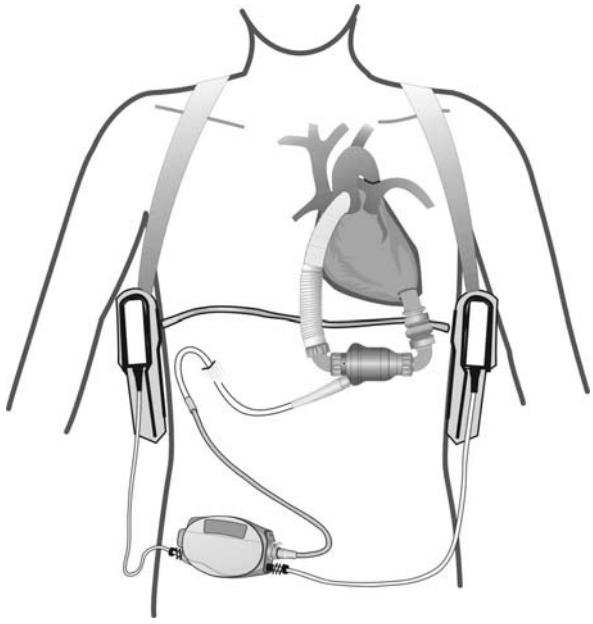
Laura J. Blue, RN, is a Nurse in the Department of Medicine, Duke University Medical Center.

G. Michael Felker, MD, **Adrian F. Hernandez, MD**, and **Paul B. Rosenberg, MD**, are Assistant Professors, and **Joseph G. Rogers, MD**, is an Associate Professor in the Department of Medicine, Duke University Medical Center.

of both the right and left heart, has achieved limited application. Approximately 200 patients have been supported in investigational studies with these devices. There are two currently utilized TAH products: the CardioWest™ device has been Food and Drug Administration (FDA)-approved as a bridge to support patients who have deterioration of native heart function and are awaiting heart transplantation. Patients with this device are tethered to a large external driver that operates the pump, making discharge from the hospital difficult. The other TAH is the AbioCor® device (ABIOMED, Inc.), which recently failed to achieve FDA panel approval.[4] Major limitations for these products have consisted of thromboembolic complication and infection.

A more positive experience has occurred with implantable LVADs. Relative to the TAH, these devices attach more simply to the native heart; the left ventricular apex is cannulated for drainage of blood to the pump, and blood is pumped into an outflow graft, attached to the ascending aorta (see Figure 1). Development and testing of implantable LVADs has been ongoing for several decades. More than 10,000 patients have been supported with LVAD devices predominately as a bridge to transplantation. Extensive experience with patients who have been bridged to transplant suggested that these devices can restore normal hemodynamics even in the setting of biventricular failure. Home discharge and even return to employment has been possible for patients with implantable LVADs.[5] This positive experience led to the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial in which end-stage HF patients who were not candidates for transplantation were randomized to optimal medical management versus implantable LVAD.[6] The Heartmate® I device (Thoratec, Inc.) was utilized exclusively in this trial. Patient's treated with LVADs experienced significant improvement in one- and two-year survival as well as improved quality of life relative to optimal medical management.[6] This trial led to FDA approval of the Heartmate® I as a destination therapy for patients with end-stage HF who fail to meet criteria for transplantation. Destination therapy refers to utilization of these devices as primary and final therapy rather than as a bridge therapy to support patients until transplantation is possible. Subsequently, the Centers for Medicare and Medicaid Services (CMS) have approved designated destination therapy (DT) LVAD centers. Duke University Medical Center has been designated as a CMS-approved DT LVAD center. In this paper we review, our early experience with implantable LVAD as primary treatment for end-stage HF.

Figure 1.
Implantable Ventricular Assist Devices



The Heartmate® II LVAD system is shown. The pump drains from the left ventricle via an apical cannula. Blood is pumped into the ascending aorta via an outflow graft. The Heartmate® II provides an axial flow with an Archimedes screw design. It is valveless and currently being tested as a DT LVAD.

Methods

From July 2003 to July 2005, 32 patients were referred for evaluation for DT LVAD at Duke University Medical Center (DUMC). Fourteen patients were excluded from treatment due to a variety of factors: (1) heart failure was not sufficiently advanced, (2) patient refused LVAD treatment, or (3) patient had inadequate financial resources. From this larger group, a subset of 18 consecutive patients underwent DT LVAD treatment at DUMC. The institutional review board of the Duke University Medical Center approved prospective collection of patient data and outcomes. Outcomes are reported as either early post-operative events occurring within the first 30 days of the LVAD implantation surgery, or late events occurring more than 30 days from the time of implant. Outcomes are reported as means for normally distributed events and medians for skewed distributions; range and standard deviations are provided where appropriate.

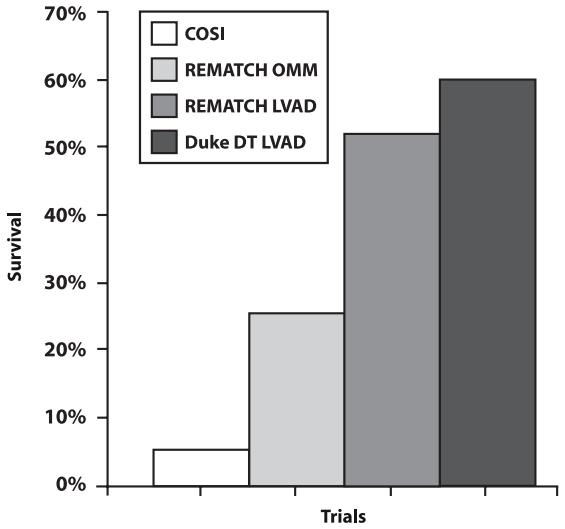
All patients were felt to be poor candidates for cardiac transplantation and did not meet traditional transplant criteria at the time of LVAD implant. Patients were ineligible for transplant due to: advanced age (n = 6), obesity (n = 5), renal insufficiency (n = 2), compliance issues (n = 2), malignancy (n = 2), and pulmonary insufficiency (n = 1). The most common reasons that patients were turned down for transplant were advanced age and obesity.

Results from the Duke DT LVAD cohort are compared to results from established cardiac surgery procedures performed on heart failure patients. Society of Thoracic Surgery data are shown for cardiac transplantation (n = 1,683 cases) and LV aneurysm resection (n = 277 cases) from 2000-2004.[13] In addition, results are compared to published data from the REMATCH and COSI trials (see Figure 2).

Results

Median age for the Duke DT LVAD group was 66 and ranged between 39 and 75; a disproportionate number were

Figure 2.
One-Year Survival for Patients with End-Stage Heart Failure



One year survival is shown for four groups of patients who had end-stage HF. The results of the REMATCH trial are shown for both the optimal medical management (OMM) group as well as the LVAD group. There was significant survival benefit to LVAD treatment compared with OMM in REMATCH. Relative to these results, the survival for 36 end stage HF patients treated by continuous outpatient support with inotropes (COSI trial) is also shown. Finally, the Duke DT LVAD (N = 18 patients) survival is shown.

older than age 65 because this is a common age cut-off for transplant surgery. One third (33%) were females. Fifty percent suffered from non-ischemic cardiomyopathy. All patients had end-stage heart failure with symptoms at rest despite standard medical treatments. Sixty-one percent of the patients were maintained on inotropic infusions preoperatively for clinical and/or hemodynamic evidence of cardiogenic shock. Preoperative mechanical support with intra-aortic balloon pump or temporary LVAD, in addition to inotropic infusions, was present in 28% of the patients (see Table 1). The HeartMate® I pulsatile LVAD was used in 16 of the 18 patients, while two smaller patients received the Heartmate® II axial flow device as part of a prospective FDA-sponsored trial (see Figure 1).

Table 1.
Preoperative Destination LVAD Patient Characteristics (N = 18)

Mean age	66
Sex (% male)	67%
Non-ischemic cardiomyopathy	50%
Mean LV ejection fraction	15% ± 5%
Inotropes	61%
Mechanical support	28%
Mean creatinine	1.5 ± 0.6

Thirty-Day Post-Operative Outcomes (see Table 2). Early death occurred in one of 18 patients (5.5%), which compares favorably to 30-day mortality in the Society of Thoracic Surgeons (STS) national cardiac surgery database of 3% for heart transplant and 7% for left ventricular aneurysm repair.[13] This patient expired due to pulmonary embolism. Most patients had an elevated preoperative creatinine, and many patients experienced elevation in post-operative serum creatinine, but none of the patients progressed to require dialysis during the post-operative period (see Tables 1, 2). There was one peri-operative stroke, which resulted in only a mild motor deficit. The incidence of serious post-operative bleeding that required patients to return to the operating room was 11%. There were no serious mediastinal or pump pocket infections during the early post-operative period. Median duration of hospitalization was 21 days, and median duration of initial intensive care unit (ICU) stay was six days (see Table 2). Discharge to independent living was achieved in 16/18 patients.

Table 2.
Post-Operative (30-day) Outcomes (N = 18)

30-day mortality	5.5%
Median ICU stay	6 days (range 1-76 days)
Median hospital stay	21 days (range 14-111 days)
Major infection	0%
Need for dialysis	0%
Take back for bleeding	11%
Embolic stroke	5.5%

Late Outcomes (see Table 3). The vast majority of patients were discharged to independent living (89%); all of these patients were ambulatory without significant neurological deficits or mental status impairment. None of the patients required permanent placement in a nursing home or chronic care facility. Overall, one-year survival was 60%, which compares favorably to survival rates (52%) for patients receiving an LVAD in the REMATCH trial. In addition to the one post-operative death, there have been a total of five additional deaths in this group. The causes of these late deaths were progression of malignancy (1), intracranial hemorrhage (2), sudden device failure (1), and overwhelming LVAD infection (1). One of the two intracranial hemorrhage deaths occurred in a patient with severe hypertension and was not thought to be attributable to LVAD therapy. Both episodes of intracranial hemorrhage occurred in patients anticoagulated with Coumadin® (one for atrial fibrillation and the other for deep venous thrombosis). Notably, the post-operative protocol for the HeartMate® I device, which was utilized in the majority of these cases, is for aspirin alone. Readmission during the first year after device implantation was 50%. Late embolic stroke occurred in two patients and neither experienced a persistent or disabling deficit. One of these embolic strokes occurred in the setting of LVAD endocarditis; this patient represented the only major LVAD infection in our cohort. A need for device replacement

Table 3.
Late Outcomes (N = 18)

Discharged to independent living	89%
Readmission	50%
Overall embolic stroke	16.5%
Major device infection	5.5%
Device replacement	16.5%
One-year survival	60%

occurred in three late survivors; two of the three replacement procedures were accomplished successfully. Reevaluation for transplantation occurred in four patients with two of these being accepted for transplant listing and ultimately receiving transplants. One patient achieved significant weight loss during LVAD support, enabling transplantation; the other patient maintained smoking cessation, allowing for transplantation.

Discussion

The preoperative status of this DT LVAD group reflects end-stage heart failure with the majority of patients requiring inotropic support or even some form of mechanical support. Most commonly pre-LVAD mechanical support consisted of intra-aortic balloon pump in patients with ischemic cardiomyopathy. Some degree of end-organ compromise existed in this group manifested by elevated serum creatinine. Despite the compromised preoperative status, post-operative survival (30-day) compares favorably to that of more conventional cardiac surgery, which is performed in HF patients. The 30-day Duke DT LVAD survival was slightly better than that reported for LV aneurysm repair, a commonly performed procedure in HF patients. The Duke DT LVAD 30-day survival is slightly less than cardiac transplant survival.

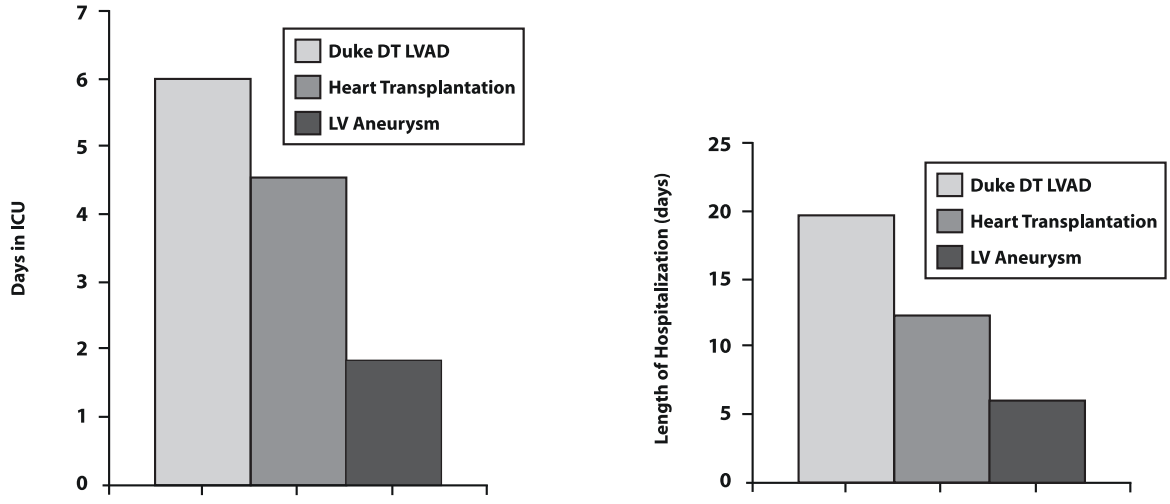
The encouraging 30-day survival rate in this population reflects increased experience with LVAD patients and perhaps improved perioperative strategies to control bleeding and right heart dysfunction.[5] Only 11% of patients returned to the operating room for bleeding, and none of the patients required mechanical support for right heart failure. All 18 patients were supported with inhaled nitric oxide and milrinone during the immediate post-operative period to prevent significant right ventricle dysfunction.

Post-operative length of hospital stay (21 days) and ICU stay (six days) for the Duke DT LVAD cohort remain high and represent an important area for future improvement. Relative to other cardiac procedures performed on HF patients, length of ICU stay and total hospitalization are markedly increased for DT LVAD (see Figure 3). These prolonged stays are important relative to patient quality of life and the economic feasibility of this therapy. The longer stays, in part, reflect the newer technology of LVADs. Furthermore, recovery of nutritional status, restoration of skeletal muscle function, and management of depression and psychological issues are additional factors inherent to this very sick cohort of patients, which prolong the post-operative hospital stay. Anticipation of these problems and a systematic treatment strategy may yield improved results.

Length of ICU stay and duration of hospitalization for surgical procedures on advanced HF patients.

The majority of patients in this series have now survived beyond the first year. Comparison of the Duke DT LVAD group to the REMATCH LVAD group suggests a trend toward improved outcomes at one year.[6] Indeed, the post-approval DT

Figure 3.
Length of ICU Stay/Hospitalization for Surgical Procedures on Advanced HF Patients



The ICU length of stay (in days) during post-operative recovery is shown for the Duke DT LVAD group (N = 18) relative to ICU length of stay for cardiac transplant and left ventricular aneurysm repair (STS national cardiac surgery database 2001-2004). Median values are shown. The total length of post-operative stay (in days) is shown for the Duke DT LVAD group (N = 18) relative to that for cardiac transplantation and left ventricular aneurysm repair (STS national cardiac surgery database 2001-2004). Median values are shown.

LVAD practice at large volume centers has shown trends toward improved one-year survival relative to REMATCH LVAD.[7,9] Relative to groups of patients with end-stage HF, who have been managed solely with infusions of inotropes, survival at one year is markedly improved with DT LVAD treatment. In fact, relative to the COSI trial, the one-year survival for the Duke DT LVAD group is an order of magnitude better (6% versus 60%) (see Figure 2). These results argue strongly that inotrope-dependent HF patients who are not eligible for transplant should be offered the option of DT LVAD.

Embolic stroke historically has represented an important limitation to mechanical heart support, but in this small series of patients, only three patients suffered documented embolic stroke. None of these events led to significant permanent deficits. These three patients remained ambulatory, did not require nursing home placement, and maintained an independent life style. One of these events occurred in a patient who also suffered LVAD endocarditis and, ultimately, died from sepsis. This favorable rate of embolic stroke is probably device-specific and reflects the low thromboembolic risk for the HeartMate® I device, which was used in the majority of cases. The HeartMate® I features a textured blood contacting surface, which allows for "neointimal deposition" and low thromboembolic rates. Most patients were maintained on aspirin as the only form of anticoagulation.

Three out of the 16 patients treated with the HeartMate® I device experienced major device wear with one patient experiencing rapid hemodynamic deterioration and death. Fortunately, device replacement has been successful at our center. Multiple modifications have been made to the HeartMate® I design to reduce valve and bearing wear and improve durability.[8] Furthermore, current destination LVAD trials including the RELIANT (Randomized Evaluation of Novacor LVAS In A Non-Transplant population) trial and the HeartMate® II trial hope to document greater durability with newer pump designs (see Figure 1).

This small series also illustrates how DT LVAD treatment may, in certain patients, enable reconsideration for transplantation. Of the 18 patients implanted, four were re-evaluated for transplant. Two patients were deemed suitable for transplant listing: one experienced substantial weight loss and achieved a specified weight goal, while the other patient achieved sustained abstinence from smoking. Many of the criteria for transplant listing represent variables that may change over time. Therefore, it is expected that some DT LVAD patients may become eligible for transplant listing after a period of extended support. Another example of this scenario is the group of patients who may have severely elevated pulmonary vascular resistance associated with advanced heart failure. Traditionally, these patients are ineligible for transplant because of the risks of right heart failure post-transplantation. Management of these patients with chronic LVAD support may restore more normal pulmonary vascular resistance enabling re-consideration for transplant.

An important limitation to this report is that it is a case series without a formal control group. Furthermore, while a variety of outcomes are reported, quantitative measures of quality of life were not performed for the Duke DT LVAD cohort. Lastly, the current cost of an implantable LVAD is approximately $70,000. Therefore, cost is a limiting factor. This increased cost may be reduced as additional types of LVADs achieve FDA approval.

In summary, implantable LVAD treatment is now a viable option for patients with end-stage HF, who do not qualify for cardiac transplantation. The appropriate population for LVAD therapy includes patients with recurrent decompensation despite optimal medical therapy. Patients who require continuous infusion of inotropic agents have very limited survival and should be offered DT LVAD. The REMATCH trial demonstrated that implantable LVAD treatment offers both a survival and a quality of life advantage for these end-stage HF patients.[6] Operative mortality for the Duke DT LVAD cohort compares favorably to that of other surgical procedures performed for advanced HF. Furthermore, trends are toward improved long-term outcomes, and newer LVAD devices, which offer greater durability (see Figure 1), are now being tested. **NCMedJ**

REFERENCES

1 Heart Disease and Stroke Statistics—2005 Update. American Heart Association. Dallas, TX. 2004.

2 Hunt SA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration with the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. Circulation 2001;104:2996-3007.

3 Hershberger RE, Nauman D, Walker TL, Dutton D, Burgess D. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory end-stage heart failure. J Card Fail 2003;9:180-187.

4 Goldfarb ZA. FDA Panel Weighs Artificial-Heart Implants. Wall Street Journal (Eastern Edition) June 17, 2005, pg. B1.

5 Morgan JA, John R, Rao V, et al. Bridging to transplant with the HeartMate left ventricular assist device: The Columbia Presbyterian 12-year experience. J Thorac Cardiovasc Surg 2004;127:1309-1316.

6 Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001;345:1435-1443.

7 Park SJ, Tector A, Piccioni W, et al. Left ventricular assist devices as destination therapy: A new look at survival. J Thorac Cardiovasc Surg 2005;129:9-17.

8 Dowling RD, Park SJ, Pagani FD, et al. HeartMate VE LVAS design enhancements and its impact on device reliability. Eur J Cardiothorac Surg 2004;25:958-963.

9 Long JW, Kfoury AG, Slaughter MS, et al. Long-term Destination Therapy with the HeartMate XVE Left Ventricular Assist Device:Improved Outcomes Since the REMATCH Study. Congestive Heart Failure 2005;11:133-138.

10 Dew MA, Kormos RL, Winowich S, et al. Quality of life outcomes after heart transplantation in individuals bridged to transplant with ventricular assist devices. J Heart Lung Transplant 2001;20:1199-212.

11 Grady KL, Meyer PM, Dressler D, et al. Change in quality of life from after left ventricular assist device implantation to after heart transplantation. J Heart Lung Transplant. 2003;22:1254-1267.

12 Stevenson LW, Miller LW, Desvigne-Nickens P, et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: A subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). Circulation 2004;110:975-981.

13 Unpublished data from the Society of Thoracic Surgeons National Cardiac Database. Available at: www.sts.org/sections/stsnationaldatabase/. Accessed March 2006.

The Price of Progress:
Destination Left Ventricular Assist Device Therapy for Terminal Heart Failure

Craig H. Selzman, MD, and Jonathan Oberlander, PhD

Heart failure (HF) is a growing epidemic in the United States. Nearly five million patients suffer from this disease, with 400,000-600,000 new cases identified each year. Within this population exists a subset of individuals, estimated between 50,000-150,000, who has a severe form of HF. These patients in New York Heart Association III/IV or class D[a] heart failure are symptomatic despite excellent medical therapy, require frequent hospitalizations, and carry a mortality rate that rivals metastatic malignancies.[1] Although heart transplant remains a viable option for these desperately ill patients, the availability of donor organs limits our use of this therapy to roughly 2,000 each year. Mechanical circulatory devices—ranging from intra-aortic balloon pumps to the total artificial heart—have been utilized to help many of these patients. Over the last decade, widespread use of left ventricular assist devices (LVAD) has significantly impacted the natural history of end-stage HF. Three conceptual paradigms exist for the use of LVADs: bridging a patient until heart function recovers, bridging until a suitable organ for transplantation is available, and implantation as end-of-life therapy in lieu of transplantation—often referred to as Destination Therapy (DT).

As observed in the seminal Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, which randomized class IV HF patients who were ineligible for heart transplantation to best medical therapy versus LVAD implantation, this disease is aggressive.[2] Compared to optimal medical managements, patients receiving LVADs had an increased one-year (52% versus 26%) and two-year (28% versus 8%) survival rate, as well as an improved quality of life.[2] In late 2003, the Centers for Medicare and Medicaid Services designated more than 50 centers nationwide as implant DT centers. Importantly, for the readers of the *North Carolina Medical Journal*, only two centers in North Carolina, South Carolina, Georgia, southern Virginia, and eastern Tennessee have been given this designation: Duke University Medical Center and the University of North Carolina at Chapel Hill.

In this issue of the *North Carolina Medical Journal*, the HF surgeons and cardiologists from Duke University Medical Center present their early series of patients over the last two years who have received LVADs for destination therapy.[3] Dr. Milano and his team should be commended for their impressive results in this challenging and severely ill group of patients. Eighteen patients deemed ineligible for heart transplant (secondary to age, obesity, renal failure, malignancy, compliance issues, or respiratory insufficiency) with end-stage HF (61% on intravenous inotropes and 28% with intraaortic balloon pumps) received the Heartmate® LVAD. Compared to the REMATCH cohort, the Duke investigators had lower operative mortality, lower stroke rate (well below the nearly 40% neurologic event rate noted in REMATCH), less perioperative bleeding, and preserved right ventricular function. Their infection rate was also markedly lower than the REMATCH group. These technical proficiencies translated to relatively low intensive care unit and hospital length of stays. At one year, 60% patients were alive with the majority living independently; again, better than the REMATCH group.

Others have reported post-REMATCH improved outcomes with DT.[4] Although the reported results are indeed admirable, the technology with pump refinement as well as new, innovative, and smaller axial flow pumps will likely make short- and long-term results for LVAD even better. Unfortunately, these therapies come with great cost. The authors spend little time discussing the economic and health policy issues intrinsic to such expensive device therapy. Although they mention the current cost of the

a Heart failure is frequently classified by the severity of symptoms. The New York Heart Association (NYHA) classified heart failure into Class I, II, III or IV. Classes III and IV are moderate and severe, respectively. The ACC/AHA have created guidelines that complement the NYHA classification.

Craig H. Selzman, MD, is an Assistant Professor in the Division of Cardiothoracic Surgery at the University of North Carolina at Chapel Hill. He can be reached at selzman@med.unc.edu or 3040 Burnett Womack, CB #7065, Chapel Hill, NC 27599. Telephone: 919-966-3381.

Jonathan B. Oberlander, PhD, is an Associate Professor in the Department of Social Medicine, at the University of North Carolina at Chapel Hill. He can be reached at jonathan_oberlander@med.unc.edu or CB# 7240 Chapel Hill, NC 27599. Telephone: 919-843-8269.

LVAD at $70,000, that only buys the actual device at the time of surgery. For this particular device, nearly $35,000 is needed to purchase components to allow their discharge from the hospital. In addition, hospital and intensive care stays are typically quite high for these patients, such that total implant costs are typically more than $200,000.

Consequently, all hospitals offering LVAD therapy as destination therapy, including Duke and UNC, as well as public and private insurers, must confront a host of ethical and economic dilemmas as use of such devices becomes more widespread. Is this a just and efficient use of medical care resources? Who should have priority to receive such treatments? Do the benefits of LVADs as DT justify their high costs at a time when healthcare inflation is pricing millions of Americans out of the health insurance market? How much money should cash-strapped state Medicaid programs spend on this technology given other competing demands? And what are the implications for a Medicare program, which already faces substantial fiscal pressures in coming years as the baby boomers retire?

These questions will not be easily resolved. Preliminary assessments of LVAD's cost effectiveness have not been favorable.[5] Clear assessment of cost-effectiveness ratios are difficult to calculate, ranging from $37,000 per quality-adjusted life year (QALY)[6] to $802,700/QALY.[7] These costs must be weighed in the context of other valuable therapies, including cholesterol testing ($330/QALY) and home hemodialysis ($25,000/QALY). Yet, given the scarcity of available transplants, the life-saving difference they make for some HF patients, and the prior contribution of medical technologies to improving cardiovascular health outcomes,[8] LVAD's promise cannot be easily dismissed. This is a rapidly changing area of medicine, and as pump technology evolves, so too will calculations of costs and benefits. That is, the cost effectiveness of LVADs is likely to improve with further technological developments and clinical experience. Conversely, even if LVAD costs decline, total spending on this technology will rise considerably if it is utilized more widely and indications broaden. Studies such as those reported in this issue of the *North Carolina Medical Journal* indeed show both the feasibility and utility of LVAD therapy as end-of-life therapy for HF patients. As LVAD therapy continues to evolve, attention to clinical effectiveness should also be accompanied by awareness of the compelling ethical and economic implications raised by widespread implementation of this innovative therapy. **NCMedJ**

REFERENCES

1 Jessup M, Brozena S. Heart failure. N Engl J Med 2003; 48:2007-2018.

2 Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001;345:1435-1443.

3 Milano CA, Lodge AJ, Blue LJ, et al. Implantable left ventricular assist devices: New hope for patients with end-stage heart failure. NC Med J 2006;67(2):110-114.

4 Park SJ, Tector A, Piccioni W, et al. Left ventricular assist devices as destination therapy: A new look at survival. J Thorac Cardiovasc Surg 2005;129:9-17.

5 AJ Clegg, et al. The Clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: A systematic review and economic evaluation. Health Technology Assessment 2005 November;9(45). Available at: http://www.ncchta.org/fullmono/mon945.pdf. Accessed April 4, 2006.

6 Moskowitz AJ, Rose EA, Gelijns AC. The cost of long-term LVAD implantation. Ann Thorac Surg 2001;71:S195-198.

7 Technology evaluation center. Special report: Cost effectiveness of left-ventricular assist devices as destination therapy for end-stage heart failure. Blue Cross and Blue Shield Association, 2002;17:1-37. Available at: http://www.bcbs.com/tec/vol17/17_19.pdf. Accessed April 4, 2006.

8 Cutler DM. Your Money or Your Life: Strong Medicine for America's Health Care System. Oxford University Press, 2004.

Call for Papers

John W. Williams, Jr., MD, MHS
Scientific Editor, *North Carolina Medical Journal*

North Carolina is blessed with some of the finest medical research institutions in the world. The work of the medical scientists that labor in our research facilities becomes complete (in many ways) and public when it is published in peer-reviewed journals.

While medical researchers in North Carolina have many journals to which they can submit their manuscripts, we want them to consider keeping their work here at home. To be more specific, we invite the authors of our state to submit their papers to the *North Carolina Medical Journal*.

The Journal seeks papers that convey the results of original research. We are especially interested in publishing research papers that have relevance to the health of the people of our state.

An editor reviews all papers received and those of sufficient quality are peer-reviewed. As with any journal of merit, only papers of high quality will be published. Papers printed in the Journal are indexed in the National Library of Medicine's MEDLINE public database.

We generally accept two types of manuscripts for review: (1) original clinical or health services research contributions and (2) systematic reviews (both regardless of specific topic).

The *North Carolina Medical Journal* is published six times a year. It is distributed free of charge to the members of the North Carolina Medical Society, the North Carolina Hospital Association, the North Carolina College of Internal Medicine, the North Carolina Academy of Physician Assistants, the North Carolina Board of Pharmacy, the North Carolina Association of Pharmacists, the North Carolina Division of Public Health, the North Carolina Association of Health Plans, and the Medical Review of North Carolina. The Journal is available by subscription to others.

For guidance on manuscript preparation, authors should consult the "Author Guidelines," which can be found at www.ncmedicaljournal.com.

North Carolina MEDICAL JOURNAL

Instructions for Authors

Unsolicited manuscripts containing original material are accepted for consideration if neither the article nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

All unsolicited manuscripts submitted for peer-review must contain a brief structured abstract including the following (when relevant): Objective; Study Design; Data Source(s)/Study Setting; Data Collection Methods; Intervention; Principal Findings; Limitations; Conclusions; Relevance. Papers submitted without a structured abstract may be considered incomplete and returned to the author.

Submit a cover letter and the article (via e-mail attachment) containing the double-spaced text, preferably in Microsoft Word. The letter should indicate that the article is not under consideration for publication elsewhere and has not previously been published in any form.

For more information visit our web site: http://www.ncmedicaljournal.com/guideline.shtml

North Carolina Medical Journal
5501 Fortunes Ridge Drive, Suite E
Durham, NC 27713
919/401-6599 ext. 21
919/401-6899 fax
ncmedj@nciom.org

North Carolina MEDICAL JOURNAL

POLICY FORUM

Prostate Cancer: Screening, Diagnosis, Treatment, and Follow-Up Care

"...some North Carolina counties have the highest incidence of and death from prostate cancer in the world, irrespective of race."

COMMENTARIES

INTRODUCTION

Policy Forum:
Prostate Cancer: Screening, Diagnosis, Treatment, and Follow-Up Care

In this issue of the *North Carolina Medical Journal*, we focus on one of the most common cancers among men in our nation—a cancer for which there are excellent technologies for early detection and definitive diagnosis, as well as several options for treatment. It is a disease where North Carolina's adult male population seems to exhibit an incidence greater than for the nation as a whole, with African American men being diagnosed with the disease more frequently than whites. Similar findings have been observed with regard to mortality from prostate cancer as well, with dramatic disparities between United States men and North Carolina men, as well as between African American and white men. Such data raise questions about disparities in access to (or participation in) proper screening for the disease, and also about the accessibility of treatment options and possible biological differences among racial groups in susceptibility to the disease itself.

Prostate cancer is a condition for which there should be fairly low mortality if screening and definitive diagnosis occur early, when the disease is localized to the prostate. Yet, it remains the second leading cancer-related cause of death among men in this country. Educational campaigns about this disease, the availability of both screening and treatment facilities, and efforts to dispel the widespread fear of the consequences of treatment (such as incontinence and/or sexual dysfunction) have not had the desired effect.

In this issue of the Journal, Dr. Culley Carson, Chief of the Division of Urology at the University of North Carolina (UNC) School of Medicine, has written an Issue Brief summarizing the overall situation with regard to the screening for and detection, diagnosis, and treatment of prostate cancer. Dr. Carson's overview is followed by North Carolina Senator David Hoyle's personal reflections on being diagnosed and treated for prostate cancer. Those who have gone through the various steps toward surgery will find familiarity in his commentary. These two papers provide both a contemporary overview of the medical science and available treatments for this condition, as well as an appreciation for how the disease can affect an individual faced with this diagnosis.

We have included commentaries by a number of experts from North Carolina and elsewhere dealing with the diagnosis and treatment, as well as the epidemiology, of this disease. Drs. Gaston and Pruthi of UNC offer a detailed discussion of the disparities among white and African American men in the experience of prostate cancer, its natural progression, and response to treatment. Similar data are reported in a succinct way by Dr. Deborah Porterfield of the North Carolina Division of Public Health in our regular "Running the Numbers" section.

Drs. Paul Maroni and David Crawford of the University of Colorado provide a detailed discussion of contemporary methods and programs for screening adult men for this disease. We invited Dr. Michael Weinstein of Director of WakeMed's Department of Clinical

Laboratories to discuss how the clinical pathologist deals with the diagnosis of prostate cancer, as well as new technologies for the assessment of laboratory specimens in reaching a definitive clinical diagnosis. Dr. Eric Wallen from the UNC Department of Surgery describes contemporary surgical approaches to the treatment of prostate cancer. Dr. Scott Sailer from Wake Radiology Associates describes current approaches from the perspective of radiation oncology. Dr. William Berry from the Cancer Centers of North Carolina provides a detailed description of endocrine and chemotherapeutic interventional options and their appropriateness for the treatment of this disease.

Following this rather comprehensive array of clinical commentaries, we are fortunate that Drs. Rachael DiSantostefano and John Lavelle of UNC-Chapel Hill have been willing to discuss the economic aspects of prostate cancer, including the implications of policies related to screening, diagnosis, and treatment.

We are grateful to our colleagues for summarizing the latest in available technologies for screening, diagnosis, treatment, and after-care and for making this information available to our extensive readership. We know there are controversial aspects to some prostate cancer approaches and unknown implications of some recently developed therapies, but this is one area of contemporary medical science and practice where considerable progress has been made. It is our view that understanding this forward movement cannot take place without an appreciation of the many clinical disciplines involved in both the diagnosis and the treatment of this disease.

As always, we welcome the comments and observations of our readers on these and other contributions to the Journal.

Gordon H. DeFriese, PhD
Editor-in-Chief

Carcinoma of the Prostate:
Overview of the Most Common Malignancy in Men

Culley C. Carson III, MD

In the United States and North Carolina carcinoma of the prostate is the most common non-cutaneous malignant process and second most common cause of cancer death among United States men. Since carcinoma of the prostate strikes middle-aged and elderly men and usually has a prolonged progression, the controversy regarding the health effects, treatment, survival, and, most importantly, screening continues throughout the medical literature. Because of this prolonged course and the difficulty with identifying the most indolent tumors, it has been widely suggested that prostate cancer is over diagnosed, as many men may live with prostate cancer with no effect on either their quality of life or ultimate longevity.

More than 230,000 men are diagnosed with prostate cancer in the United States annually. Of these, more than 30,000 die of their disease. Mortality from prostate cancer is, therefore, second only to lung cancer for men in the United States.[1] The possibility of an American man acquiring prostate cancer during his lifetime is approximately 15%. Of great importance, however, is the fall in prostate cancer mortality witnessed since 1994. Similarly, the incidence of prostate cancer in all populations has begun to decline, with the initial decline beginning in 1993. This decline is observed in both white and black patients.[1] While the etiology of carcinoma of the prostate remains elusive, some associated risk factors have been identified.

Risk Factors

Genetic influences may determine the risk of carcinoma of the prostate in some men. Indeed men with first-degree male relatives with prostate cancer have more than a two-fold increase in their incidence of prostate cancer, and men with two or three first-degree relatives with carcinoma of the prostate may have as high as a five-to-ten fold increased risk. Approximately 10-12% of prostate cancer cases are genetically influenced, and these most often manifest as prostate cancer in patients under age 60. This genetic increase is most marked in African American men. The highest risk for prostate cancer for African American men is seen in eastern North Carolina.[2] The reason for the high prevalence of prostate cancer remains controversial. Men living in Africa have one of the lowest prevalences of prostate cancer in the world. Diet may have an influence, as diets high in saturated fat have been associated with increased risk for prostate cancer, while antioxidants, such as selenium, lycopenes, and vitamin E, have been reported to decrease risk.

"...it has been suggested that the PSA threshold for biopsy of 4.0 ng/ml should be lowered. Such lowering, however, will increase the number of biopsies performed..."

Indeed, the lifestyle trait in United States men that is most highly associated with both the incidence and mortality of prostate cancer is diet. Diets high in meat with high animal fat and low levels of fruits and vegetables appear to be associated with higher risks and mortality from prostate cancer.[3] A prospective study of more than 50,000 men reporting diet and associated risk of prostate cancer demonstrated that red meat consumption was highly associated with carcinoma of the prostate.[3,4] Studies have also demonstrated decreased prostate cancer among men consuming the antioxidant, selenium, and vitamin E.[4] A current, ongoing study (SELECT) further elucidates this association.[5] Because of the many basic science and epidemiologic studies that suggest there is decreased prostate cancer prevalence with the intake of antioxidants, it appears that oxidative stresses may contribute to the genesis of prostate

Culley C. Carson III, MD, is Rhodes Distinguished Professor and Chief, Division of Urology, Department of Surgery, School of Medicine, UNC. He can be reached at carson@med.unc.edu or CB# 7235, Chapel Hill, NC 27599-7235. Telephone: 919-966-9144.

cancer. These oxidants, in addition to diet, may be produced by environmental exposures and inflammation. Indeed androgens (steroid hormones, such as testosterone) associated with prostate cancer may increase oxidant effects in prostate cancer cells.[6]

Increasing evidence suggests that chronic inflammatory processes may have an etiologic role in human cancers, including prostate cancer.[7] While the symptoms of inflammation or infection in the prostate are uncommon preceding the diagnosis of prostate cancer, radical prostatectomy specimens often demonstrate evidence for chronic inflammatory conditions. Although the association of these prostatic conditions continues to strengthen, no specific etiology has been defined. Inhibition of GSTP1 gene expression, which encodes glutathione S-transferase capable of cell damage from oxidant stress, and is frequently found in prostate cancer cells. Lesions of proliferative, inflammatory atrophy with activated inflammatory and epithelial cells may be precursors to prostatic carcinoma.[7] Clinically, other non-specific inflammatory markers, such as C-reactive protein also have been associated with rising PSA levels and prostate cancer.[8]

Prostate Cancer Prevention

The fact that prostate cancer occurs in such high numbers of men and later in life in addition to evidence suggesting environmental influences in its etiology, chemoprevention has long been discussed and investigated. Prostate cancer prevention, if simple and well tolerated, would significantly limit the financial costs of screening and treatment, as well as, the psychological cost and morbidity and, ultimately, the mortality from prostate cancer of a large portion of the 30,000 or more men who die each year from this difficult disease. Because it is well known that males with low androgen levels have a decreased prevalence for prostate cancer (and eunuchs rarely are afflicted with prostate cancer), androgen manipulation is a natural target for prostate cancer prevention.

Certain Pharmaceuticals May Help Prevent Prostate Cancer

The Prostate Cancer Prevention Trial (PCPT) was the first large population-based trial to test chemoprevention in men with carcinoma of the prostate.[9] This study, begun in 1993, accrued more than 18,000 men over age 55 with normal digital rectal examination (DRE) and prostate-specific antigen (PSA) values of less than or equal to 3.0 ng/ml. Because men with congenital deficiency of Type II, 5 alpha reductase[a] do not suffer from either benign prostatic hyperplasia (BPH)—enlargement of the prostate or prostate cancer, Finasteride (a pharmacologic agent designed to block Type II, 5 alpha reductase) was used in this trial. Men were randomized into two groups: (1) a placebo group or (2) a treatment group that took 5 mg of Finasteride each day for seven years. Subject's in both groups received a biopsy during the study if any of the following three indications occurred: (1) PSA level exceeded 4.0 ng/ml, (2) digital rectal examination was abnormal, or (3) PSA values rose significantly with Finasteride. Subjects who completed the seven-year study without indication received an end-of-study biopsy. Because the National Institutes of Health (NIH) Data Safety and Monitoring Committee identified a substantial reduction in risk among subjects taking Finasteride, the study was concluded 15 months prior to its scheduled end date. Once analyzed, data from this study demonstrated a reduction in the prevalence of prostate cancer by 24.8% in patients randomized to Finasteride. However, a larger percentage of subjects treated with Finasteride (6.4%) were found to have more severe malignant tumors (Gleason scores[b] of 7-10) than subjects in the placebo group (5.1%). While sexual side effects were experienced by patients in the Finasteride arm, urinary symptoms (lower urinary tract symptoms) were more common in the placebo group. Although researchers found that a reduction in prostate cancer risk among patients treated with Finasteride was present in subjects who received biopsies due to the three indications and to those who completed the study without indication, there were equal numbers of deaths due to prostate cancer in each group. While this study continues to be controversial, and the increased incidence of higher-grade cancers in the Finasteride-treated men appears to be explained by changes in prostate size and tumor interpretation, the PCPT trial is the first convincing demonstration that prostate cancer can be prevented by a tolerable oral medication without significant adverse events.

Prostate Cancer Screening

Because prostate cancer rarely causes early symptoms, the diagnosis of prostate cancer is best performed by physical examination and laboratory testing. Digital rectal examination (DRE) has long been the cornerstone for the diagnosis of carcinoma of the prostate. Areas of palpable induration (hardness), firmness, and asymmetry of the prostate gland strongly suggest the presence of carcinoma. While BPH produces prostate enlargement, induration of the posterior prostatic lobe strongly suggests a diagnosis of prostate cancer. However, cancers found on DRE are more often of advanced pathologic stage; a diagnosis before nodules are formed improves prognosis.[10] DRE alone may miss as many as 45% of cancers subsequently identified by prostate biopsy following observation of rising PSA.[11] Abnormal DRE appears to

a Type II, 5 alpha reductase is an enzyme responsible for regulating the conversion of testosterone to dihydrotestosterone (DHT) in the liver.

b The Gleason scoring system grades prostate cancer patterns from 1 (well differentiated malignancy) to 5 (poorly differentiated malignancy). The Gleason combined score or grade is then computed by adding the most abundant Gleason grade pattern to the second most abundant Gleason grade pattern to obtain a Gleason sum. This score from 2 to 10 has been demonstrated to be accurate in predicting patient outcomes. Gleason scores of 2 to 6 respond best to primary treatment with significantly lower recurrence rates than Gleason scores of 8 to 10. In a group of more than 8,000 men diagnosed between 1989 and 2001, men with low-risk histories rose from 29.8% to 45.3%.[27]

be dependent upon PSA level, patient race, and age. There is a higher predictive value for DRE in African American men, older men, and men with higher PSA levels.[12]

PSA testing has significantly changed the diagnosis of prostate cancer since its introduction in the early 1990s. PSA is an enzyme (human kallikrein serine protease) that is encoded by the genes of chromosome 19. PSA is produced predominantly by the columnar secretory cells of the prostate and is present in high levels in the ejaculate. PSA first becomes detectable in the serum during puberty when steroid hormone levels increase. As patients age, their PSAs continue to rise, and there is an age-associated PSA value. Similarly, PSA rises with prostate volume and can be used as a surrogate marker for prostate size. Baseline PSAs in patients without prostatic malignancies are higher in African American men than in white men.[13]

Produced by the prostate in both benign and malignant conditions, PSA is a more accurate *prostate marker* than a *prostate cancer marker*. Any condition that produces prostate inflammation or disrupts prostate tissue will produce an elevation in PSA. This includes benign conditions such as BPH, prostatitis, urinary retention, prostatic infarction, prostate biopsy, and vigorous prostatic massage. While these inflammatory and surgical conditions produce changes in PSA, studies of ejaculation prior to PSA determination have not demonstrated convincingly a change in PSA level.[14] The 5 alpha reductase inhibitors, such as Finasteride and Dutasteride, reduce PSA levels to approximately 50% of baseline by six to 12 months following treatment.[15] While the use of PSA screening in identifying prostate cancer continues to be controversial, there are many studies that have demonstrated the importance of PSA testing to diagnose prostate cancer. Because PSA is more sensitive and specific than DRE alone, the detection of prostate cancer with a combination of PSA and DRE has a significantly higher predictive value than either study alone. In fact, PSA values in screening populations have the highest predictive value.[11] Longitudinal follow-up population studies using banked serum samples have reported a five-year lead time of prostate cancer diagnosis from PSA levels with 4.0 ng/ml as initial cutoffs.[16] Because PSA can be elevated by benign conditions, and elevations in PSA trigger prostate biopsies, efforts have been made to improve the accuracy of PSA determinations. Newer tests, such as the free and total PSA ratio,[c] prostate specific membrane antigen (PSMA),[d] complexed PSA,[e] and others, are under investigation for improving PSA accuracy. Current practice, however, can employ *PSA density*, an adjustment in PSA level to account for prostate volume. Adjusting the PSA level for prostate volume permits increased accuracy. More commonly, however, *PSA velocity* is used. PSA velocity measures changes in serum PSA values over time.[17]

PSA Threshold for Prostate Biopsy

Controversy continues regarding the interpretation of PSA values and the threshold for which a biopsy is required. The ideal PSA value for differentiating prostate cancer from benign prostates remains elusive. The standard PSA value differentiating normal from abnormal prostates of 4.0 ng/ml was established in 1990.[18] Because many prostate cancers can be present and even significant at PSA levels below 4.0 ng/ml, investigation has focused on the percentage of cancers missed at levels below 4.0. In the PCPT trial, end-of-study biopsies were correlated to PSA levels. Of 2,950 men biopsied, 449 (15.2%) were found to have prostate cancer with PSA levels less than 4.0. Of those men with PSAs between 3.1 and 4.0, 26.9% had positive biopsies, of which 25% were high-grade malignancies. Even among patients with PSA levels less than 0.5 ng/ml, 6.6% had positive biopsies at end-of-study. These data strongly suggest that PSA is better when focused on *density* or, more conveniently, *velocity* to differentiate those patients at high risk for prostate cancer and positive biopsies.[19] Based on this study, it has been suggested that the PSA threshold for biopsy of 4.0 ng/ml should be lowered. Such lowering, however, will increase the number of biopsies performed. The controversy continues.

"Because a single PSA value may be less accurate, PSA velocity, rise in PSA over time, may be a better indicator for prostate biopsy."

PSA velocity appears to be more helpful in a clinical setting. Outcome studies have demonstrated that PSA velocity of greater than 2.0 ng/ml per year is associated with significantly higher death rates from prostate cancer when compared with lower PSA velocities.[20,21] Thus, annual PSAs in patients at risk are important for the identification and treatment of carcinoma of the prostate. Because a single PSA value may be less accurate, PSA velocity, rise in PSA over time, may be a better indicator for prostate biopsy. In a prospective screening study, a velocity threshold of 0.75 ng/ml per year was used to differentiate patients. Using this threshold of velocity, 47% of men with velocities greater than 0.75 ng/dl were diagnosed with prostate cancer compared with only 11% of those with velocities less than 0.75 ng/ml.[22] In a European study where men were followed for four years, PSA velocity was 0.62 ng/dl per year for men with prostate cancer compared with

c The free and total PSA ratios are used to measure the percentage of free PSA relative to the total amount of PSA in a patient's blood sample.

d Prostate specific membrane antigen is a PSA produced by the membrane of prostate cancer cells.

e Complexed PSA is a test that measures the level of PSA, which has been complexed or bound with a certain protein (alpha-1-antichymotrypsin) in a patient's blood sample.

0.46 ng/dl per year for those without cancer. PSA doubling time was 5.1 years with prostate cancer and 6.1 years with negative biopsies.[23] In men with low PSAs, however, PSA velocity appears to be less accurate in selecting men for prostate biopsy.[24] Thus, PSA change over time appears to be more valuable than static values in selecting which men will require prostate biopsy.

Biopsy

Once a suspicious PSA has been identified by value, density, or velocity, a transrectal, ultrasound-guided prostate biopsy is the most accurate technique for identifying prostate cancer. This outpatient procedure is usually performed using local anesthetic injection of the periprostatic nerves and can be done in an office setting. Although transrectal ultrasound typically does not demonstrate specific areas of suspicion, the procedure permits prostate targeting, which allows accurate sampling of all portions of the prostate. For repeat biopsies where initial malignancy is not identified and PSA continues to rise, careful sampling of the transition zone is important to eliminate less common foci of prostate malignancy.

Biopsies of the prostate are safe and have a low incidence of morbidity. In a series of more than 5,800 prostate biopsies, fewer than 0.5% of men required hospitalization; however, only 2.6% of men reported self-limiting hematuria (blood in urine) and occasional 50.4% hematospermia (blood in semen) early following biopsy.[25]

The diagnosis of prostate cancer, once made through transrectal needle biopsy of the prostate, is graded by histopathology using the previously mentioned Gleason grading system.[26] Staging of prostate cancer is performed using the standard TNM system (see Table 1). TNM describes the extent of the primary *tumor* (T stage), the absence or presence of spread to nearby lymph *nodes* (N stage), and the absence or presence of distant spread, or *metastasis* (M stage). Staging can be performed pre- and post-treatment, and the most definitive staging occurs following radical prostatectomy. With the advent of PSA testing, there has been a dramatic shift to diagnoses at lower stages and, thus, more likelihood of organ-confined cancer.[27] While imaging studies can be helpful in patients with extensive carcinoma of the prostate, further staging assistance using cross sectional imaging of the pelvis by computerized tomography or magnetic resonance imaging have not added to the accuracy of cancer staging.

Treatment of Localized Prostate Cancer

Treatment of localized prostate cancer requires significant discussion with patients regarding outcomes, morbidity, mortality, and requirement for treatment. Choices include: watchful waiting, radical prostatectomy, interstitial brachytherapy (radioactive seed implantation), and external beam radiation therapy. Choice of treatment alternative is based upon the individual, his family, and prognostic factors, such as stage, grade, and the patient's general physical condition. Over the past decade with the use of PSA, treatment of prostate cancer patients has decreased in average patient age and average stage. During this same time, surgery and radiation therapy for prostate cancer has significantly improved. Radiation therapy applied with conformal external beam techniques or the implantation of small radioactive seeds using brachytherapy has improved the efficacy of cancer control and decreased treatment morbidity. The combination of these treatment modalities with androgen deprivation therapy using luteinizing hormone-releasing hormone (LHRH) agonist[f] treatment has further improved outcomes.[28]

Radical prostatectomy has likewise improved markedly over the past two decades. The introduction of the bilateral nerve sparing radical prostatectomy in the early 1990s has improved continence levels and potency post-radical prostatectomy, while preserving cancer control rates and limiting positive margin rates. The introduction of laparoscopy and robot-assisted laparoscopic prostatectomy has further improved the morbidity from radical prostatectomy. With these inventions, the hospitalization time of patients undergoing modern robotic-assisted laparoscopic prostatectomy has declined from more than seven days in the mid 1990s to one day or less in the 21st century.

Table 1.
Clinical TNM Staging of Prostate Cancer

T1	Cancer is clinically inapparent, not palpable or visible by imaging
T1a	Incidental histologic finding, less than or equal to 5% of resected tissue
T1b	Incidental histologic finding, greater than 5% of resected tissue
T1c	Tumor indetified by needle biopsy, for any reason (e.g., elevated PSA)
T2	Palpable or visible tumor, confined within the prostate
T2a	Less than or equal to one half of one lobe
T2b	One lobe
T2c	Both lobes
T3	Tumor extends through the capsule
T3a	Extracapsular extension, unilateral or bilateral
T3b	Seminal vesicle involvement
T4	Tumor is fixed or invades adjacent structures
T4a	Tumor invades bladder neck, external sphincter or rectum
T4b	Tumor Invades to the floor and/or the wall of the pelvis

f Luteinizing hormone-releasing hormone is a naturally occurring hormone that controls sex hormones in both men and women. LHRH agonist is a compound similar to LHRH (luteinizing hormone-releasing hormone) that serves in a manner similar to LHRH to control the same sex hormones.

This decreased hospitalization time has been accompanied with improved potency and continence rates, decreased blood loss, and decreased mortality rates. In a landmark randomized study comparing radical prostatectomy with watchful waiting with median 8.2 year follow-up, there was a 44% decrease in cancer death, 40% decrease in metastatic disease, and 67% decrease in disease progression.[29] Thus, radical prostatectomy appears to reduce disease-specific mortality, overall mortality, and risks of metastases and local progression.

Because prostate cancer is associated with slow progression and few deaths within ten years of diagnosis, men with life expectancies of less than ten years or significant comorbidities may be safely and effectively managed with a watchful waiting program. Watchful waiting generally consists of follow-up with regular PSA, monitoring PSA velocity, symptomatic treatment for obstructive uropathy and lower urinary tract symptoms (LUTS), and repeat biopsy if necessary.[30]

Systemic treatment of progressive prostate cancer continues to evolve and improve. The association of prostate cancer control with castrate levels[g] of testosterone was first identified by Huggins et al. in the 1940s.[31] The use of physical castration was widely used until the introduction and wide acceptance of luteinizing hormone releasing hormone agonist (LHRH). These agents, which rapidly produce castrate levels of testosterone, are associated with prostate cancer suppression. Androgen deprivation therapy, therefore, appears efficacious irrespective of method of treatment. Current depo preparations allow LHRH agonist to be administered monthly, or every three or four months. Implantable devices permit yearly changes of LHRH implants. While androgen deprivation therapy is associated with the side effects of castration including: hot flashes, osteoporosis, loss of libido, and decreased muscle mass and strength, prostate cancer control is quite satisfactory. In fact, survival can be increased by many years (average 3.5 years). Timing of initiation of androgen deprivation therapy, however, has been controversial. Since recent studies have demonstrated a prolongation of survival, many feel that androgen deprivation therapy should be initiated with initial detections of PSA rise.[32] Due to the significant morbidity, including an increase in osteoporosis and fracture risk, however, patients and physicians may chose to delay androgen deprivation therapy to preserve sexual function, muscle mass, and bone health.[33]

Newer concepts in LHRH agonist therapy with intermittent therapy are being utilized and investigated throughout the world. With this technique, testosterone is decreased using an LHRH agonist to castrate levels and until PSA response is observed. LHRH agonists are then withdrawn until the PSA value again climbs. Survival outcomes and effectiveness of treatment of this approach remain controversial.

Other methods for treatment of advanced prostate cancer have now progressed to agents beyond androgen deprivation. Newer chemotherapeutic agents, such as mitoxantrone and paclitaxel, have improved the outcomes of systemic chemotherapy.[34] These agents, which are currently reserved for patients with systemic malignancy unresponsive to androgen deprivation, provide some promise for improving survivals and prostate cancer control in patients with advanced disease.

Future Directions

Over the past decade, PSA testing, screening, and evaluation has revolutionized the diagnosis and treatment of prostate cancer. Indeed, urologists in clinical practice in the United States have observed a significant shift in stage of disease at diagnosis with few patients presenting in the 21st century with locally advanced or metastatic prostate cancer. This "stage shift" has permitted better diagnosis and more effective treatment of those patients at risk. Unfortunately, however, PSA as a prostate marker and prostate-specific marker is an imperfect screening tool. Current research on newer, more specific markers continues; however, PSA with modified use that incorporates measures of PSA density and velocity remain the mainstay for diagnosis. Newer imaging modalities are being developed to localize prostate cancers with the goal of localized treatment. Treatment of localized prostate cancer continues to be best carried out with radiation therapy or radical prostatectomy.

Modifications in radical prostatectomy over the past two decades, to include nerve sparing, laparoscopic approaches, and robotically assisted laparoscopic approaches, have improved morbidity, mortality, and outcomes. The United States' decrease in prostate cancer mortality over the past decade may, arguably, be a result of this improved diagnosis and treatment. Better serum diagnostic testing and imaging studies are being investigated in an effort to improve the specificity of diagnosis. Similarly, studies to identify tumors that are biologically aggressive and important, versus those that are more indolent, are ongoing. Identification of biologically less active and more indolent tumors may increase the number of men eligible for safe watchful waiting and active surveillance. Active investigation into gene and vaccine therapy may assist in the treatment of men with locally advanced or metastatic cancer. Similarly, this sub-categorization of prostate malignancies may assist in identifying patients most in need of early androgen deprivation therapy. With the advances in systemic chemotherapy and post-operative radiation therapy, more patients with aggressive, advanced prostate malignancies can be effectively treated with expected increased survival and decreased morbidity. **NCMedJ**

g Castrate-level occurs when the levels of the body's testosterone drop 90-95%, which is consistent with the loss of the testicles.

REFERENCES

1 Centers for Disease Control and Prevention. Prostate Cancer: The Public Health Perspective. 2003 Fact Sheet. Available at: http://www.cdc.gov/cancer/prostate/prostate.htm. Accessed March 23, 2006.

2 Mohler JL, Gaston KE, Moore DT, Schell MJ, Cohen BL, Weaver C, Petrusz P. Racial differences in prostate androgen levels in men with clinically localized prostate cancer. J Urol 2004;171:2277-2280.
3 Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC. A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer Inst 1993;85:1571-1579.
4 Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci EL, Stampfer MJ. Prospective study of plasma fatty acids and risk of prostate cancer. J Natl Cancer Inst 1994;6:281-286.
5 Hoque A, Albanes D, Lippman SM, Spitz MR, Taylor PR, Klein EA, Thompson IM, Goodman P, Stanford JL, Crowley JJ, et al. Molecular epidemiologic studies within the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Cancer Causes Control 2001;12:627-633.
6 Ripple MO, Henry WF, Schwarze SR, Wilding G, Weindruch R. Effect of antioxidants on androgen-induced AP-1 and NF-kappaB DNA-binding activity in prostate carcinoma cells. J Natl Cancer Inst 1999;91:1227-1232.
7 Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. J Urol 2004;172:S6-11;discussion S11-12.
8 Lehrer S, Diamond EJ, Mamkine B, Droller MJ, Stone NN, Stock RG. C-reactive protein is significantly associated with prostate-specific antigen, metastatic disease in prostate cancer. BJU Int 2005;95:961-962.
9 Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215-224.
10 Schroder FH, van der Maas P, Beemsterboer P, Kruger AB, Hoedemaeker R, Rietbergen J, Kranse R. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 1998;90:1817-1823.
11 Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, deKernion JB, Ratliff TL, Kavoussi LR, Dalkin BL, et al. Comparison of digital rectal examination, serum prostate specific antigen in the early detection of prostate cancer: Results of a multicenter clinical trial of 6,630 men. J Urol 1994;151:1283-1290.
12 Carvalhal GF, Smith DS, Mager DE, Ramos C, Catalona WJ. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. J Urol 1999;161:835-839.
13 Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW. Age-specific reference ranges for prostate-specific antigen in black men. N Engl J Med 1996;335:304-310.
14 Stenner J, Holthaus K, Mackenzie SH, Crawford ED. The effect of ejaculation on prostate-specific antigen in a prostate cancer-screening population. Urology 1998;51:455-459.
15 Carson C III, Rittmaster R. The role of dihydrotestosterone in benign prostatic hyperplasia. Urology 2003;61:2-7.
16 Carter HB, Pearson JD. Prostate-specific antigen velocity and repeated measures of prostate-specific antigen. Urol Clin North Am 1997;24:333-338.
17Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, Fozard JL and Walsh PC. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 1992;267:2215-2220.
18 Cooner WH, Mosley BR, Rutherford CL, Jr., Beard JH, Pond HS, Terry WJ, Igel TC, Kidd DD. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. J Urol 1990;143:1146-1152; discussion 1152-1154.
19 Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. N Engl J Med 2004;350:2239-2246.
20 D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 2004;351:125-135.
21 Schroder FH, Roobol M. Prostate-specific antigen levels in the United States: Implications of various definitions for abnormal. Eur Urol 2006;49:412-413.
22 Smith DS, Catalona WJ. Rate of change in serum prostate specific antigen levels as a method for prostate cancer detection. J Urol 1994;152:1163-1167.
23 Raaijmakers R, Wildhagen MF, Ito K, Paez A, de Vries SH, Roobol MJ, Schroder FH. Prostate-specific antigen change in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. Urology 2004;63:316-220.
24 Roobol MJ, Kranse R, de Koning HJ, Schroder FH. Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: Results of second screening round of ERSPC (ROTTERDAM). Urology 2004;63:309-313; discussion 313-315.
25 Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002;60:826-830.
26 DeMarzo AM, Nelson WG, Isaacs WB, Epstein JI. Pathological and molecular aspects of prostate cancer. Lancet 2003;361:955-964.
27 Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Horninger W, Klocker H, Mikolajczyk SD. Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/ml prostate specific antigen. J Urol 2004;171:2239-2244.
28 D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. JAMA 2004;292:821-827.
29 Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, Spangberg A, Busch C, Nordling S, Garmo H, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005;352:1977-1984.
30 Kirby RS, Fitzpatrick JM. Radical prostatectomy vs watchful waiting. BJU Int 2005;96:953-954.
31 Huggins C, Hodges C. Studies on Prostate Cancer II: The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941;43:209-222.
32 Studer UE, Hauri D, Hanselmann S, Chollet D, Leisinger HJ, Gasser T, Senn E, Trinkler FB, Tscholl RM, Thalmann GN, et al. Immediate versus deferred hormonal treatment for patients with prostate cancer who are not suitable for curative local treatment: Results of the randomized trial SAKK 08/88. J Clin Oncol 2004;22:4109-4118.
33 Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154-164.
34 Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Turesson I, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-1512.

Confronting Prostate Cancer:
A Personal Reflection

Senator David W. Hoyle

Editorial Note: Because prostate cancer, its early detection and treatment, raise so many issues of personal concern, we considered it important to include a discussion of some of these matters from a personal perspective. We are fortunate that one of our state's leading public policy makers, Senator David Hoyle of Gaston County, was willing to share his own experience with all phases of the process from detection and diagnosis to surgical intervention and post-operative care. We hope that this narrative will help bring clear focus to many of the issues raised by the authors in this issue of the Journal and encourage men who are not regularly screened at appropriate ages to raise these issues with their personal physicians.

No one likes the sound of the word "cancer," especially when it applies to you. In this respect, I was just like everyone else.

But, I had heard from many that "most of us [men] have this condition, whether we know it or not, and that we may all die from this disease if we live long enough. Although most of us die from something else long before symptoms of prostate cancer appear." The fact that the disease is slow-growing (in most) and more prevalent in older men makes many feel less concerned at younger ages. I was one of those, although I had been having prostate-related problems for many years, since my mid-40s. Off and on, I had experienced problems with discomfort, inflammation, and something my doctors referred to as prostatitis. My PSA levels had been slowly rising (from around 2, then 3, then 4, and eventually to 6; the so-called "velocity" of change was notable, but still failed to raise the concern of my physician).

Finally, my primary care physician, who had been taking care of me for years, after a usual digital rectal examination as part of a normal physical, noted a lump or hard spot on my prostate. My doctor thought it would be good for me to see a urologist for a consultation visit.

This preliminary unusual finding from a regular primary care visit began a long and convoluted series of events that caused no small amount of anxiety for me and my family.

Importance of Follow-Up to Preliminary Findings

Right away, my physician helped me get an appointment at the University of North Carolina Hospital (UNC) in Chapel Hill. A biopsy was performed and laboratory results came back with the unwelcome news that I did have cancer of the prostate, with a Gleason score of "6." My urologist at UNC explained several (surgical and non-surgical) options, but recommended that I consider surgery to remove the prostate.

I consulted a number of friends, including friends in the field of surgery and urology, about my situation and asked several of them: "If you had this condition, where would you go to have the surgery performed." A physician friend, with whom I had often played golf, recommended a surgeon at Johns Hopkins University in Baltimore. On his recommendation, I contacted that surgeon and arranged an appointment to be seen in his clinic. He recommended surgery within two weeks of that appointment.

The "Ups and Downs" of Good and Not-So-Good News

Then, a startling thing happened. A week later, after I returned to my regular work at the North Carolina General Assembly, I was summoned from a committee meeting by my secretary who said the surgeon from Baltimore was trying to reach me rather urgently. I rushed from the room and spent a nervous 20 minutes or so trying to page the surgeon. I had all sorts of images racing through my mind. Were the results of my laboratory tests found to be even more serious than they first appeared to be? Was it necessary for surgery to take place even sooner for some reason? What could it be?

When my surgeon and I managed to speak, he explained that when the pathologists at Johns Hopkins looked at the slides I brought with me from North Carolina, they concluded that I did not have prostate cancer after all! My surgeon was

Senator David W. Hoyle represents the 25th Senatorial District in the North Carolina General Assembly, which includes portions of Cleveland, Gaston, and Lincoln counties. He lives in Gastonia and can be reached at davidh@ncleg.net or 300-A Legislative Office Building, Raleigh, NC 27603-5925. Telephone: 919-733-5734.

calling to tell me that he had cancelled my scheduled surgery for the next week.

Even though there was a certain sense of "relief" in this news, my surgeon followed his announcement of these results with the request that I try to have an immediate second biopsy done here in North Carolina. He felt that was necessary to confirm the Hopkins pathologist's opinion that no disease existed, and then we would re-evaluate further options.

So, a few days later, I was scheduled for a second biopsy. This time, different from my first experience, the procedure was less painful and more extensive. Instead of six "punches," they did 12. But this time, I was more psychologically prepared and knew what to expect.

Two days later, the results were disappointing in that they confirmed the initial diagnosis: I did have prostate cancer. Surgery was scheduled for a second time, just before Christmas, after my prostate had time to heal from the extensive biopsy procedure. I got out of the hospital after surgery two days before Christmas and checked into a Baltimore hotel to rest for a few days before traveling home. The Hopkins surgeons wanted to make certain that I had no post-operative complications.

"No one likes the sound of the word "cancer," especially when it applies to you. In this respect, I was just like everyone else."

After the surgery, I had a catheter to assist with bladder issues, which I kept in place for 20 days when it was removed by my own physician in Gastonia. I also wore paper diapers to make certain that I did not have a problem with incontinence. Thankfully, these were necessary for only a few days. I had no problems with urination or anything else after that.

I was relieved to learn that the surgical margins of my disease were contained (localized) within the prostate, and the disease had not spread to other parts of my body. Therefore, I had no post-surgical radiation. I am now followed on a regular basis (every six months) by a urologist in Charlotte, and my PSA has dropped to "zero." Several other tests have been done, such as a bone scan in Chapel Hill, to make certain that the disease was not transmitted to other parts of the body. In every respect, this has been a complete success, and I am pleased to have been disease-free for the seven-to-eight years since the surgery was performed.

Lessons Learned

This experience provides a number of "lessons" that I would pass along to others who may yet have to confront this same set of circumstances. First, it is important to have a regular primary care physician who knows you and your health situation well. It was important that my physician who had been seeing me off and on for many years was able to note the appearance of a "hard spot" on my prostate during a routine examination. Were it not for that finding, one might have concluded that an elevated PSA level alone, which had remained high for many years, was simply benign prostatic hypertrophy (BPH) and no cause for concern. I have a family history of prostate cancer, so I knew that this was something that might likely develop in my case.

Second, once I followed-up this initial finding with a more thorough urological examination and biopsy, and once I had a definitive diagnosis, I asked lots of questions of my doctors and my friends who had gone through this before. I read everything I could get my hands on about this condition, so I would know what courses of action were available to me, and what the likely (or possible) outcomes might be of any given course of action. One of my friends, who had considered the option of the implantation of radiological "seeds" instead of surgery, had worried (before taking that route) about problems with both incontinence and impotence. Neither of these problems resulted in his case. But, I learned that once radiation is chosen as an option, surgery is no longer an option.

Third, it is important to realize that medicine is not "perfect." Mistakes do happen, and test results are often inaccurate. It is important, especially with diseases like cancer, to double check test results and, if possible, with a different laboratory or clinical setting. I was fortunate that my Hopkins physicians recommended that I have another biopsy performed here in North Carolina. That second set of biopsy results confirmed the findings of the first biopsy—I did, in fact, have cancer and needed surgery. I've tried many times to figure out how the Hopkins pathologists could have been so certain that I didn't have cancer. My only explanation is that somehow the slides I brought with me from Chapel Hill were either the wrong slides, or they got mixed up in some way in the lab at Hopkins. In any event, a second set of biopsy results were necessary to actually detect the disease.

Finally, the combination of early diagnosis and immediate follow-through with a detailed diagnostic workup and consultation can lead to better treatment outcomes. Also, although there are risks of post-operative complications, for large numbers of men who undergo these procedures, results are similar to mine. In this day and age, there is really no reason for men to die from prostate cancer if they follow these recommended procedures for clinical examination and testing.

I am one of those grateful patients who has been well-served by many healthcare professionals here in North Carolina and elsewhere, as my family and I have confronted what, for some, is a very unnerving diagnosis. **NCMedJ**

Racial Differences in Prostate Cancer

Kris E. Gaston, MD, and Raj S. Pruthi, MD

Prostate cancer is the most common non-cutaneous cancer diagnosed in American men and the second leading cause of male cancer deaths.[1] African American men suffer disproportionately with almost double the incidence of and death from prostate cancer. Many sociologic and biologic theories have been applied to solve this conundrum; however, there is still great contention over what the isolated causes of these racially divided outcomes are.

Epidemiology

United States Statistics

In 2006, it is estimated that 234,460 men will be diagnosed, and 27,350 men will die from prostate cancer.[1] Data from the Surveillance, Epidemiology, and End Results (SEER) database 1998-2002 revealed the median age at diagnosis for prostate cancer was 69 years of age. Approximately 0.0% were diagnosed under age 34; 0.5% between 35 and 44; 8.0% between 45 and 54; 26.1% between 55 and 64; 37.5% between 65 and 74; 23.2% between 75 and 84; and 4.7% at 85 years of age or greater.[2] The age-adjusted incidence rate from 1998-2002 was 173.8 per 100,000 men per year. SEER data from 1998-2002 also revealed the median age at death from prostate cancer was 79 years of age. Approximately 0.0% died under age 34; 0.1% between 35 and 44; 1.2% between 45 and 54; 6.3% between 55 and 64; 22.1% between 65 and 74; 42.3% between 75 and 84; and 27.9% at 85 years of age or greater. The age-adjusted death rate was 30.3 per 100,000 men per year.[2]

African Americans suffer a disproportionately high incidence of and mortality from prostate cancer compared to whites. Relative to whites, African Americans suffer from a 1.6 times higher incidence of prostate cancer. According to SEER 13 registries from 1998-2002, whites were diagnosed with prostate cancer at a rate of 169.0 per 100,000 men compared to African Americans diagnosed at a rate of 272.0 per 100,000 men.[2] African Americans compared to whites also suffer from a 2.5 times greater mortality from prostate cancer. Whites died with prostate cancer at a rate of 27.7 per 100,000 men compared to African Americans who died at a rate of 68.1 per 100,000 men.[2]

North Carolina Statistics

In 2006, it is estimated that 7,120 men will be diagnosed and 830 men will die from prostate cancer in North Carolina.[1] The age-adjusted incidence rate for all races from 1999-2001 in North Carolina was 159.4 per 100,000 (United States 161.2 per 100,000).[2] The age-adjusted death rate from 1999-2001 for all races in North Carolina was 35.6 per 100,000 (United States 30.3 per 100,000).[2] More alarmingly, some North Carolina counties have the highest incidence of and death from prostate cancer in the world, irrespective of race (see Table 1 and 2). The etiology for such high prostate cancer incidence remains unknown.

Racial differences in the incidence of and death from prostate cancer persist when examined at the state-specific level. SEER data from North Carolina from 1999-2001 showed that whites had an incidence rate of 143.6 per 100,000 (United States white incidence in 2001 was 144 per 100,000) compared to African Americans who had an incidence rate of 238.5 per 100,000 (United States African American incidence in 2001 was 234.1 per 100,000).[2] During a similar time period (1998-2002),

"African Americans should be screened aggressively and early (after age 40) if any survival benefit from treatment is to be shown."

Kris E. Gaston, MD, is a resident in the Department of Surgery, Division of Urology, at the University of North Carolina at Chapel Hill. Dr. Gaston can be reached at kris_gaston@med.unc.edu or or CB# 7235, Chapel Hill, NC 27599-7235. Telephone: 919-966-9147.

Raj S. Pruthi, MD, is an Assistant Professor and Director of Urologic Oncology in the Division of Urologic Surgery and with the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill. Dr. Pruthi can be reached at raj_pruthi@med.unc.edu or CB# 7235, Chapel Hill, NC 27599-7235. Telephone: 919-966-9147.

Table 1.
Ten Counties with the Highest Incidence of Prostate Cancer (per 100,000)
(United States White Incidence 144 per 100,000/African American Incidence 234.1 per 100,000)

	All		White		African American
Lenoir County	262.7	***Lenoir County***	213.6	***Onslow County***	464.7
Onslow County	247.8	***Onslow County***	212.4	***Perquimans County***	419.3
Perquimans County	245.2	***Craven County***	212.0	***Lenoir County***	376.2
Hertford County	243.0	***Perquimans County***	199.3	***Craven County***	334.7
Craven County	233.1	***Hertford County***	194.1	Burke County	319.0
Pamlico County	231.5	Pamlico County	192.0	***Alamance County***	316.8
Pasquotank County	216.7	Transylvania County	189.4	Catawba County	313.9
Camden County	212.8	***Alamance County***	187.1	Cleveland County	309.6
Alamance County	206.7	Pasquotank County	186.4	***Hertford County***	303.9
Northampton County	204.3	Alleghany County	186.3	Chowan County	298.9

Bold italic indicates counties with the highest incidence of prostate cancer shared by African Americans and whites.

Table 2.
Ten Counties with the Highest Mortality from Prostate Cancer (per 100,000)
(United States White Mortality 27.7 per 100,000/African American Incidence 68.1 per 100,000)

	All		White		African American
Caswell County	62	***Pender County***	49.3	Richmond County	143.8
Warren County	61.1	Franklin County	41.8	Catawba County	141.6
Pender County	60.7	Watauga County	39.4	Sampson County	120.0
Perquimans County	58.9	Lenoir County	38.5	Cleveland County	115.8
Granville County	58.8	Montgomery County	38.5	***Pender County***	108.2
Hoke County	57.2	Yancey County	37.7	Wayne County	103.6
Halifax County	55.8	Craven County	36	Duplin County	99.8
Richmond County	55.2	Carteret County	35.9	Caswell County	98.9
Northampton County	55.1	Granville County	35.9	Gaston County	97.7
Vance County	55.1	Halifax County	35.9	Northampton County	97.1

Bold italic indicates counties with the highest incidence of prostate cancer shared by African Americans and whites.

whites in North Carolina had a mortality rate of 27.9 per 100,000 (United States white mortality rates 1998-2002 were 27.7 per 100,000) compared to African Americans who had a death rate of 79.3 per 100,000 (United States African American mortality rates 1998-2002 were 68.1 per 100,000).[2] African Americans in North Carolina suffer a 1.6 times greater incidence of and 2.8 times greater mortality from prostate cancer compared to whites. These differences are similar to differences seen on a national level.

Possible Explanantions for Prostate Cancer Differences

Access and Allocation of Healthcare

Many studies have shown that minorities do not receive the same allocations of procedures as do whites who have the same disease processes.[3-5] Peterson et al. showed in a Veteran Affairs study of 33,641 men that African Americans with an acute myocardial infarction were 33% less likely than whites to undergo cardiac catheterization, 42% less likely to receive coronary angioplasty, and 54% less likely to receive coronary bypass surgery.[3] Similar outcomes were demonstrated by Ayanian et al. who studied a retrospective cohort of 27,485 men and women from various hospital systems who underwent inpatient angiography for coronary heart disease in 1987.[4] Results showed that whites are more likely than African Americans to receive revascularization procedures after coronary angiography. With regard to cancer care, Armstrong et al. studied 408 women with a family history of breast or ovarian cancer, of whom 217 underwent genetic counseling for breast cancer (BRCA1/2) testing (cases), and 191 women did not (controls).[5] Results showed that African Americans were significantly less

likely to undergo genetic counseling for BRCA1/2 testing than were white women.

Access to and allocation of healthcare alone cannot explain the racial differences in prostate cancer outcomes. Robbins et al. studied men insured within the Kaiser Permanente organization and found that African American men presented with higher stages and worse survival from prostate cancer compared to white men.[6] This study showed that even in an equal access system, racial differences in prostate cancer outcomes still remained. In contradiction to the Kaiser study, Freedland et al. found an equal percentage of African American and white men presenting with clinically localized and metastatic prostate cancer in the Veterans Affairs system.[7] No differences were found in patient age or clinical stage of prostate cancer between black and white men at the time of diagnosis, but African American men presented with higher median serum prostate-specific antigen (PSA) values (14.2 versus 9.4 ng/mL, p = 0.0001) and slightly higher median Gleason scores (6.2 versus 5.9, p = 0.025).[7] More recent studies have shown that African Americans and whites, when matched by pathologic stage and grade after radical prostatectomy, have similar disease outcomes.[8] Eastham et al. demonstrated that African American and white men with clinical T1c[a] prostate cancer (diagnosed by PSA alone) have similar pathologic outcomes and PSA recurrence rates after radical prostatectomy, which further illustrates that in the modern era of PSA testing, stage for stage/grade for grade, African Americans and whites have similar outcomes.[9] These data re-enforce the argument that African Americans should be screened aggressively and early (after age 40) if any survival benefit from treatment is to be shown.

Prostate Cancer Screening Participation

The frequency of incidental prostate cancer detection in African Americans and whites appears similar;[10] however, African Americans are more frequently diagnosed with higher tumor volumes,[11] more advanced tumor stages,[12] more diffuse and greater volumes of high-grade prostatic intraepithelial neoplasia (HGPIN),[13,14] higher Gleason grades,[15,16] and higher PSA levels[11,14,16,17] compared to whites. Several studies have shown that when African Americans and whites are matched for stage and grade and undergo radical prostatectomy, there are no differences in PSA recurrence or risk of death from prostate cancer. [18-20] In light of the disparity in the incidence and mortality statistics, it would be reasonable to think that African American men would participate in more prostate cancer screening when offered. Unfortunately, several studies have shown quite the contrary. Ashford et al. evaluated 404 African American men in Harlem, New York and analyzed those who received prostate cancer screening.[21] Results showed that the prevalence of self-reported PSA screening in Central Harlem was lower than that reported for other populations, with only 24% of men 50-74 years of age ever having had a PSA test.

Choice of Definitive Therapy

Many studies have shown that African Americans compared to whites choose radical prostatectomy less often. Hoffman et al. studied 1,144 African American and white men with clinically localized prostate cancer and found that among men with more aggressive cancers (PSA greater than or equal to 20 ng/mL or Gleason score greater than or equal to 8), African Americans were less likely to undergo radical prostatectomy than whites (35.2% versus 52.0%), but more likely to receive conservative management (38.9% versus 16.3%, p = 0.003).[22] Treatment differences may reflect the greater likelihood for African Americans to present with pathologically advanced disease. Yan et al. analyzed men that underwent PSA screening and followed outcomes of therapy in men subsequently detected to have prostate cancer.[23] Non-African American patients had a greater than four times likelihood of selecting radical prostatectomy versus watchful waiting compared to African Americans. In an analysis of SEER data from 1995-1999, Denberg et al. showed that African Americans received equal amounts of definitive therapy for curative intent; however, African Americans compared to whites were significantly more likely to choose radiotherapy versus radical prostatectomy.[24]

Biologic Explanations for Prostate Cancer Differences

Androgen Axis: Steroids

In studies that would later win the Nobel Prize in Medicine, Charles Huggins and Clarence Hodges demonstrated that withdrawal of testosterone causes prostate cancer to go into remission, but that it is almost certainly to recur in its testosterone-insensitive form.[25] Since prostate cancer is an androgen-stimulated cancer, could racial differences in prostate cancer be attributable to differences in androgen levels? In a study by Ross et al., male college students (mean age 20 years) living in southern California had testosterone levels measured. Total testosterone and free testosterone levels were 15% and 13% higher, respectively, in African Americans compared to whites.[26] Ellis et al. also measured androgen levels in over 4,000 male Army veterans ranging from 31-50 years of age (mean 38 years), but found that African Americans had only a 3.3% higher mean testosterone level compared to whites.[27] Kubricht et al. reported serum testosterone levels were similar between 189 African American and 264 white men undergoing biopsy for prostate cancer.[28] Beyond 40 years of age, African Americans and whites appear to have similar testosterone levels. If there are any differences in androgen levels, it occurs earlier in life and not in the prostate cancer-risk group after age 40.

Dihydrotestosterone (DHT) binds to the androgen receptor with affinity similar to testosterone, but DHT reduces androgen receptor degradation rates more than testosterone because of its slower dissociation.[29,30] Small racial differences in DHT or 5-alpha

a Prostate cancer with a T1c stage is traditionally characterized as being early-stage disease and having the best prognosis.

reductase, which catalyzes the conversion of testosterone to DHT, may increase androgen receptor protein levels in African Americans compared to whites. Accordingly, Ross et al. studied serum DHT metabolites in 100 university students and 54 Japanese medical students.[31] African Americans and whites, respectively, had 25% and 31% higher levels of the DHT metabolite A-diol-glucuronide compared to Japanese students. Four recent studies have reported serum levels of DHT, and none found differences between cases and controls; however, in each of these studies, African Americans were either not included or race was unspecified.[32-35]

The aforementioned studies measured serum androgens that may not accurately reflect the true androgenic environment within the prostate. Mohler et al. analyzed steroid hormones that were extracted from snap frozen prostate tissue obtained intraoperatively from radical prostatectomy specimens of 36 African Americans and 59 whites.[36] Although tissue levels of testosterone and DHT did not differ by race, African American men had higher tissue androstenedione (ASD) and sex hormone-binding globulin (SHBG) than white men.

Androgen Receptor Expression

Lubahn et al. at the University of North Carolina at Chapel Hill (UNC-Chapel Hill) was the first to isolate the androgen receptor in 1988.[37] Extensive androgen receptor research continues at UNC-Chapel Hill. Recently, Gaston et al. performed a study looking at archived radical prostatectomy specimens obtained from 25 white and 25 African American men who had androgen receptor protein antigen retrieved and immunostained.[38] Androgen receptor protein expression was 22% higher in the benign prostates and 81% higher in the cancerous prostates of African American men when compared with white men. Similar results were found in a study by Olapade-Olaopa et al. The Olapade-Olaopa study compared androgen receptor expression in benign prostatic hyperplasia (BPH) and prostate cancer tissue of non-American blacks and non-American whites and found a similar increased expression of androgen receptor in blacks compared to whites.[39] Accordingly, prostate cancer may occur at a younger age and progress more rapidly in African American men compared to white men due to racial differences in androgenic stimulation of the receptor.

Racial differences in androgen receptor gene polymorphisms have also been described in the literature. African Americans, compared to whites, have been shown to express more androgen receptor polymorphisms, which may increase the risk of developing prostate cancer.

Racial Polymorphisms in the 5-alpha Reductase

Reichard et al. described genetic polymorphisms in the gene encoding the 5-alpha-reductase type II enzyme and compared allelic frequencies between three major United States populations—African Americans, whites, and Asian Americans. The authors found three different allelic families [containing 87 base pairs (bp), 103-107 bp, and 121-131 bp].[40] Whereas 18% of African Americans exhibited the 121-131 bp alleles, these alleles were not found in white or Asian Americans. Consequently, this 5-alpha-reductase type II enzyme polymorphism may result in more efficient conversion of testosterone to DHT within the prostate, and thereby may have a role in carcinogenesis.

Diet and Nutrition

Genetic differences cannot be the sole basis for difference of prostate cancer incidence. Epidemiological studies have demonstrated that as populations migrate from geographic areas with a low-incidence rate of prostate cancer to areas with higher-incidence rate, the migrating population begins to exhibit higher-incidence rates of prostate cancer. The incidence of prostate cancer varies throughout the world, yet African Americans have the highest incidence of prostate cancer in the world. The highest incidence of prostate cancer is in the United States, and the lowest is in Asia (as low as 0.5 per 100,000 in Qidong, China).[41] Asia also has a low consumption of saturated animal fat and a high consumption of fiber and soy protein.[41] Soy protein is abundant in the Asian diet, but is rarely consumed in the American diet. Soy has long been thought to have broad anti-neoplastic effects.[42] There are two broad isoflavonoid components found in soy—genistein and daidzein, both of which may have mild estrogenic effects, which may cause apoptosis (cell death) of prostate cancer cells.[42-44]

Dietary fat intake is thought to be a major factor involved with the increased incidence of prostate cancer in the United States.[45-48] Omega-6 fatty acids are thought to act as promoters of prostate cancer.[49] It is thought that at the cellular level, these fatty acids influence cellular proliferation, the immune system, and the potential for the tumor to invade locally and metastasize.[49] It is also thought that Omega-6 fatty acids (found in cereals, eggs, poultry, most vegetable oils, etc.) affect prostaglandin synthesis.[49] It has been shown that increased levels of prostaglandin E_2 increases oncogene Bcl-2 expression leading to carcinogenesis.[50] On the other hand, Omega-3 fatty acids found in fish oils, appear to be protective against prostate cancer.[49] These Omega-3 fatty acids are consumed in high amounts in Asia, whereas Omega-6 fatty acids are consumed in low amounts. The opposite occurs in the United States where Omega-3 fatty acids are consumed in low amounts and Omega-6 fatty acids are consumed at high amounts. Subsequent studies have shown that the African American diet contains the highest overall saturated fat and Omega-6 fatty acid content in the world.[47,48]

Obesity may be an independent factor of prostate cancer progression. Amling et al. examined the relationship between obesity and race in predicting adverse pathological variables in patients undergoing radical prostatectomy.[51] This was a multi-institutional retrospective analysis of the clinical and pathologic parameters on 860 patients with prostate cancer undergoing radical prostatectomy between 1992 and 1998. Obesity was defined as a Body Mass Index (BMI) greater than 30 kilograms/meter^2 (kg/m^2). Obese patients presented with prostate cancer at younger ages, higher Gleason grades, and more advanced pathologic stages. These data suggest a racial correlate of prostate cancer because African Americans tend to have higher

grade prostate cancer and significantly higher average BMI compared to whites.

Insulin Growth Factor Pathways

Insulin-like Growth Factor 1 (IGF-1) stimulates cellular proliferation and inhibits apoptosis.[52] IGF-1 is a stimulator prostate cancer growth factor and 95% circulates bound to specific high-affinity IGF binding proteins (IGFBPs 1–6).[53] Blood levels of IGFs in each individual are relatively constant with no apparent diurnal or circadian variation. Studies have shown that African Americans have low IGFBP-3 compared to whites.[54] This may allow for more free IGF-1 to stimulate neoplastic growth of the prostate. Abdominal obesity and hyperinsulinemia are associated with decreased serum levels of sex hormone-binding globulin, with a resultant increase in testosterone, lower serum levels of IGFBP-1, increased serum levels of IGF-1, and estrogenic compounds.[55-58] Since African Americans have the highest BMI in the world, one can assume these IGF pathways may directly affect carcinogenesis of the prostate.

Vitamin D

Vitamin D may have protective benefits against prostate cancer. Vitamin D is believed to decrease bcl-2 expression increasing apoptotic cell death.[59] Some have suggested that endogenous Vitamin D synthesis may be impaired in African Americans because of the darker skin pigmentation.[60]

Conclusion

Striking differences in the incidence of and mortality from prostate cancer between African Americans and whites have persisted even after the advent of PSA testing. African Americans do not appear to fair worse than whites when matched by cancer stage and grade. More must be done to target this population for early and aggressive screening. **NCMedJ**

REFERENCES

1 American Cancer Society. Cancer Facts & Figures 2006. Atlanta, GA. 2006. Available at: http://www.cancer.org. Accessed April 27, 2006.
2 National Cancer Institute. Surveillance, Epidemiology, and End Results Database. Available at: http://seer.cancer.gov/. Accessed April 27, 2006.
3 Peterson ED, Wright SM, Daley J, Thibault GE. Racial variation in cardiac procedure use and survival following acute myocardial infarction in the Department of Veterans Affairs. JAMA 1994;271(15):1175-1180.
4 Ayanian JZ, Udvarhelyi IS, Gatsonis CA, Pashos CL, Epstein AM. Racial differences in the use of revascularization procedures after coronary angiography. JAMA 1993;269(20):2642-2646.
5 Armstrong K, Micco E, Carney A, Stopfer J, Putt M. Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer. JAMA 2005;293(14):1729-1736.
6 Robbins AS, Whittemore AS, Van Den Eeden SK. Race, prostate cancer survival, and membership in a large health maintenance organization. J Natl Cancer Inst. 1998;90(13):986-990.
7 Freedland SJ, Sutter ME, Naitoh J, Dorey F, Csathy GS, Aronson WJ. Clinical characteristics in black and white men with prostate cancer in an equal access medical center. Urology 2000;55(3):387-390.
8 Underwood W III, Wei J, Rubin MA, Montie JE, Resh J, Sanda MG. Postprostatectomy cancer-free survival of African Americans is similar to non-African Americans after adjustment for baseline cancer severity. Urol Oncol 2004;22(1):20-24.
9 Eastham JA, Carver B, Katz J, Kattan MW. Clinical stage T1c prostate cancer: Pathologic outcomes following radical prostatectomy in black and white men. Prostate. 2002;50(4):236-240.
10 Guileyardo JM, Johnson WD, Welsh RA, et al. Prevalence of latent prostate carcinoma in two United States populations. J Natl Cancer Inst 1980;65:311-316.
11 Moul JW, Connelly RR, Mooneyham RM, et al. Racial differences in tumor volume and prostate-specific antigen among radical prostatectomy patients. J Urol 1999;162:394-397.
12 Brawn PN, Johnson EH, Kuhl DI., et al. Stage at presentation and survival of white and black patients with prostate carcinoma. Cancer 1993;71:2569.
13 Sakr WA, Grignon DJ, Haas GP, et al. Age and race distribution of prostatic intraepithelial neoplasm. Eur Urol 1996;30:138-144.
14 Fowler JE Jr, Bigler SA, Lynch C, et al. Prospective study of correlations between biopsy detected high-grade prostatic intraepithelial neoplasia, serum prostate-specific antigen concentration, and race. Cancer 2001;91:1291-1296.
15 Fowler JE Jr, Bigler SA, Bowman G, et al. Race and cause specific survival with prostate cancer: influence of clinical stage, Gleason score, age and treatment. J Urol, 2000;163:137-142.
16 Fowler JE Jr, Bigler SA. A prospective study of serum prostate-specific antigen concentration and Gleason histologic scores of black and white men with prostate carcinoma. Cancer 1999;86:836.
17 Vijayakumar S, Winter K, Sause W, et al. Prostate-specific antigen levels are higher in African Americans than in White patients in a multi-center registration study: Results of RTOG 9412. Int J Radiat Oncology and Biol Phys 1998;40:17-25.
18 Tewari A, Horninger W, Badani KK, Hasan M, Coon S, Crawford ED, Gamito EJ, Wei J, Taub D, Montie J, Porter C, Divine GW, Bartsch G, Menon M. Racial differences in serum prostate-specific antigen (PSA) doubling time, histopathological variables and long-term PSA recurrence between African-American and white American men undergoing radical prostatectomy for clinically localized prostate cancer. BJU Int 2005 Jul;96(1):29-33.
19 Freedland SJ, Amling CL, Dorey F, Kane CJ, Presti JC Jr, Terris MK, Aronson WJ; Shared Equal Access Regional Cancer Hospital Database Study Group. Race as an outcome predictor after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Urology 2002;60(4):670-674.
20 Bianco FJ Jr, Kattan MW, Scardino PT, Powell IJ, Pontes JE, Wood DP Jr. Radical prostatectomy nomograms in black American men: accuracy and applicability. J Urol 2003 Jul;170(1):73-76; discussion 76-77.
21 Ashford AR, Albert SM, Hoke G, Cushman LF, Miller DS,

Bassett M. Prostate carcinoma knowledge, attitudes, and screening behavior among African-American men in Central Harlem, New York City. Cancer 2001;91(1):164-172.
22 Hoffman RM, Harlan LC, Klabunde CN, Gilliland FD, Stephenson RA, Hunt WC, Potosky AL. Racial differences in initial treatment for clinically localized prostate cancer. Results from the prostate cancer outcomes study. J Gen Intern Med. 2003;18(10):845-853.
23 Yan Y, Carvalhal GF, Catalona WJ, Young JD. Primary treatment choices for men with clinically localized prostate carcinoma detected by screening. Cancer. 2000;88(5):1122-1130.
24 Denberg TD, Beaty BL, Kim FJ, Steiner JF. Marriage and ethnicity predict treatment in localized prostate carcinoma. Cancer. 2005;103(9):1819-1825.
25 Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–297.
26 Ross R, Bernstein L, Judd H, Hanisch R, Pike M, and Henderson B. Serum testosterone levels in young black and white men. J Natl Cancer Inst 1986;76:45-48.
27 Ellis L, Nyorg H. Racial and ethnic variation in male testosterone levels: A probable contributor to group differences in health. Steroids 1992;57:72-75.
28 Kubricht WS, Williams BJ, Whatley T, Pinckard P, and Eastham JA. Serum testosterone levels in African American and white men undergoing prostate biopsy. Urology 1999;54:1035-1038.
29 Kemppainen JA, Lane MV, Sar M., Wilson EM. Androgen receptor phosphorylation, turnover, nuclear transport and transcriptional activation: Specificity for steroids and antihormones. J Biol Chem 1992;267:968-974.
30 Grino PB, Griffin JE, Wilson JD. Testosterone at high concentrations interacts with the human androgen receptor similar to dihydrotestosterone. Endocrinology 1990;126:1165-1172.
31 Ross RK, Bernstein L, Lobo RA, Shimizu H, Stanczyk FZ, Pike MC, Henderson BE. 5-alpha reductase activity and the risk of prostate cancer among Japanese and United States white and black males. Lancet 1992;339:887-889,.
32 Ghanadian R, Puah CM, O' Donoghue EP. Serum testosterone and dihydrotestosterone in carcinoma of the prostate. Br J Cancer 1979;39:696-699.
33 Gustafsson O, Norming U, Gustafsson S, Enroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: A study of a randomized population. Br J Urol 1996;77:433-440.
34 Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88:1118-1126.
35 Hsing AW, Comstock GW. Serological precursors of cancer: Serum hormones and risk of subsequent prostate cancer. Cancer Epidemiol Biomarker & Prent 1993;2:27-32.
36 Mohler JL, Gaston KE, Moore DT, Schell MJ, Cohen BL, Weaver C, Petrusz P. Racial differences in prostate androgen levels in men with clinically localized prostate cancer. J Urol 2004 Jun;171(6 Pt 1):2277-2280.
37 Lubahn DB, Joseph DR, Sullivan PM, Willard HF, French FS, Wilson EM. Cloning of human androgen receptor complementary DNA and localization to the X chromosome. Science 1988;240(4850):327-330.
38 Gaston KE, Kim D, Singh S, Ford OH 3rd, Mohler JL. Racial differences in androgen receptor protein expression in men with clinically localized prostate cancer. J Urol 2003;170(3):990-993.
39 Olapade-Olaopa EO, Muronda CA, MacKay EH, Danso AP, Sandhu DP, Terry TR, Habib FK. Androgen receptor protein expression in prostatic tissues in black and Caucasian men. Prostate 2004;59(4):460-468.
40 Reichardt JK, Makridakis N, Henderson B, Yu MC, Pike MC, Ross RK. Genetic variability of the human SRD5A2 gene: Implications for prostate cancer risk. Cancer Res 1995;55:3973-3975.
41 Miller GJ. Prostate cancer among the Chinese: Pathologic, epidemiologic, and nutritional considerations. In Resnick MI and Thompson IM, eds. Advanced therapy of prostate disease. London, BC Decker, 2000:18-27.
42 Messina MJ, Persky V, Setchell K, Barnes S. Soy intake and cancer risk: a reiview of the in vitro and in vivo data. Nutr Cancer 1994;21:113-131.
43 Herman C, Aldercreutz T, Golden BT, et al. Soybean phytoestrogen intake and cancer risl. J Nutr 1995;125:713S-716S.
44 Steele VE, Pereira MA, Sigman CC, Kelloff GJ. Cancer chemoprevention agent development strategies for genistein. J Nutr 1995;125:713S-716S.
45 Berg JW. Canmetabolism explain the pattern of international epidemiology of hormone-dependent cancers? Cancer Res 1975;35:3345-3350.
46 Blair A, Fraumeni JF. Geographical patterns of prostate cancer in the United States. J Natl Cancer Inst 1978;61:1379-1384.
47 Hill P, Wynder E, Gardies H, Walker AR. Environmental factors, hormone status and prostate cancer. Prev Med 1980;9:657-666.
48 Hestimat M, Kaul L, Koui J, Jackson MA, Jackson AG, Jones G, Edson M, et al. Nutrition and prostate cancer: A case-control study. Prostate 1985;61:1379-1384.
49 Pandalai PK, Pilat MJ, Yamazaki K, et al. The effects of omega 3 and omega 6 fatty acids on in vitro prostate cancer growth. Anticancer Res 1996;16:15-20.
50 Bonkhoff H, Fixemer T, Reinberger K. Relation between bcl-2, cell proliferation, and the androgen recptor status in prostate tissue and precursors of CaP. Prostate 1998;34:251-258.
51 Amling AL, Kane CJ, Riffenburgh RH, Ward JF, Roberts JL, Lance RS, Friedrichs PA, Moul JW. Relationship between obesity and race in predicting adverse pathologic variable in patients undergoing radical prostatectomy. Urology 2001;58:723-727.
52 Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: Biological actions. Endocr Rev 1995;16:3-34.
53 Mohan S and Baylink DJ. IGF-binding proteins are multifunctional and act via IGF-dependent and-independent mechanisms. J Endocrinol 2002;175:19-31.
54 Platz EA, Pollak MN, Rimm EB, et al. Racial variation in insulin-like growth factor-1 and binding protein-3 concentrations in middle-aged men. Cancer Epidemiol Biomarkers Prev 1999;12:1107–1110.
55 Wolk A, Mantzoros CS, Andersson SO, et al. Insulin-like growth factor 1 and prostate ca, er risk: A population-based, case-control study. J Natl Cancer Inst 1998;12:911-915.
56 Moyad MA. Is obesity a risk factor for prostate cancer, and does it even matter? A hypothesis and different perspective, Urology 2002;59:41-50.
57 Yip I, Heber D, Aronson W. Nutrition and prostate cancer. Urol Clin North Am 1999;26: 3-411.
58 Tymchuk CN,. Barnard RJ, Ngo TH, Aronson WJ. Role of testosterone, estradiol, and insulin in diet- and exercise-induced reductions in serum-stimulated prostate cancer cell growth in vitro. Nutr Cancer 2002;42:112-116.
59 Blutt S, McDonnell TJ, Poleck TC, Weigel NL. Calcitriol induced apoptosis in LNCaP cells is blocked by overexpression of bcl-2. Endocrinology 2000, 141:10-17.
60 Feldman D, Glorieux FH, Pike JW, eds. In: Vitamin D. San Diego, CA: Academic Press, 1997.

Screening for Prostate Cancer in 2006:
PSA in the 21st Century

Paul D. Maroni, MD, and E. David Crawford, MD

Few issues in urologic oncology seem so intrinsically correct, but empirically unproven as the utility of screening for prostate cancer. For a predominantly asymptomatic disease until an incurable stage, preemptive diagnosis at a time when intervention might be curative seems intuitively beneficial. As treating physicians, we have patients with clear elements of biologically aggressive disease found through screening and cured with local therapy, who otherwise should have succumbed to the disease. We attribute this "cure" to the screening process, and this serves as anecdote for future patients facing the decision of whether to screen or not. We also have patients with low-volume, low-grade cancers detected through screening and experiencing chronic mental or physical debilitation as a result of their cancer diagnosis or treatment, which may serve as anecdote as well, especially considering the potential that the disease may have followed a benign course.

Critics of screening typically cite concerns related to overdiagnosis and the attendant overtreatment, diagnosis at a time when cure is not possible, economic issues, and the morbidity of screening. Autopsy studies demonstrate that about 35% of men in their fifties have prostate cancer, yet only 15% of men are diagnosed and 3-4% die from it.[1] This contributes to the idea that "men die *with* prostate cancer, not *from* it." Others worry that prostate cancer screening could potentially misuse important resources with initial estimates of about $25 billion per year for screening men between ages 50 and 70. Critics also raise the issue of patient morbidity with the anxiety and discomfort associated with the biopsy, the complications of treatment, and the potential for disease recurrence. Additionally, the heterogeneous behavior of prostate cancer allows a relatively narrow window for screening to be effective in the men most likely to benefit from it. The diagnosis and treatment of incurable, but asymptomatic disease is debatable for some when diagnosis and treatment upon symptomatic progression might have avoided emotional morbidity. One might argue that prostate-specific antigen (PSA) screening is more efficient at identifying the less important, slow-growing tumors and, therefore, contributes to overdiagnosis. These seemingly potent arguments cast doubt on the overall utility of screening and leave the internist or general practitioner wondering what to do since the burden of complaints among patients with low-volume, low-grade cancers primarily falls on them.

While an issue of reasonable contention, overdiagnosis tends to not burden men that typically proceed to surgical therapy. In analyses of radical prostatectomy series, less than 10% of tumors removed are considered "insignificant" as generally judged by pathologic stage, grade, and size.[2] Over-diagnosis has not been overlooked by oncology care providers, and most men diagnosed with prostate cancer will have a care plan considering comorbidities, the benefits/side effects of treatment, and the likelihood of disease progression. While broad screening could potentially incur high costs, as a matter of resource allocation, the cost of prostate cancer screening would be between $9,000 and $145,000 (best and worst case scenarios, respectively) per quality-adjusted life year (QALY) saved.[3] This is on par

"While screening might not benefit certain individuals, taken as a whole, screening appears to decrease morbidity and mortality.

Paul D. Maroni, MD, is a resident in Urology, Division of Urology, Department of Surgery, University of Colorado Health Sciences Center. He can be reached at paul.maroni@uchsc.edu or 4200 East Ninth Avenue, C-319, Denver, Colorado 80262. Telephone: 303-315-0911.

E. David Crawford, MD, is Professor of Surgery and Radiation Oncology and Head of Urologic Oncology at the University of Colorado Health Sciences Center. Dr. Crawford can be reached at david.crawford@uchsc.edu or 1665 N. Ursula Street, Suite 1004, Aurora, CO 80010. Telephone: 720-848-0170.

with using hydrochlorothiazide or captopril for treating hypertension and much less expensive than mammography screening ($232,000/QALY gained). There are other ways to make screening more cost effective. Early data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial suggests that men with PSA values between 1 and 2 ng/mL might only require screening every two years, while men with PSA levels less than 1 ng/mL might be screened every five years.[4] This alone would still detect 99% of men eventually progressing to a PSA greater than 4 ng/mL and would result in savings up to $1 billion per year. Morbidity reduction and management are well-developed areas of prostate cancer treatment. Prostate biopsies are much more tolerable with local anesthesia, and pathology results are typically available within a week. The competition of local therapies has enticed providers to pursue and achieve real decreases in rates of side effects. Also, our understanding of what constitutes aggressive cancer has advanced, allowing for active surveillance trials in patients with low-risk disease. While screening might not benefit certain individuals, taken as a whole, screening appears to decrease morbidity and mortality.

Most of the data supporting screening has been inferential by analyzing trends in morbidity and mortality before and after the addition of the PSA blood test. Analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database has demonstrated a 20% reduction in prostate cancer mortality between 1991 and 1999.[5] Over a similar time period, men in Mexico have experienced a small increase in mortality presumably due to the lack of screening available.[6] These inferences are complicated by the fact that improvements in treatments, including the massive expansion of androgen-deprivation therapies, may have affected prostate cancer survival and the development of metastasis. In Tyrol, Austria, men over 50 years old were offered screening while men in other regions were not. Tyrol men have experienced greater than a 40% decrease in mortality from prostate cancer, which has not been experienced in other regions in Austria.[7] Numerous large randomized trials are currently underway regarding prostate cancer screening, including the PLCO Cancer Screening and the European Randomized Screening for Prostate Cancer (ERSPC) trials that have collectively accrued over 230,000 men. Results from these trials will not be available for several years and are eagerly awaited. Currently, most expert organizations recommend some form of cancer screening using PSA and/or digital rectal exam beginning at the age of 50 in men with a life expectancy of more than ten years with informed decision making. The United States Preventive Services Task Force does not recommend prostate cancer screening with the absence of supportive Level 1 evidence.

Informed Consent and Ethical Concerns

Along with this lack of Level 1 evidence and the need for informed consent are numerous ethical concerns. Unfortunately, most PSA screening performed today does not involve a thorough consent process. The "required" discussion is an impediment to PSA screening, as internists might forego the discussion and, thus, the test, focusing instead on other prudent medical issues. Given time constraints in today's practice environment, this lengthy discussion cannot happen in a practical manner without some sort of supplemental material in the form of videos or pamphlets that would ideally be reviewed prior to the office visit. Many institutions have constructed these sorts of materials (see Table 1). Even with results of randomized trials, some level of informed consent would still be beneficial prior to including PSA in a general lab panel. Maybe prostate cancer screening is not for "everyone." Patients may forgo diagnostic procedures based on individual utilities of sexual and urinary function. Our philosophical approach is that "knowledge is power," and patients may make educated decisions about treatment choice (including active surveillance) after diagnosis.

Several years ago, enthusiasm was building for the next round of PSA-related markers, such as free, complexed, and pro-PSA. The use of these markers has been examined, but has not realized wide acceptance. While their use results in increases in sensitivity and specificity of diagnostic testing, the benefits are incrementally small, and the complexity of interpreting results is often an intellectual endeavor. Newer diagnostic tests using advanced laboratory techniques are also in development. The addition of these tests also creates a logistic and systemic problem. Some combination of tests may be optimal, but how can this be prospectively studied in a randomized fashion when these types of trials are time-consuming and potentially obsolete when results are available? At this point, PSA velocities have proven more clinically valuable. Recent studies have demonstrated a link between prostate cancer mortality and pre-treatment PSA velocity. Generally, an increase of PSA greater than 0.75 ng/mL in a year would support prostate biopsy, while an increase of greater than 2 ng/mL in a year carries a worse prognosis.[8,9] The threshold for PSA screening has also decreased, with some authorities recommending biopsies in patients with age-specific

Table 1.
Informational Resources for Prostate Cancer Screening

Resources for Prostate Cancer Screening
Prostate Cancer Screening: A Decision Guide *www.cdc.gov/cancer/prostate/decisionguide/index.htm*
Screening for Prostate Cancer: Sharing the Decision *www.cdc.gov/cancer/prostate/screening/index.htm*
Leaflet from the Centre for Reviews and Dissemination *www.york.ac.uk/inst/crd/em22b.htm*
Link from UpToDate® Patient Information *http://patients.uptodate.com/topic.asp?file=cancer/6435*
Patient Guide from the American Urologic Association *www.auanet.org/timssnet/products/guidelines/patient_guides/prostate_awareness.pdf*

PSA values as low as 2.0 ng/mL. This approach can diagnose a number of potentially aggressive cancers at a more curable stage.

Screening techniques for other malignancies, such as cervical, breast, and colon cancer, tend to be much more invasive than a blood test or digital rectal exam (DRE). Yields of these exams vary widely based on risk group, age, etc., but tend to be less than 10% for the detection of a malignancy (pre-malignant lesions not included). By logical extension, a prostate biopsy could almost be considered as a screening device as the degree of invasiveness is on par with other screening exams, and the yields are universally greater than 10% in men over the age of 62 regardless of age or rectal exam.[10] Improvements in ultrasound probes, biopsy devices (smaller, spring-loaded needles), and local anesthetic techniques have made a diagnostic prostate biopsy fast and tolerable for most men. This approach is not accepted, considered, or even being examined with large trials in regard to prostate cancer screening. Clearly, the approach to prostate cancer is different largely due to estimates of over-diagnosis of up to 50%. The above diseases are universally more fatal in a shorter period of time. Additionally, the social consequences of local prostate therapy tend to be more personally destructive. As a requirement of expanding the indication of prostate biopsy to a screening instrument, we would need to have a better understanding of morbidity and lethality after diagnosis, more accurate staging tools, and embrace an active surveillance approach, initiating treatment at a time prior to the development of advanced disease. Ongoing active surveillance trials and the use of molecular markers hold much promise in this area.

One of the problems with screening trials is the approach to treatment after diagnosis. While treatment of other malignancies tends to follow a step-wise course based on evidence, in the prostate cancer literature, there is only one randomized trial that demonstrates that local treatment of prostate cancer will extend life (prostatectomy versus no treatment) and one other comparison trial with only 100 patients.[11,12] Numerous impediments limit academic production in this area and accruals in head-to-head treatment trials have historically been dismal, resulting in early abandonment. Most sources accept that treatment choice probably does not substantially affect mortality in a seven-to-ten-year window, but time periods beyond this, parenthetically the most important, are subject to speculation and debate. Hopefully, retrospective analysis of treatment choice in the larger screening studies will contain homogenous groups of the different treatment modalities, but these results could be decades away. Unfortunately, questions in this area may never be fully answered through randomized trials without an acceptable short-term endpoint that is a surrogate for death from prostate cancer.

Conclusion

On speculation, the future for prostate cancer screening will likely consist of: (1) occasional PSA (or other unspecified blood or urine molecular marker) checks at long intervals based on risk group in the fifth decade, (2) PSA/molecular marker checks based on level after the sixth decade, and (3) 12-core prostate biopsy with local anesthesia and digital rectal exam at intervals based on risk group after the sixth decade. Screening will probably be discontinued when a patient has a negative prostate biopsy and a functional index score that would predict an eight-to-ten year life expectancy. Using this hypothetical algorithm for experiment generation, simultaneous advances would need to occur for more sensitive screening instruments, individual risk assessment (including genetic susceptibility testing pre/post-diagnosis), and screening interval modification.

As physicians who treat prostate cancer, we have an enormous problem with expectation management related to imperfect predictive modeling and unique nuances increasing the complexity of patient discussion. Our patients reasonably expect that we will recommend care that will extend the quality and the quantity of their lives. Clearly, not all prostate cancer behaves the same; however, the connotations of a cancer diagnosis from a patient's perspective are usually different from the clinical reality. Actuarial estimates of average gain from prostate cancer treatment are between zero and three years of additional "quality-adjusted life years" per patient.[13] True or perceived effects of treatment on urinary and sexual function appropriately guide many men's choice of treatment, but results of treatment (e.g., potency after prostatectomy) are not universally reproducible. The empathetic physician thoroughly reviews these and other issues and generally receives reward in conscience only. The wise physician recommends directed patient research and deliberate decision making, while the unwise recommends urgent and narrow treatment options. Walking hand-in-hand with better knowledge about PSA screening will be improvements in treatment, morbidity reduction, and other technological advances in detection. In theory, a negative PSA screening study may not be valid considering this dynamic process. The face of prostate cancer screening might change substantially in the future and may no longer even involve PSA blood testing. **NCMedJ**

REFERENCES

1 Sakr WA, Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. J Urol 1993;150(2 Pt 1):379-385. [PMID: 8326560]

2 Loeb S, Gonzalez CM, Roehl KA, et al. Pathological characteristics of prostate cancer detected through prostate-specific antigen based screening. J Urol 2006;175(3 Pt 1):902-906. [PMID: 16469576]

3 Thompson IM, Optenberg SA. An overview cost-utility analysis of prostate cancer screening. Oncology (Williston Park) 1995;9(11 Suppl):141-145. [PMID: 8608045]

4 Crawford E, Chia D, Andriole G, et al. PSA testing interval reduction in screening intervals: data from the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. Program and abstracts of the American Society of Clinical Oncology 38th Annual Meeting, May 18-21, 2002; Orlando, Florida. Abstract 4.

5 Stephenson RA. Prostate cancer trends in the era of prostate-specific antigen. An update of incidence, mortality, and clinical factors from the SEER database. Urol Clin North Am 2002;29(1):173-181. [PMID: 12109343]
6 Tovar-Guzman V, Hernandez-Giron C, Lopez-Rios O, Lazcano-Ponce EC. Prostate cancer mortality trends in Mexico, 1980-1995. Prostate 1999;39(1):23-27. [PMID: 10221262]
7 Horninger W, Berger A, Pelzer A, et al. Screening for prostate cancer: updated experience from the Tyrol study. Curr Urol Rep 2004;5(3):220-225. [PMID: 15161571]
8 D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 2004;351(2):125-135. [PMID: 15247353]
9 D'Amico AV, Renshaw AA, Sussman B, Chen MH. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. JAMA 2005;294(4):440-447. [PMID: 16046650]
10 Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004;350(22):2239-2246. [PMID: 15163773]
11 Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005;352(19):1977-1984. [PMID: 15888698]
12 Akakura K, Isaka S, Akimoto S, et al. Long-term results of a randomized trial for the treatment of stages B2 and C prostate cancer: Radical prostatectomy versus external beam radiation therapy with a common endocrine therapy in both modalities. Urology 1999;54(2):313-318. [PMID: 10443731]
13 Bhatnagar V, Stewart ST, Bonney WW, Kaplan RM. Treatment options for localized prostate cancer: Quality-adjusted life years and the effects of lead time. Urology 2004;63(1):103-109. [PMID: 1471359]

The Role of the Pathologist in Diagnosing Prostate Cancer and Guiding Therapy

Michael H. Weinstein, MD, PhD

Introduction

The recognition that serum prostate-specific antigen (PSA) concentration is a marker for adenocarcinoma of the prostate and the ability to measure PSA concentration represent major watersheds in the treatment of prostate cancer. Prior to these advancements in the 1980s, enlargement of the prostate gland detected by digital rectal exam, local symptoms, or sequelae of metastatic disease were the usual means of discovery of prostate cancer. In this pre-PSA era, prostate cancers were usually incurable at the time of diagnosis. PSA screening has lead to earlier detection and, although interpretation of recent epidemiologic data is still being debated, there is good evidence that PSA screening, prostate biopsy, and therapy with curative intent have lead to decreased morbidity and mortality from this disease.[1]

Also during the 1980s, refinements in the surgical technique for radical prostatectomy, which is potentially curative, yielded significant advancement in the treatment of prostate cancer by reducing the risk of morbidity associated with the surgery. These refinements hinged on two discoveries. First, elucidation of the venous plexus in the region of the prostate allowed operation in a "bloodless" field. This led to more accurate dissection, especially at the prostatic apex and, thus, greater preservation of urinary continence. Second, understanding the anatomy and function of the network of nerves around the prostate allowed "nerve-sparing" surgery and greater preservation of sexual function following radical prostatectomy.

These advancements required better means of screening and definitive diagnosis. PSA measurement and the thin-needle biopsy technique and equipment, although not perfect, are powerful tools for these purposes. Thin-needle biopsies cause less morbidity than open biopsy or biopsy with larger needles. As the pieces of tissue obtained by biopsy became much smaller, pathologists had to develop new techniques and expertise in interpreting these very thin biopsies.

PSA measurement has limitations, primarily in specificity, making this non-invasive test most useful as a first-line or screening detection method. While a few patients with prostate cancer have a normal serum PSA concentration, there are a significant number of men without cancer who have an abnormal concentration for whom therapy would not be warranted.

Thin-needle biopsy, by contrast, has essentially 100% specificity. The sensitivity of this test is estimated to be at least 75%, meaning that it will accurately detect three-out-of-four true cancers. Although more than one set of biopsies may be required for diagnosis, the morbidity associated with thin-needle biopsy is very low.

"PSA screening has lead to earlier detection, and... there is good evidence that PSA screening, prostate biopsy, and therapy with curative intent have lead to decreased morbidity and mortality from this disease."

Pathologists have played a crucial role in the accumulation of the data upon which modern therapy is based, and they continue to provide essential information upon which medical oncologists, radiation oncologists, surgeons, and patients base their therapeutic and management decisions. This commentary is meant to outline the ways in which the clinical pathology laboratory and the work of pathologists serve as crucial components of the clinical decision-making process.

Michael H. Weinstein, MD, PhD, is Director of Pathology Laboratories at WakeMed Health and Hospitals in Raleigh, NC. Dr. Weinstein can be reached at MWeinstein@wakemed.org or 3000 New Bern Avenue, Raleigh, NC 27610. Telephone: 919-350-8260.

PSA Testing

Prostate-specific antigen (PSA) is a serine protease enzyme secreted by the glandular epithelium of the prostate into the ducts of the gland. It ultimately contributes to the composition of the seminal fluid. Its normal function is thought to be liquefaction of semen. Much lower concentrations are typically found in the blood, where the majority of PSA is protein-bound. Measurement of PSA concentration is based upon binding of a PSA-specific antibody to the substance. Multiple tests have been developed using different antibodies, and there is a variation in results between laboratories of up to 25% or more in the range of 0-6.0 ng/ml.[2] Moreover, some methods show greater precision than others. PSA testing has two principal uses. It is widely used to screen for prostate cancer and to monitor individual patients, either following therapy or during a "watchful-waiting" period. The variation between laboratories is of less significance when PSA testing is used for screening purposes than when following an individual patient. In the latter circumstance, it may be helpful to use a single, reliable laboratory for serial testing.

PSA Screening

The "normal" PSA concentration in men has been given as less than 4.0 ng/ml, although there is considerable disagreement over the threshold value that should prompt additional testing for prostate cancer. More recently, age-specific ranges have been given, including an upper limit of 2.5 ng/ml for men under the age of 50.[3,4] Elevated serum PSA concentration is associated with multiple pathological processes and some situations in which there is no disease. Benign prostatic hyperplasia (BPH), prostatitis, and prostate cancer are the main pathologic states in which increased serum PSA is often seen. Prostate biopsy itself, ejaculation, and, possibly, exercise may also lead to an increase in the PSA.

It is the association of elevated PSA concentration with prostate cancer that has lead to its utility in screening. The test is non-invasive (requiring only a blood sample through venipuncture) and is relatively inexpensive. Unfortunately, the range of PSA concentrations seen in patients with prostate cancer overlaps with the range seen in benign processes. The essential limitation is that there is no single value separating men with cancer from those without.

The *sensitivity* of a test is defined as the fraction of individuals with a specific disease for whom the test will yield a positive result. The *specificity* of a test is defined as the fraction of all abnormal results that represent individuals who do have the disease for which they are being tested. Decreasing the maximum PSA value that is considered "normal" increases the sensitivity of the test in detecting prostate cancer. However, this also leads to an increase in the number of men who are labeled "abnormal" who do not have this disease (decreased specificity). Thus, while measurement of serum PSA concentration has proved to be a powerful tool in the ability to detect prostate cancer, appreciation of its limitations is critical for maximization of its utility. In fact, average PSA concentration in men without prostate cancer increases with age. This is largely due to BPH, which increases in incidence and severity. In truth, the PSA test is best used to estimate the chance that an individual has carcinoma of the prostate. PSA testing cannot be used to render a definitive diagnosis.

In an effort to increase sensitivity and specificity, derivative PSA tests have been developed. These include measurement of free PSA and calculation of the ratio of free/total PSA. These methods have yielded some increase in sensitivity and specificity with increased cost, but still suffer from an overlap in ranges in the populations of men with and without prostate cancer.[5,6] They may provide additional guidance in difficult circumstances, such as when PSA levels are significantly elevated, multiple sets of biopsies have been negative, and no other explanation for the elevation in PSA level is apparent.

The ratio of free/bound PSA is considered abnormal by many when it falls below 25%. This cutoff is associated with sensitivity and specificity of approximately 90% and 25%, respectively, for the detection of prostate cancer.

PSA velocity is the rate at which the serum PSA concentration rises over time. This calculation is of some use in men with borderline elevated PSA.[7] A PSA velocity greater than or equal to 0.75 ng/ml per year with measurements spanning at least 18 months has sensitivity and specificity of approximately 70% and 90%, respectively. Specific measurement of bound PSA has not been demonstrated to offer a significant improvement in detection.

PSA density, which is defined as the serum PSA concentration divided by the volume of the prostate as measured by transrectal ultrasound, has proven to have limited value.

Other tests potentially on the horizon include pro-PSA and human kallikrein-2, but these are not ready for routine clinical use in screening for prostate cancer.

PSA Monitoring

Serum PSA concentration is also useful for monitoring patients for progression of disease. Until late in the disease when the tumor may become so poorly differentiated that its ability to produce PSA protein becomes impaired, increasing PSA concentration is associated with advancing disease. Thus, the serum PSA typically falls to near zero following prostatectomy, since all of the prostate tissue, both benign and malignant has usually been removed. Minute amounts of tumor that may have spread beyond the prostate prior to surgery may not produce enough PSA to be detected until they grow, at which time the PSA concentration begins to rise.

The PSA often does not fall to zero in patients who have received radiation therapy without surgery. However, the PSA does fall for months following the treatments. In fact, the lower the nadir (lowest concentration detected) in PSA, the greater the chance of cure or long-term remission. Moreover, the longer the time it takes to reach the PSA nadir, the better the prognosis.[8]

Some patients with proven prostate cancer choose "watchful waiting" over therapy in order to avoid the morbidity associated with prostatectomy, radiation therapy, and hormonal therapy. A significant rise in serum PSA concentration may prompt physicians to recommend therapy to avoid morbidity and mortality associated with progression of the disease.

Prostate Biopsy

The thin-core needle biopsy technique and equipment allow multiple biopsies to be performed in the doctor's office with minimal morbidity (significant complications less than 0.5%) and provide material for definitive diagnosis of prostate cancer. The sensitivity of this procedure is very difficult to gauge. In the absence of metastatic disease, there is no way to tell with certainty whether a man has prostate cancer without pathologic examination of the entire prostate gland, which requires removal. Moreover, the sensitivity likely varies with the prevalence and type (i.e., grade, stage) of prostate cancer in the population being studied. However, based on data that do exist, a reasonable estimate for the sensitivity of needle biopsy of the prostate in patients with elevated PSA is at least 75%, if cancers detected on a second or later set of biopsies are included.

There is little debate about which areas of the prostate to biopsy, at least on the initial attempt to demonstrate tumor. However, the optimal number of biopsies to perform is not clear. The sextant biopsy technique (six biopsies) was considered adequate and was, by far, the most commonly used technique for approximately a decade. In recent years, it has become clear that performing more biopsies improves the chances of detecting cancer on the first attempt.[9] This is especially true when the prostate is markedly enlarged due to BPH. However, more biopsies are associated with greater discomfort, a greater chance of complications, and greater cost. Moreover, the incremental increase in sensitivity with each additional biopsy diminishes progressively. At the present time, there is no agreement on how many biopsies more than six should be performed.

In addition to identifying the presence of cancer, the pathologist interpreting the biopsies routinely provides other indispensable information regarding the tumor. The following diagnostic categories should be included in the pathologist's report. The clinical significance of each is summarized in Table 1.

Tumor Grade

Tumor grade is probably the single most important tumor characteristic assessed on needle biopsy of the prostate. The Gleason grade, also termed Gleason score or Gleason sum, is very useful in predicting the behavior of a given patient's tumor. Thus, it is used in planning therapy and estimating prognosis. Although the grade of the tumor in the biopsies is not a perfect predictor of the grade of the tumor in the prostate as a whole, the correlation is good. The lack of perfect correlation is not surprising, since the volume contained in an entire set of biopsies usually comprises less than one thousandth of the volume of the entire prostate gland.

It is worth noting that each type of cancer specific to an organ in the body has its own histopathologic (microscopic) grading scheme. The Gleason grading scheme is very unusual in that it ignores the appearance of the individual cancer cells and concentrates purely on the patterns of growth of the malignant prostate glands. The method takes into account the common occurrence of multiple glandular patterns of cancer being present in a single patient's tumor. Numerals 1-5 have been assigned to recognized categories of tumor patterns, and, traditionally, the two most prevalent pattern types are given as well as the numeric sum. Thus, a Gleason grade of 3+4 = 7 might be reported, where "3" represents the tumor pattern most prevalent in a specimen and "4" represents the second most prevalent pattern. The Gleason score of a homogeneous tumor will simply have the same number repeated in the sum (e.g., 3+3 = 6). A consensus of genitourinary pathologists has recommended long-overdue modifications to the original scheme, which was devised around 1970, but the essential concepts remain unchanged. It is now recommended that small amounts of high-grade tumor (i.e., Gleason pattern 4 or 5) be reported even when they represent neither the first nor second most prevalent pattern, as this finding correlates with more aggressive tumor behavior.[10]

The combination of PSA concentration, findings from digital

Table 1.
Pathologic Parameters Assessed on Thin-Needle Core Biopsy of the Prostate and the Clinical Significance of Each Parameter.

Parameter	Clinical Importance
Tumor Grade	Used to predict aggressiveness of tumor, stage, response to non-surgical therapy, and chance of cure with various types of therapy.
Location and Extent of Tumor in Biopsy Cores	Used to predict stage and response to some types of therapy (e.g., radiation therapy).
Perineural Invasion	May be used to plan extent of surgery (e.g., whether to sacrifice neurovascular bundle).
Atypical Glands	Re-biopsy should be performed—indicate ~50% chance of finding cancer on re-biopsy.
High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)	~30% or less chance of finding cancer on re-biopsy, depending on how many biopsies originally performed. HGPIN may represent a precursor of prostate cancer.
Tumor Characteristics Following Therapy: Grade of tumor and whether therapy effect is present.	Used to assess prognosis and predict whether additional therapy is likely to be of benefit.

rectal exam, and biopsy Gleason grade has been used to estimate the stage of the tumor. The likelihood that the tumor is confined to the prostate, the chance of local spread into the surrounding fibroadipose tissue, the chance of invasion into the seminal vesicles, and the chance of local lymph node metastases can be estimated. These data have been compiled in the "Partin Tables,"[11] providing useful summary information to help each patient and his physician to make sensible decisions regarding choice of therapy.

Location and Extent of Tumor

The pathologist should report the amount of cancer present in the biopsy core(s) originating from each biopsy site. This information can be useful in estimating stage and predicting long-term outcome following therapy (e.g., prostatectomy, radiation therapy), especially when combined with other parameters, such as PSA concentration and tumor grade.[12,13]

Perineural Invasion

The presence of invasion of small nerves in the biopsy cores by the cancer is predictive of spread beyond the prostate when viewed in univariate analyses.[14] The reasoning behind these initial studies stemmed from the hypothesis, which is still accepted, that one of the main routes of tumor escape from the prostate is by tracking along nerves that traverse the surface of the prostate and comprise a portion of the periprostatic neurovascular bundles. However, most of the predictive power of the finding of perineural invasion on needle biopsy disappears in multivariate analyses when other variables, such as Gleason grade, are taken into account. Still, it may provide marginal additional information and may play a role in deciding whether or not to sacrifice one or both neurovascular bundles during surgery.

Atypical Glands

Unfortunately, a significant minority (≈5%) of prostate biopsies are neither definitively benign nor definitively diagnostic of carcinoma. The term often used in this situation is "atypical," sometimes in the phrase "atypical small acinar proliferation" (ASAP). The frequency of this occurrence is somewhat dependent on the experience of the pathologist interpreting the biopsies. Special studies (e.g., immunohistochemical staining) can occasionally lead to a more definitive diagnosis, but diagnosis usually hinges on tried and true ordinary techniques (i.e., H&E staining). The finding of atypical glands suspicious for carcinoma without other, definitively diagnostic areas warrants repeat biopsy.[15,16] In fact, the chance of finding prostate cancer on subsequent re-biopsy (one or more sets) is approximately 50%. Should re-biopsy prove inconclusive, other factors, such as total PSA concentration, free/total PSA ratio, clinical findings, and patient desire, provide guidance in choosing a course for repeat re-biopsy or longer-term follow-up with measurement of PSA velocity.

It should be noted that it is important for each biopsy to be separately labeled to designate the area of the prostate from which it originated. One reason for this is that 90% of all cancers discovered following an initial atypical, non-definitively diagnostic biopsy are identified in the same region or an area adjacent to the one from which the atypical biopsy originated. Thus, these areas are preferentially sampled on re-biopsy in order to maximize the sensitivity of the procedure in detecting tumor.

High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)

Other findings that may increase the suspicion of cancer in the absence of definitively diagnostic biopsy material include the presence of high-grade prostatic intraepithelial neoplasia (HGPIN). Early studies indicated that the risk of unsampled carcinoma in the prostate gland associated with the isolated finding of HGPIN on needle biopsy was approximately 30%.[16,17] At the time, re-biopsy was required. However, if no carcinoma was detected on two sets of re-biopsies, additional biopsies were unlikely to contain tumor. More recent data, especially in the case of more than six biopsies to a set, suggest that the increased risk associated with this circumstance may be less than originally estimated, and the significance of this finding is somewhat diminished.

Since HGPIN is thought by many to represent a precursor of prostate cancer, it is postulated that potential chemopreventive agents may help to prevent prostate cancer in men who have been diagnosed with isolated HGPIN.

Other Clues to Tumor Behavior

Needle biopsy may provide other clues to tumor behavior. For example, prostate cancer clearly identifiable within fat at one end of a core biopsy is indicative of extraprostatic tumor spread. Clearly such information must be factored into therapeutic decisions.

Biopsy Following Therapy

Biopsy following therapy for prostate cancer is useful in a limited set of circumstances and poses challenges for the pathologist interpreting the biopsy. Therapy often alters the microscopic appearance of the tumor, sometimes making recognition of the malignant prostate tissue difficult. It can also alter the appearance of the tumor in ways that abolish the correlation between microscopic pattern and biologic behavior, so that Gleason grading of tumor following therapy is not meaningful in some circumstances.

A rising PSA following therapy is indicative of growing tumor. However, it does not indicate whether the tumor is growing at the primary site (i.e., in the prostate or in the prostatic bed after prostatectomy) or at a metastatic site. Radiographic studies (e.g., x-ray studies or computerized tomography scans) can be used to detect metastases. In the absence of detectable metastatic disease, biopsy of the prostate or prostatic bed may be performed to assess for local tumor growth. As with initial biopsy, skill is required on the part of the pathologist to properly interpret the changes due to therapy and to give an accurate assessment of the presence of cancer and, sometimes, whether it shows effects of therapy.

Pathologic Assessment of Prostatectomy Specimens

Pathologic review of the prostate after it has been removed for cancer also provides important information regarding prognosis and whether further therapy (e.g., radiation therapy) might be of benefit. The main pathologic parameters evaluated are tumor grade, stage (extent of cancer), and whether there is cancer at the surface of the specimen, which might indicate that not all of the tumor was removed. Other parameters may also have prognostic impact.

Tumor Grade

As with prostate biopsy, the recently modified Gleason grading system is used to grade prostate cancer in the prostatectomy specimen. Tumor grade is a powerful predictor of outcome, including risk of recurrence and time to recurrence. Minor discrepancies between the grade assigned on biopsy and the grade obtained from the whole prostate specimen are common. This is typically due to the fact that prostate cancers are usually heterogeneous. Only about one thousandth of the prostate is sampled even with multiple thin-needle core biopsies, and the tissue obtained may not be perfectly representative of the entire tumor.

Lymphvascular Invasion

Careful microscopic examination of the prostatectomy specimen may reveal the presence of tumor within minute lymphatic or blood vessels. It is a significant factor indicative of a poorer prognosis. This finding is rarely discernable on biopsy.

Tumor Stage

Tumor stage is crucial in determining whether adjuvant therapy is likely to be of benefit. Staging is performed according to the American Joint Committee on Cancer (AJCC) guidelines.[18] For example, invasion of the tumor into the adjacent fibroadipose tissue is designated stage T3a. Tumor invasion into either or both of the seminal vesicles is designated T3b, which supercedes T3a, and invasion into surrounding organs, such as the bladder, is designated T4. The absence or presence of metastatic spread into local lymph nodes (i.e., pelvic lymph nodes) is noted as N0 or N1, respectively, and the absence or presence of metastatic spread beyond this is designated M0 or M1. Thus, one might have a patient with staging "T3b N0 M1" if tumor has spread to the seminal vesicles and the spine, but is absent from the pelvic lymph nodes.

Margin Status

The final feature that must be assessed on the prostatectomy specimen is whether prostate cancer is present at the surface of the specimen. This is termed margin positivity and may, especially if it is present in more than a small area, be indicative of local tumor that could not be excised at the time of surgery. The pathologist should report the extent and location of tumor present at the margins. Like tumor stage, this information is needed to make decisions regarding subsequent adjuvant therapy.

Summary

In summary, the role of the pathologist has proven indispensable in diagnosing prostate cancer, planning initial therapy,

Table 2.
Utilities of Various Pathologic Parameters in Detecting Prostate Cancer and in Guiding Therapy.

	Determining need for biopsy/ re-biopsy	Planning initial therapy/ prognosis	Assessing likelihood of benefit from adjuvant therapy	Assessing for recurrance/ progression
PSA				
PSA Concentration	X	X	X	X
PSA Velocity	X			
PSA Density	X			
Free/Total PSA	X			
Biopsy				X
Tumor Grade		X	X	
Location/Extent of Tumor		X		
Perineural Invasion		X		
Atypical Glands	X			
HGPIN	X			
Prostatectomy				
Tumor Grade		X	X	
Stage		X	X	
Lymphvascular Invasion		X	X	
Margin Status		X	X	

assessing prognosis, estimating the likely benefit of adjuvant therapy following prostatectomy or radiation therapy, and in following patients for possible recurrent disease. Moreover, the work of pathologists has been pivotal in the research that has lead to our present understanding of the natural history of prostate cancer and the present methods for estimating the likelihood of benefit from various therapies. Such work continues to be integral to scientific advancement in these areas. **NCMedJ**

REFERENCES

1 Horninger W, Berger A, Pelzer A, Klocker H, Oberaigner W, Schönitzer D, Severi G, Robertson C, Boyle P, Bartsch G. Screening for prostate cancer: Updated experience from the Tyrol study. Can J Urol 2005;12(suppl 1):7-13.

2 College of American Pathologists. Participant Summaries for Ligand (General) Proficiency Surveys K/KN-A, K/KN-B, K/KN-C, 2005.

3 Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, Crowley JJ, Coltman CA. Prevalence of prostate cancer among men with a prostate-specific antigen level less than/equal to 4.0 ng per milliliter. N Engl J Med 2004;350(22):2239-2246.

4 Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology 2006;67(2):316-206.

5 Froehner M, Hakenberg OW, Koch R, Schmidt U, Meye A, Wirth MP. Comparison of the clinical value of complexed PSA and total PSA in the discrimination between benign prostatic hyperplasia and prostate cancer. Urologia Int 2006;76:27-30.

6 Basso D, Fogar P, Piva MG, Navaglia F, Mazza S, Prayer-Galetti T, Castellucci E, Pagano F, Plebani M. Total PSA, free PSA/total PSA ratio, and molecular PSA detection in prostate cancer: Which is clinically effective and when? Urology 2000;55:710-715.

7 Carter HB, Pearson JD. Prostate-specific antigen velocity and repeated measures of prostate-specific antigen. Urol Clin North Am 1997;24:333-338.

8 Ray ME, Thames HD, Levy LB, Horowitz EM, Kupelian PA, Martinez AA, Michalski JM, Pisansky TM, Shipley WU, Zelefsky MJ, Zietman AL, Kuban DA. PSA nadir predicts biochemical and distant failures after external beam radiotherapy for prostate cancer: A multi-institutional analysis. Int J Radiat Oncol Biol Phys 2006;64(4):1140-1150.

9 Siu W, Dunn RL, Shah RB, Wei JT. Use of extended pattern technique for initial prostate biopsy. J Urol 2005;174(2):505-509.

10 Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL, ISUP Grading Committee: The 2005 International Society of Urologic Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29(9):1228-1242.

11 Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI., Pearson JD. Prostate Cancer: The Partin Tables. Available at: http://urology.jhu.edu/prostate/partintables.php. Accessed March 27, 2006.

12 Rubin MA, Bassily N, Sanda M, Montie J, Strawderman MS, Wojno K. Relationship and significance of greatest percentage of tumor and perineural invasion on needle biopsy in prostatic adenocarcinoma. Am J Surg Pathol 2000;24(2):183-189.

13 D'Amico, AV. Combined-modality staging for localized adenocarcinoma of the prostate. Oncology 2001;15(8):1049-1059.

14 Cannon GM Jr, Pound CR, Landsittel DP, Bastacky SI, Dhir R, Becich MJ, Nelson JB. Perineural invasion in prostate cancer biopsies is not associated with higher rates of positive surgical margins. Prostate 2005;63(4):336-340.

15 Girasole CR, Cookson MS, Putzi MJ, Chang SS, Smith JA Jr, Wells N, Oppenheimer JR, Shappell SB. Significance of atypical and suspicious small acinar proliferations, and high grade prostatic intraepithelial neoplasia on prostate biopsy: implications for cancer detection and biopsy strategy. J Urol 2006;175(3):929-933.

16 Schlesinger C, Bostwick DG, Iczkowski KA. High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. Am J Surg Pathol 2005;29(9):1201-1207.

17 Weinstein MH, Epstein JI. Significance of high-grade prostatic intraepithelial neoplasia on needle biopsy. Hum Pathol 1993;24(6):624-629.

18 American Joint Committee on Cancer. AJCC Cancer Staging Manual, 6th Ed, Springer-Verlag, New York, 2002.

Treatment for Localized Prostate Cancer:
Surgical Approaches

Eric M. Wallen, MD

Men who are diagnosed with prostate cancer face a dizzying and growing array of treatment options. These include watchful waiting, two forms of radiation, and three types of surgery. In addition, ever more therapies are entering the field of prostate cancer treatment, such as cryosurgery and high-frequency ultrasound therapy.

Each option comes with a set of risks, including inadequate treatment of the cancer, rectal problems, urinary incontinence, and erectile dysfunction. In the medical field, a great deal of controversy exists regarding the treatment of prostate cancer, and the patient is faced with a great deal of uncertainty when considering his treatment options. The patient's urologist and his primary care physician play crucial advisory roles in the patient's treatment decision. Ultimately each patient must navigate this complex process and make the decision himself.

"Unlike many medical diagnoses, there is not an absolutely correct treatment for prostate cancer, and given this uncertainty, the patient (and his spouse or partner) must participate in the decision-making process."

Most, if not all, urologists are trained to be capable of discussing three major pathways for patients to consider once the diagnosis of prostate cancer is made. These are watchful waiting, radiation therapy, and surgery. Unlike many medical diagnoses, there is not an absolutely correct treatment for prostate cancer, and given this uncertainty, the patient (and his spouse or partner) must participate in the decision-making process. Notably, research has shown that most patients are comfortable in this role.[1]

Watchful Waiting

Watchful waiting is an important option for urologists to discuss with patients and for patients to seriously consider. The rationale for watchful waiting is based on the high incidence but low mortality of prostate cancer in the United States. As of 2005, a man in the United States has a one in six chance of being diagnosed with prostate cancer during his lifetime.[2] However, due to the biologic nature of prostate cancer, most men are destined to die from other causes before they die from prostate cancer—the likelihood of a man dying from prostate cancer is approximately one in 34.[2] More than ever, it is becoming clear that many men do not need to undergo treatment for prostate cancer. Given the risks and the costs of treatment, watchful waiting is an important option to consider, both as a patient and for healthcare systems.

Watchful waiting requires that patients have semi-annual examinations and testing for changes in the prostate-specific antigen (PSA) blood test. In addition, watchful waiting in healthy patients mandates that the patient undergo a repeat prostate biopsy to assess for changes in cancer grade and volume. This should be performed approximately one year after the initial biopsy.

Radiation or Surgical Treatment?

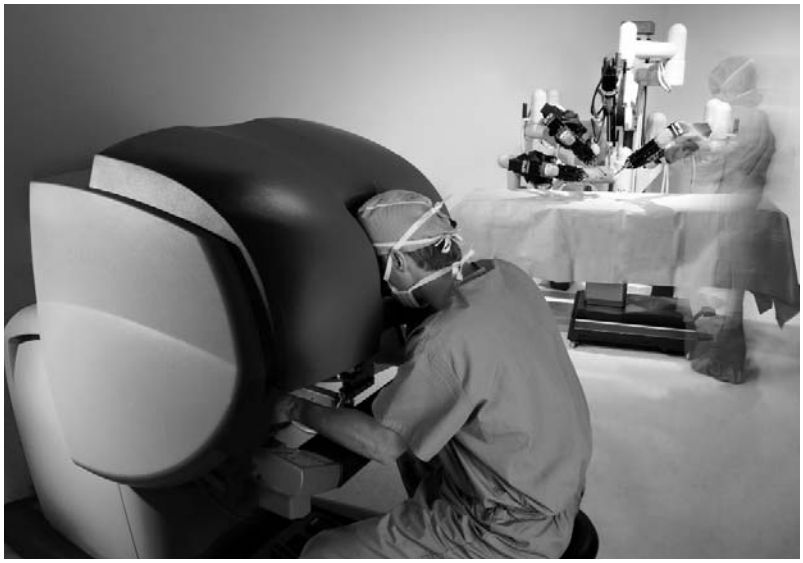
The next level of discussion regarding treatment for prostate cancer involves consideration of intervention in the form of radiation or surgery (i.e., local radical treatment in an attempt to cure what is expected to be organ-confined disease). Both radiation and surgery in all forms generally confer a disease-

Eric M. Wallen, MD, is Assistant Professor of Surgery at the University of North Carolina and Director of Urologic Laparoscopy at UNC Hospitals. Dr. Wallen can be reached at ewallen@med.unc.edu or CB# 7235 Chapel Hill, NC 27599-7235. Telephone: 919-966-9251.

specific survival of at least ten years. Of course, disease-specific survival varies greatly based on the individual patient's disease biology. Most patients with screen-detected prostate cancer have a disease with slow biological progression and can expect little, if any, impact on their lives for 15-20 years. A smaller proportion of patients have more aggressive disease as identified by PSA levels found in their blood and Gleason[a] parameters and may indeed, succumb to the cancer.

Urologists are familiar with the efficacy and side effects of both radiation and surgical treatment, and they can discuss both with patients. Ideally, the radiation modality should be discussed with a radiation oncologist familiar with both brachytherapy (permanent or temporary implantation of the prostate with radioactive seeds) and external beam radiation therapy, so the patient may obtain a balanced view of his treatment options. It is well known that urologists, as surgeons, and radiation oncologists each favor their own treatment modality, and the best way for a patient to navigate this complexity is to discuss treatment with both specialists. However, many urologists perform brachytherapy and can discuss this treatment with the patient in terms of disease control and the potential side effects of lower urinary tract symptoms and erectile dysfunction.

Dr. Wallen controls the robotic instruments using sophisticated joysticks.



At the robotic console, the surgeon views the operation through a 3-D viewfinder and controls the instruments.

Surgical Options

Radical Retropubic Prostatectomy

The discussion of surgery for prostate cancer has become more complex in the past five years, as laparoscopic approaches to surgery have increased the number of surgical techniques available to the patient. The current standard of care, radical retropubic prostatectomy (RRP), has been performed and refined for several decades. This technique, also known as "open surgery," is performed through a vertical incision made below the umbilicus. Data on disease control and the two major functional outcomes, erectile dysfunction and urinary continence, are well known, and these complications are much less common than even ten years ago.[3] Research into healthcare quality is also well defined and indicates that outcomes are better and complications are fewer at medical centers where many RRPs are performed.[4] Similar findings have also been demonstrated when looking at individual surgeons. In the community setting, this information may be difficult for the patient to obtain. Patients who research their treatment options usually learn that an important question to ask their urologist is how many RRPs he or she has performed and how often.

Laparoscopic Radical Prostatectomy

Laparoscopic techniques for performing radical prostatectomy have become more common since the start of the new millennium. Laparoscopy has supplanted open surgery for many surgical procedures, including gall bladder removal, appendectomy, adrenal surgery, Nissen fundoplication (a procedure to alleviate gastroesphageal reflux), and some gynecologic surgeries. Laparoscopic surgery is performed through buttonhole-sized incisions with the aid of a scope placed internally to visualize the operation. The major driving force for laparoscopic surgery is decreased pain and faster recovery; additional benefits are improved visualization of anatomic structures and cosmetic outcomes.

Initially, laparoscopic radical prostatectomy (LRP) was developed as a standardized series of steps by surgeons in France. Adoption of this technique worldwide was limited due to the difficulty in learning this procedure, and it was

a The Gleason scoring system grades prostate cancer patterns from 1 (well-differentiated malignancy) to 5 (poorly differentiated malignancy). For more information see page 123 of Dr. Culley Carson's article in this issue of the Journal.

abandoned by many urologists after their initial efforts. At a small number of medical centers, however, the technique for LRP has been mastered and is the standard surgical treatment offered to patients. Data evaluating outcomes for cancer control, complications, continence, and erectile function show that LRP is equivalent to RRP in experienced, capable hands.[3]

Robotic-Assisted Radical Prostatectomy

Robotics came to the field at approximately the same time that laparoscopic prostatectomy was being attempted around the world. Surgical robotics was developed over the past two decades by the military, and private companies brought these instruments to the bedside in the late 1990s. Only one surgical robotic platform, the da Vinci® Surgical System, is in widespread use today, with approximately 300 of these systems in place around the United States. The major benefit of this instrument is that it makes LRP feasible for many more surgeons, by virtue of creating a three dimensional (3-D), immersive environment for the surgeon and providing instruments with superior manipulation. The downside of this tool is its cost—more than $1 million—to individual hospitals and to the healthcare system in general.

Due to widespread purchase and use of the da Vinci® Surgical System, robotic-assisted radical prostatectomy (RARP) is rapidly becoming a new standard of care in the surgical treatment of prostate cancer. Access to the prostate is very similar to LRP, in the sense that small incisions are made to permit scope and instrument placement. However, the instruments used to perform the operation are controlled by a surgeon who sits away from the patient at a console. There, the surgeon looks into a viewfinder that provides 3-D visualization of the surgical field, and controls the instruments with sophisticated joysticks and foot pedals. Compared to traditional laparoscopic instruments, the robotic-controlled instruments have more flexibility to perform the delicate nerve sparing and sewing parts of the procedure. In addition, the robot eliminates tremor, thereby steadying the surgeon's hands.

Results from RARP appear to be at least as good as RRP and LRP, and some studies have claimed that oncologic and functional outcomes are even better.[5,6] Compared to RRP, LRP and RARP have shorter hospitalizations and lower rates of blood transfusion.[7] The results of RARP, as with the other techniques, are best at medical centers where many of the procedures are performed.[8] Indeed, patients undergoing surgery for prostate cancer by an experienced surgeon can expect to have an excellent chance for recovery of urinary control and baseline sexual function, regardless of the technique. Currently, the field of urology is witnessing patient migration to centers where RARP is performed, based on good results and effective marketing of the robot. I expect that over the next decade, robotic-assisted laparoscopic radical prostatectomies will become the most common surgery performed for patients with prostate cancer.

Conclusion

Prostate cancer as a disease entity is rife with controversy. As common as it is, it certainly does not warrant aggressive treatment in many patients. This is a difficult concept for physicians and patients alike to understand. Over and beyond the next decade, the option of watchful waiting will be further explored by researchers and recommended for more and more patients, spurred by the recognition that most prostate cancer is not lethal. The presence of newer surgical techniques should not obscure this, and urologists, as well as other physicians must recognize this.

At the same time, surgery for prostate cancer is in a state of evolution. The emergence of RARP as a less invasive option has encouraged more physicians and patients to consider surgical treatment. So how are patients supposed to make sense of these developments? Urologists play a crucial role in facilitating patient education through discussion, providing or recommending written material, and directing them to appropriate Internet resources. Patients should be made aware of all options, including watchful waiting, and should understand that the slow pace of the disease process allows them time to carefully consider these options. Patients should advocate for their healthcare by inquiring about the experience of their potential surgeon, investigating outcomes through prostate cancer support groups, becoming educated via media resources, and discussing options with their partner and other family members. At the conclusion of this process a patient is empowered to make a choice with which he is comfortable. **NCMedJ**

REFERENCES

1 Davison BJ, Parker PA, Goldenberg SL. Patients' preferences for communicating a prostate cancer diagnosis and participating in medical decision-making. BJU Int 2004 Jan;93(1):47-51.

2 American Cancer Society. What are the key statistics about prostate cancer? Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_prostate_cancer_36.asp?sitearea=/. Accessed April 3, 2006.

3 Rassweiler J, Hruza M, Teber D, Su LM. Laparoscopic and robotic assisted radical prostatectomy—critical analysis of the results. Eur Urol 2006 Apr;49(4):612-624. Epub 2006 Jan 18.

4 Ellison LM, Heaney JA, Birkmeyer JD. The effect of hospital volume on mortality and resource use after radical prostatectomy. J Urol 2000 Mar;163(3):867-869.

5 Ahlering TE, Eichel L, Skarecky D. Rapid communication: Early potency outcomes with cautery-free neurovascular bundle preservation with robotic laparoscopic radical prostatectomy. J Endourol 2005 Jul-Aug;19(6):715-718.

6 Ahlering TE, Eichel L, Edwards RA, Lee DI, Skarecky DW. Robotic radical prostatectomy: a technique to reduce pT2 positive margins. Urology 2004 Dec;64(6):1224-1228.

7 Menon M, Shrivastava A, Tewari A. Laparoscopic radical prostatectomy: conventional and robotic. Urology 2005 Nov;66(5 Suppl):101-104. Review.

8 Tewari A, Menon M. Vattikuti Institute prostatectomy: Surgical technique and current results. Curr Urol Rep 2003 Apr;4(2):119-123.

Radiation Therapy for Prostate Cancer:
External Beam, Brachytherapy, and Salvage

Scott L. Sailer, MD

Radiation is a viable curative treatment option for localized prostate carcinoma. It can be used as primary therapy and can also be used to cure patients who have failed surgery or are at high risk of recurrence after prostatectomy. For locally advanced tumors, radiation is the preferred treatment and, based on randomized trials, should be combined with hormonal therapy for optimal results. Watchful waiting is another option for patients with low-risk disease.

Radiation as Primary Therapy

Radiation can be delivered using external beam radiation therapy, brachytherapy (permanent or temporary implantation of the prostate with radioactive seeds), or a combination of these methods. There are no randomized trials comparing the various radiation techniques to each other or to radical prostatectomy, so comparisons of outcomes after various treatments is based on retrospective reviews. Risk groups have been developed to categorize the aggressiveness of prostate carcinomas so that patient cohorts who have similar prostate cancers can be compared. One of the more popular risk-group categorizations has been developed by D'Amico et al.[1,2] (see Table 1).

Table 1.
Risk Groups for Clinically Localized Prostate Carcinoma[1,2]

Risk Group	Characteristics	Expected ten-year PSA failure-free survival
Low	PSA < 10 and Gleason score < 6 and 1992 AJCC stage T1c, T2a	80-85%
Intermediate	PSA > 10 and < 20 or Gleason score = 7 or 1992 AJCC stage T2b	50-60%
High	PSA > 20 or Gleason score > 8 or 1992 AJCC stage T2c, T3	30-40%

American Joint Committee on Cancer (AJCC).

These risk groups can be used to compare patients treated at different institutions with different techniques, but as always, there are pitfalls with retrospective reviews arising from patient selection and unknown bias. Patients treated with radiation tend to be older, have more advanced local disease, have higher prostate-specific antigen (PSA) levels, and have higher Gleason scores.[a] Because of this bias, outcomes after radiation will be inferior to surgery unless there is an attempt to compare patients with similar prostate cancers. Risk-group stratification is a simple way to adjust for this bias, but is obviously not as rigorous as randomized trial data. Another difficulty that limits retrospective comparisons is that both surgical and radiation techniques have improved over the past ten-to-15 years, so there is no long-term follow-up of prostate cancer patients treated with modern techniques.

Nevertheless, retrospective comparisons using appropriate risk groups are the best datasets available during patient counseling. Kupelian et al.[3] reported results for 2,507 patients treated with external beam radiation (greater than or equal to 72 Gy), surgery, brachytherapy, or a combination of brachytherapy and external beam from 1990 to 1998 (see Table 2). The data are not "clean" in that a fraction of patients in each treatment group also received hormonal therapy. For some patients receiving radiation, hormonal therapy can improve survival, but at a minimum, patients treated with hormonal therapy will have a delay in PSA recurrence. Hormone use was limited to six months in this study, so the impact of hormonal therapy should be minimal. The patients in the intermediate- and high-risk

a The Gleason scoring system grades prostate cancer patterns from 1 (well-differentiated malignancy) to 5 (poorly differentiated malignancy). For more information see page 123 of Dr. Culley Carson's article in this issue of the Journal.

Scott L. Sailer, MD, is in private practice at Wake Radiology Oncology in Cary, NC. Dr. Sailer can be reached at ssailer@wakeradiology.com or 300 Ashville Avenue, Suite 110, Cary, NC 27511. Telephone: 919-854-4588.

group were primarily intermediate risk. There were no T3 patients (patients with tumors that had spread outside the prostate capsule), 27% of patients had a PSA level greater than 20, and 19% had a Gleason score greater than 7. D'Amico has also reported outcomes for surgery and radiation based on risk groups.[1] No patients received hormonal therapy (see Table 3). These retrospective series show that the results after surgery and radiation are similar at five years. There is also little difference between brachytherapy and external beam radiation. Of note, even within the same risk group, the outcome after surgery is better at the Hospital of the University of Pennsylvania in Philadelphia than it is at Brigham and Women's Hospital in Boston (see Table 3), implying selection of more favorable patients at the University of Pennsylvania even within similar risk groups (assuming surgery is equivalent at the two institutions). While some patients in these series have been followed for ten years, the number of patients followed for ten years is too small to provide reliable data. With additional follow-up, long-term comparisons within these databases will be possible.

"...both surgical and radiation techniques have improved over the past ten-to-15 years, so there is no long-term follow-up of prostate cancer patients treated with modern techniques."

For patients with intermediate- and high-risk prostate cancers, however, comparing surgery to radiation alone no longer reflects clinical practice. There are randomized data that support the use of hormonal therapy in patients with intermediate- and high-risk prostate carcinoma who are treated with radiation.[4-6] Several studies have shown a statistically significant survival advantage from the addition of hormonal therapy to radiation (see Table 4). Patients in the D'Amico et al. study[5] had slightly less severe prostate cancer compared to the other two studies, although many of the patients would still be considered high risk. The optimal duration of hormonal therapy when combined with radiation is not known, but higher-risk patients are probably best treated with two-to-three years of hormonal therapy.

Over a five-to-ten-year time frame, the outcome after radiation or surgery is similar, based on the above retrospective reviews of patients stratified by risk groups. Outcome beyond ten years is less certain. On theoretical grounds, surgery should have a slight advantage over radiation because, if a prostate cancer is truly localized to the prostate gland (without extracapsular spread or occult distant metastasis), surgical removal of the gland should be permanently curative. Surgery is not always successful in clinically localized, low-risk tumors, however, because of inadequate surgical technique or tumor biology, which often leads to early dissemination or extracapsular spread. If the "horse is out of the barn," no local therapy is curative, although radiation probably has an advantage if there is only local

Table 2.
PSA Failure-Free Survival for Stage T1-T2 Prostate Carcinomas at the Cleveland Clinic and Memorial Sloan Kettering at Mercy Hospital, 2003[3]

		Five-year PSA failure-free survival		
Treatment	Number	Low risk	Intermediate and high risk	Percent with hormonal therapy (duration < 6 months)
Radical Prostatectomy	1,034	90%	70%+	17%
External Beam Radiation (> 72 Gy)	301	92%	75%*	39%
Permanent Implant	950	90%	75%++	24%
External Beam and Implant	222	92%	75%**	36%

\+ 21% Gleason score > 7, 26% PSA > 20
* 22% Gleason score > 7, 35% PSA > 20
++ 12% Gleason score > 7, 21% PSA > 20
** 22% Gleason score > 7, 35% PSA >20

Table 3.
PSA Failure-Free Survival after Surgery or Radiation[1]

		Five-year PSA failure-free survival		
Treatment	Number	Low risk	Intermediate risk	High risk
Radical Prostatectomy*	1027	90%	71%	40%
Radical Prostatectomy+	1100	85%	55%	30%
External Beam Radiation^	473	90%	61%	42%

* Hospital of the University of Pennsylvania, Philadelphia
\+ Brigham and Women's Hospital, Boston
^ Joint Center for Radiation Therapy, Boston

Table 4.
Randomized Trials Evaluating Hormonal Therapy in Intermediate and High-Risk Prostate Carcinoma

			Five-year survival	
Study	Number	Duration of hormones	Radiation alone	Radiation and hormones
D'Amico[5]	206	6 months	78%	88%
Hanks[6*]	361	2 years	71%	81%
Bolla[4]	415	3 years	62%	78%

* Gleason score 8-10 only

extension of disease, since radiation delivers a margin of effective dose around the prostate gland and seminal vesicles.

In contrast, the long-term efficacy of radiation, if a cancer is truly localized to the gland, is less certain based on a number of theoretical arguments. Although atrophied, the prostate is still present after radiation, and new cancers may develop ten-to-20 years after initial treatment. Second, there is variability in the sensitivity of prostate cancer cells to radiation. Finally, radiation kills clonogenic (replicating) cells in a random fashion. A given dose of radiation theoretically kills a fixed fraction of clonogenic cells, and with repeated doses of radiation, the fraction of surviving cells approaches, but never reaches, zero:

$$\text{survival fraction} = e^{-(\text{constant} * \text{radiation dose})}$$

For a given survival fraction, the chance of cure is mathematically described by the tumor control probability. If the surviving fraction is 0, the tumor control probability is 100%:

$$\text{tumor control probability} = e^{-(\text{surviving fraction} * \text{number of clonogens})}$$

Although the above is supported by laboratory work, tumor control probability *in vivo* is also dependent on host factors that are not well characterized. Radiation can definitely cure many prostate cancers, but if a large number of similar, truly localized tumors are radiated, there will likely be a few that are not cured because of the random nature of radiation killing, variability in radiation sensitivity, and variability in host factors. These tumors would have been cured with adequate surgical resection.

Based on these theoretical arguments and the lack of long-term randomized or retrospective data, I usually recommend radical prostatectomy for patients with low- and intermediate-risk cancers who are healthy and have a greater than ten-year life expectancy. For patients in poor health or older than 70 years, I will usually recommend radiation, since I am fairly confident that the ten-year results are similar to surgery. The patient with high-risk, localized prostate cancer, however, may be better treated with radiation and hormonal therapy, regardless of age, although there may be a role for surgery and adjuvant radiation in the younger patient.

Radiation Modality

For patients choosing brachytherapy, the most important consideration is the experience of the brachytherapy center. The quality of the prostate implant as judged by dosimetric parameters increases with the number of implants performed. If appropriately proctored, however, treatment is likely satisfactory at less-experienced centers.

For external beam radiation, newer techniques that allow greater doses of radiation to be delivered safely should be used. At a minimum, this should include three-dimensional (3D) conformal therapy, which allows more accurate targeting of the prostate and seminal vesicles while avoiding the rectum and bladder. Intensity-modulated radiation therapy (IMRT) should also be considered in patients with intermediate- and high-risk disease. IMRT is an extension of 3D, which modulates the intensity of each radiation beam in a way that allows for dose escalation while minimizing dose to sensitive normal structures. A similar dose escalation with standard 3D techniques results in excess late rectal toxicity.

Image-guided radiation therapy (IGRT) is another new technology that is being introduced into the clinic. Using a variety of techniques, IGRT increases the daily accuracy of tumor localization, which results in lower doses to surrounding normal tissue by allowing a decrease in the margin from the tumor to the edge of the radiation beam.

The choice of radiation modality is partially based on disease characteristics. Treatment with brachytherapy alone is best for patients with low-risk disease as long as the prostate is not too large (greater than 60-70 cc) or too small (less than 30 cc). Hormonal therapy is occasionally used with brachytherapy to decrease the size of the prostate prior to the implant. External beam radiation is used alone for low-risk disease and is combined with hormonal therapy for intermediate- and high-risk disease. Some centers will combine external beam radiation, hormonal therapy, and brachytherapy for patients with intermediate- or high-risk disease. As briefly reviewed above, there are no data to support one type of radiation over another for appropriate patients.

Patient preference and expected side effects also influence treatment choice. Brachytherapy as sole therapy has the distinct advantage of being completed in a single appointment although it requires general or spinal anesthesia, and treatment effects are felt for several months after the implant. External beam radiation typically involves daily treatments for seven-to-eight weeks (35-to-40 treatments). During treatment, brachytherapy tends to result in more urinary symptoms (frequency, burning, and urgency), and external beam radiation tends to cause more rectal symptoms (tenesmus, increased bowel frequency, hemorrhoid discomfort, and diarrhea), although both treatments can result in urinary and rectal symptoms. A small percentage of brachytherapy patients require bladder catheterization during the first few months after implantation, while this rarely occurs

during or after external beam radiation. Both techniques can result in rectal injury, which manifests as rectal bleeding several months to years after treatment. Urinary incontinence is rare with both treatments, although it is more likely following brachytherapy. Sexual dysfunction is probably more frequent after external beam radiation compared to brachytherapy.

Radiation after Radical Prostatectomy

After prostatectomy, the PSA should become undetectable. If the PSA fails to fall to zero or becomes detectable after initially falling to zero, radiation is often used in a curative attempt to "salvage" the failure. As a local modality, radiation will only be effective if residual disease is confined to the prostate bed or pelvic nodes, although pelvic (nodal) radiation is less frequently used than prostate bed radiation after prostatectomy. Post-prostatectomy radiation is more effective with lower post-prostatectomy PSAs, an initially undetected PSA after surgery, a long disease-free interval prior to PSA failure, and adverse pathologic features, which predict residual local disease (extracapsular extension or positive margin). If a patient's PSA does not initially decline to zero, he likely had occult metastatic disease at diagnosis and would not benefit from localized radiation, unless the source of the residual PSA is a positive margin and the Gleason score less than 8. A ProstaScint® scan[b] is often used to confirm a prostate bed recurrence or, at least, attempt to rule out distant disease, but the low sensitivity and specificity of this examination limits its usefulness. The PSA disease-free survival after salvage radiation for all patients is approximately 25-40% at five-to-ten years after radiation.[7,8] Favorable patients (PSA less than 2.0, Gleason score less than 8, positive surgical margins) may experience PSA disease-free survivals of 60-70%.[8]

Adjuvant radiation for high-risk prostate cancer after radical prostatectomy is rarely used. Adjuvant refers to a situation where all clinically detectable disease has been removed. Most urologists will follow patients with high-risk prostate cancer and only consider radiation if the PSA does not fall to zero or if it becomes detectable, at which time the treatment is considered salvage therapy. The rationale for this "wait-and-see" approach is that not all high-risk patients are destined to fail, failures can be picked up "early" with PSA, and many patients are spared the toxicity of unneeded radiation. Arguments pointing out that PSA becomes detectable only after a million cells are present[9] have not increased the use of adjuvant radiation. Theoretically, radiation is most effective when the tumor burden is smallest. A randomized study of adjuvant radiation showed that the biochemical relapse was reduced from 47% to 26% at five years with the use of radiation.[10]

Watchful Waiting

For the older patient with low-risk prostate carcinoma, watchful waiting is a reasonable option. This is especially true if the patient has multiple co-morbidities or the Gleason score is less than 6. A group of patients identified from the Connecticut Tumor Registry had data extracted from chart review. For patients with Gleason 2-5 carcinomas who were not treated with local therapy, only 4-11% died from prostate carcinoma.[11] D'Amico showed that for low-risk prostate carcinoma, the risk of dying from prostate cancer after radiation or surgery was 1-2% at ten years, while the risk of dying from other causes was ten-to-30%.[12]

Most radiation oncologists are comfortable following patients without treatment, although this is usually done in conjunction with an urologist. Ideally, these patients should be enrolled in a study so outcomes of watchful waiting can be determined, but this is not usually possible in a community setting. A reasonable approach to watchful waiting is to monitor PSA every three months and consider treatment if the PSA doubling time (velocity) is less than 12 months. If the PSA is fairly stable after one-to-two years, monitoring can be decreased to every six months. While patients initially agree to watchful waiting, many elect to proceed with treatment as their anxiety rises with the rise in their PSA, even if the doubling time is greater than 12 months.

Summary

Radiation is a curative treatment for prostate cancer that is most appropriate for the older patient or the patient with significant co-morbidities. Younger patients with a greater than ten-year survival are probably best treated with surgery unless the disease is high risk. For all patients, high-risk disease is best treated with hormones and radiation. The long-term superiority of surgery over radiation, however, has not been demonstrated in randomized or retrospective studies, and the recommendation for surgery in the younger, healthy patient with favorable local disease is largely based on theoretical considerations. If chosen for appropriate indications and delivered with appropriate techniques, radiation can be delivered using external beam or brachytherapy with equal efficacy. The choice of radiation treatment is based on tumor characteristics and patient preference. Radiation can be used after prostatectomy to cure patients who are not cured with surgery. Watchful waiting may be appropriate for patients with low-risk disease. **NCMedJ**

b ProstaScint® scan involves injecting a small amount of radioactive material into the body to determine if and where any prostate cancer cells may be.

REFERENCES

1 D'Amico AV. Combined-modality staging for localized adenocarcinoma of the prostate. Oncology 2001;15(8):1049-1059.
2 D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280(11):969-974.
3 Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. Int J Radiat Oncol Biol Phys 2004;58(1):25-33.
4 Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. Lancet 2002;360(9327):103-106.
5 D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. JAMA 2004;292(7):821-827.
6 Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol 2003;21(21):3972-3978.
7 Pazona JF, Han M, Hawkins SA, Roehl KA, Catalona WJ. Salvage radiation therapy for prostate-specific antigen progression following radical prostatectomy: 10-year outcome estimates. J Urol 2005;174(4 Pt 1):1282-1286.
8 Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004;291(11):1325-1332.
9 Anscher MS. Adjuvant radiotherapy following radical prostatectomy is more effective and less toxic than salvage radiotherapy for a rising prostate-specific antigen. Int J Cancer 2001;96(2):91-93.
10 Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: A randomised controlled trial (EORTC trial 22911). Lancet 2005;366(9485):572-578.
11 Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 1998;280(11):975-980.
12 D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. J Clin Oncol 2003;21(11):2163-2172.

Systemic Therapy for Prostate Cancer

William R. Berry, MD

Systemic therapy plays an important role in the management of prostate cancer. Since the pioneering work of Dr. Charles Huggins in the 1930s, medical science has known that prostate cancer cells were, to some extent, dependent on the presence of androgens (steroid hormones) for their growth and survival.[1] Hormonal therapy, with various forms of androgen manipulation and androgen receptor interaction, has been the primary form of systemic therapy for prostate cancer since that time. In recent years, a role has been proven for systemic chemotherapy as well. Clinical research trials are now investigating the role of new biologic agents and immunotherapy. This commentary will review the current status of the systemic therapy for prostate cancer.

Hormonal Therapy: General Principles

The androgen receptor is the primary driver of cell growth for prostate cancer.[2] Stimulation of the androgen receptor can be reduced by depletion of circulating androgens, blocking the binding of androgens to the androgen receptor, or a combination of the two methods.

Depletion of androgens can be accomplished directly by bilateral orchiectomy (castration) or indirectly by administration of estrogens or luteinizing hormone releasing hormone (LHRH) analogues.[3] Both of these classes of drugs exert their effect indirectly via reduction of the production of luteinizing hormone by the pituitary, with subsequent loss of luteinizing hormone signal to the testicles to produce testosterone. Both classes of drugs are capable of reducing serum testosterone levels to levels equivalent to orchiectomy.

Blocking the binding of androgens to the androgen receptor can be accomplished with anti-androgens. Anti-androgens accomplish inhibition of prostate cancer cell growth by competitive binding to the androgen receptor versus androgens. Anti-androgens administered to a patient with functional testes do not decrease testosterone levels, but actually cause some increase.

A third means of manipulation of the androgen and androgen receptor interaction could have a role in the management of prostate cancer, but has not been well studied. Medications approved only for the treatment of benign prostatic hypertrophy, such as 5-alpha reductase inhibitors, block the conversion of testosterone to dihydrotestosterone (DHT).[3] DHT binds more strongly to the androgen receptor than testosterone, and theoretically, blocking the conversion of testosterone to DHT could diminish prostate cancer cell growth.

Roles of Hormonal Therapy

Hormonal therapy has been used to treat various states of prostate cancer, including metastatic disease, disease manifest only by a rising prostate-specific antigen (PSA) after primary therapy, as adjuvant therapy[a] post primary therapy, as neoadjuvant therapy[b] prior to and/or with primary therapy, and as a primary therapy for localized disease.

Metastatic Disease

The role of hormonal therapy in metastatic disease is well accepted as first-line therapy. All of the three methods of testosterone depletion, (e.g., orchiectomy estrogens, or LHRH analogues) are equally effective.[3] LHRH analogues, although expensive, are the primary therapy used in most patients. Many patients prefer injections to orchiectomy, and estrogens can be associated with significant thrombo-embolic cardiovascular risk. Between 70-90% of patients will respond initially with a decrease in PSA and clinical improvement in symptoms. Median duration of response to this therapy is about 18

a Adjuvant therapy is treatment, such as chemotherapy, radiation therapy or hormone therapy, given to a patient after the primary treatment to increase the chances for a cure.

b Neoadjuvant therapies are similar to adjuvant therapies except they are given prior to the primary treatment.

William R. Berry, MD, is a private practice physician at the Cancer Centers of North Carolina in Raleigh, NC and Chairman of the Genito-Urinary Cancer Research Committee, United States Oncology. Dr. Berry can be reached at william.berry@usoncology.com or 216 Asheville Avenue, Suite 20, Cary, NC 27511. Telephone: 919-854-6930.

months. There is controversy over whether treatment should begin when metastatic disease is diagnosed or only at the onset of symptoms. A review of the randomized clinical trials suggests that there is a benefit with higher rates of one- and five-year disease-free progression and ten-year survival among those who receive immediate versus deferred therapy.[4]

Anti-androgens in standard doses as monotherapy have been demonstrated to be inferior to testosterone depletion.[5] Their use as single agents in general should be restricted to patients who refuse testosterone depletion because of concern over loss of sexual function.

Combined androgen blockade (CAB), the addition of anti-androgen to testosterone depletion, is also controversial. Randomized trials have produced mixed results. Three meta-analyses of the data have all suggested a small improvement in five-year survival as opposed to simple testosterone depletion with orchiectomy or LHRH analogues.[6,7,8,9] There are some minor side effects with anti-androgens (e.g., diarrhea, gynecomastia, etc.), but the biggest objection to the addition of anti-androgens is the significant monetary cost of these drugs as compared to marginal survival benefit. It should be determined by each patient and his physician whether the potential benefit of CAB is worth the cost.

"Since the pioneering work of Dr. Charles Huggins in the 1930s, medical science has known that prostate cancer cells were, to some extent, dependent on the presence of androgens (steroid hormones) for their growth and survival."

PSA Recurrence as the Only Sign of Disease

It has become common clinical practice in the PSA era to treat patients who have a PSA level that begins to rise but have no evidence of metastases, at some point after primary surgery or radiation therapy. The rationale is to prevent or delay the onset of overt metastatic disease. Not all patients who have a PSA recurrence die of prostate cancer. Recent studies have demonstrated that several factors, including time to PSA recurrence, Gleason score at diagnosis, and PSA doubling time, are all important in determining a patient's risk of dying of prostate cancer when he does have a rising PSA.[10,11,12]

There has also been a trend toward the use of intermittent hormonal therapy in patients with a rising PSA. The rationale for intermittent therapy is to have periods of time away from the side effects (hot flashes, fatigue, etc.) and toxicities (deterioration of bone density, loss of muscle mass, etc.) of testosterone depletion, but also there is speculation that the onset of hormone refractory prostate cancer could be delayed.[13] This method is not yet supported by data from a large randomized clinical trial, but is attractive to many patients and physicians.

Adjuvant Hormone Therapy

There are minimal data on the use of hormone therapy after prostatectomy. In a trial reported by the Eastern Cooperative Oncology Group (ECOG), men who were discovered to have positive lymph nodes when their pathology was reviewed after surgery were given continuous LHRH analogue therapy either immediately post surgery or at the time of recurrence .[14] At ten years there was a dramatic survival benefit (72% versus 49%) for those men who received immediate versus deferred treatment, respectively. This trial has been criticized because there were only 98 men accrued. However, the data are so compelling that one would be hard pressed not to recommend immediate adjuvant hormonal therapy to all men who have positive nodes at the time of prostatectomy.

Neoadjuvant Hormonal Therapy

Neoadjuvant hormonal therapy has been tested in clinical trials prior to surgery and also prior to (as well as concurrent to and after) primary radiation therapy. The neoadjuvant surgical studies have consistently failed to demonstrate any disease-free or overall survival benefit for neoadjuvant hormonal therapy given for anywhere from three-to-eight months pre-surgery.

On the other hand, several large clinical trials have shown a disease-free and, in some, a survival benefit for hormonal therapy administered prior to and continued concurrent with radiation therapy for patients with high-risk prostate cancer. Three of these important trials include RTOG 86-10, the Bolla study from EORTC, and the D'Amico trial.[15,16,17] There are preclinical data to suggest that androgen depletion does make prostate cancer cells more sensitive to radiation, and this phenomenon could explain why neoadjuvant hormonal therapy is beneficial with radiation and not surgery.[18]

Hormonal Therapy as Primary Therapy

Some physicians advocate hormonal therapy as primary therapy for prostate cancer.[19] There are no data to suggest that primary hormonal therapy can be done with curative intent. For that reason, the use of primary hormonal therapy should probably be reserved for those who need treatment, but are unwilling or unable due to co-morbidities or age to pursue a curative primary treatment, such as surgery or radiation.

Hormonal Resistance

As noted previously, the median duration of response to hormonal therapy in patients with metastatic prostate cancer is about 18 months. Virtually all patients develop disease that progresses in spite of this first-line hormonal treatment. This condition has variably been termed androgen-independent prostate cancer or hormone-refractory prostate cancer (HRprostate cancer). Regardless of the terminology, there is evidence to suggest that the androgen receptor is still the predominant driver of prostate cancer cell growth, even in this state of the disease.[20] Therefore, LHRH analogues are usually continued.

Secondary hormonal manipulations may be effective in some patients with HRprostate cancer, with reported response rates of 20-60%.[21] These secondary therapies include the addition of anti-androgen, anti-androgen withdrawal, estrogens, corticosteroids, and suppression of adrenal androgen production with drugs like ketoconazole. There are no clinical trials to suggest a survival benefit from any of these second-line therapies, but in general, they are not especially toxic and are, therefore, useful in selected patients.

Systemic Cytotoxic Chemotherapy

As in other metastatic cancers, clinical trials using chemotherapeutic agents have been undertaken in an attempt to find effective therapy for HRprostate cancer. Early trials were limited by the lack of conspicuously effective agents and the lack of significant numbers of patients with measurable disease. After the discovery of PSA, declines in this serum protein could be used as a marker of disease response to therapy in phase II trials. The PSA Working Group recommended a sustained decline in PSA of 50% or more from baseline as an indicator of response in phase II trials.[22]

In the 1990s, two phase III trials compared mitoxantrone and a corticosteroid to the steroid alone in patients with HRprostate cancer.[23,24] Both of these trials showed a significant benefit in terms of palliation of pain, although there was no survival benefit. Based on this palliative benefit, the combination of mitoxantrone and prednisone was the first chemotherapy regimen to be approved by the Food and Drug Administration (FDA) for the treatment of HRprostate cancer.

The results of these trials led to renewed interest in the use of chemotherapy in HRprostate cancer and a more rigorous preclinical and clinical search for new active agents. Drugs that affected intracellular microtubules, including vinca alkaloids, taxanes, and the combination of either of these classes with estramustine, had enough activity to generate a large number of phase II trials. Docetaxel was the most active of these agents.

The documentation of 50% PSA decline rates in 30-65% of the phase II trials with docetaxel led to the initiation of two large phase III trials using docetaxel in combination with another agent versus the then standard mitoxantrone and prednisone.[25,26] Both of these trials, SWOG 9916 and TAX 327, demonstrated an improvement in overall survival for docetaxel given every three weeks in combination (with estramustine or prednisone, respectively) versus mitoxantrone and prednisone. In addition, patients on docetaxel did better in terms of pain relief and quality of life than those receiving mitoxantrone. These were truly historic studies, which were the first phase III trials to demonstrate that chemotherapy can prolong survival in patients with HRprostate cancer (hazard ratios 0.80 and 0.76). There were increased adverse thromboembolic events in the SWOG 9916 trial, which used estramustine with docetaxel. For that reason, docetaxel every three weeks with daily oral prednisone is now FDA-approved and the standard of care for chemotherapy in HRprostate cancer.

The Next Steps

Now that we have a regimen that can prolong survival in HRprostate cancer, the next steps will be to improve on the first-line therapy of docetaxel and prednisone, develop new agents or regimens for patients who have progressed on docetaxel, explore the role of chemotherapy in the earlier states of prostate cancer, and develop effective biologic and immunotherapy for prostate cancer.

Agents that have been combined with docetaxel include carboplatin;[27] high-dose calcitriol;[28] thalidomide;[29] various small molecule growth factor tyrosine-kinase inhibitors, such as gefitinib and imatinib;[30,31] large molecule antibody-to-cell-surface receptors, such as vascular endothelial growth factor;[32] the endolthelin A receptor antagonist atrasentan;[33] proteosome inhibitors, such as bortezomib;[34] and even vaccines for prostate cancer.[35]

Currently no agents are approved for second-line treatment of HRprostate cancer after failure of initial chemotherapy. A phase III trial of the oral agent satraplatin has recently been completed, and the results are awaited with anticipation.[36]

Systemic chemotherapy, which is effective in an advanced cancer, is often more effective in early states of disease. Two large clinical trials of chemotherapy in combination with androgen depletion in earlier states of prostate cancer are underway as adjuvant therapy post-prostatectomy in patients with high risk for recurrence. An Intergroup United States trial is comparing mitoxantrone and hormone therapy to hormonal adjuvant therapy alone. A large international pharmaceutical company-sponsored trial will test the addition of docetaxel to hormonal therapy in the adjuvant setting. In addition neoadjuvant chemotherapy with docetaxel will be tested in combination with hormonal therapy prior to and concurrent with radiation in patients with high-risk disease. The results of these trials will determine the effectiveness of these chemotherapy strategies in early stage prostate cancer.

Finally, as we learn more about the cancer genome and the immune system, new biologic agents that can be directed at specific targets and new ways to stimulate the host immune system to recognize and destroy prostate cancer cells are being developed and nearing routine use in patients. The progress being made should greatly enhance our ability to alter the course of prostate cancer with systemic therapy. **NCMedJ**

REFERENCES

1 Huggins C, Hodges CV. Studies on Prostate Cancer: 1. The effect of castration, of estrogen, and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293-297.

2 Small EJ, Prins GS, Taplin ME. The Androgen Receptor and Prostate Cancer. In Comprehensive Textbook of Genitourinary Oncology, 2nd Ed., Vogelzang NJ et al, Eds. 580-582.

3 McLeod DG, Vogelzang NJ. Androgen Blockade: Monotherapy and Quality of Life Issues. In Comprehensive Textbook of Genitourinary Oncology, 2nd Ed., Vogelzang NJ et al., Eds. 824-833.

4 Nair B, Wilt T, MacDonald R, et al. Early Versus Deferred Androgen Suppression in the Treatment of Advanced Prostate Cancer (Cochrane Review). Cochrane Database Syst Rev 2002; CD003506.

5 Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-agent androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. Ann Int Med 2000;132:566.

6 Bertagna C, DeGery A, Hucher M, et al. Efficacy of the combination of nilutamide plus orchidectomy in patients with metastatic prostate cancer. A meta-analysis of seven randomized double-blind trials (1056 Patients). Br J Urol 1994;73:396.

7 Maximum androgen blockade in advanced prostate cancer: An Overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet 2000;355:1491.

8 Schmitt B, Bennett C, Seidenfeld J, et al. Maximum androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev 2000; CD001526.

9 Samson DJ, Seidenfeld J, Schmitt B, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer 2002;95:361.

10 Jhaveri FM, Zippe CD, Klein EA, et al. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. Urology 1999;54:884.

11 Eisenberger ME, Partin AW, Pound C, et al. Natural history of progression of patients with biochemical (PSA) relapse following radical prostatectomy (abstract). Proc Am Soc Clin Oncol 2003;21:380a.

12 Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294:433.

13 O'Reilly KJ, Crawford ED, and Thrasher JB. Intermittent Androgen Suppression. In Comprehensive Textbook of Genitourinary Oncology 2nd ed. Vogelzang NJ, et al. Eds. 851-852.

14 Messing EM, Manola J, Saosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive cancer. N Eng J Med 1999;342:1781-1788.

15 Pilepich MV, Winter K, John MJ, et al. Phase III Radiation Therapy Oncology Group (RTOG) Trial 86-10 of androgen deprivation adjuvant to definitive radiation therapy in locally advanced carcinoma of the prostate. Int J RadiatOncol Biol Phys 2001;50:1243.

16 Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC Study): a phase III randomized trial. Lancet 2002;360:103.

17 D'Amico AV, Manola J, Loffredo M, et al. 6-month Androgen Suppression plus Radiation Therapy vs. Radiation Therapy Alone for Patients with Clinically Localized Prostate Cancer: A randomized controlled trial. JAMA 2004;292:821.

18 Pinthus JH, Bryskin B, Wilson J, et al. Androgens Induce Adaptation to Oxidative Stress: Implications for Prostate Cancer radiation therapy. Proc 2006 Prostate Cancer Symposium 2006;247 (abstract 308).

19 Leibowitz RL, Tucker SJ. Treatment of localized prostate cancer with intermittent triple androgen blockade: Preliminary results in 110 consecutive patients. Oncologist 2001;6(2):177-182.

20 Taplin ME, Bubley GJ, Shuster TD, et al. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. N Engl J Med 1995;332:1393-1398.

21 Lam JS, Leppert JT, Vemulapalli SN, et al. Secondary hormonal therapy for advanced prostate cancer. J Urol 2006;175:27.

22 Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II trials in androgen-independent prostate cancer: Recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 1999;17:3461.

23 Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: A Canadian randomized trial with palliative end points. J Clin Oncol 1996;14:1756-1764.

24 Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: Results of the Cancer and Leukemia Group B 9182 study. J Clin Oncol 1999;17:2506-2513.

25 Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513-1520.

26 Tannock IF, deWit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone and prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-1512.

27 Miglietta L, Cannobio L, Boccardo F. Assessment of response to carboplatin in patients with hormone-refractory prostate Cancer: a critical analysis of drug activity. Anticancer Res 1995;15:2825-2828.

28 Beer TM, Ryan CW, Venner PM, et al. Interim results from ASCENT: A double-blinded randomized study of DN-101 (high dose calcitriol) plus docetaxel versus placebo plus docetaxel in androgen-independent prostate cancer. Proc Am Soc Clin Oncol 2005;23:382s.

29 Figg WD, Dahut W, Duray P, et al. A randomized phase II trial of thalidomide, an angiogenesis inhibitor, in patients with androgen-independent prostate cancer. Clin Cancer Res 2001;7:1888-1893.

30 Canil CM, Moore MJ, Winquest E, et al. Randomized study of two doses of gefitinib in hormone-refractory prostate cancer: A trial of the National Cancer Institute of Canada-Clinical Trials Group. J Clin Oncol 2005;23:455-460.

31 Mathew P, Thall PF, Jones D, et al. Platelet-derived growth factor receptor inhibitor imatinib mesylate and docetaxel: A modular phase I clinical trial in androgen-independent prostate cancer. J Clin Oncol 2004;22(16):3323-3329.

32 Picus J. Bevacizumab (Avastin) in advanced prostate cancer. Chemotherapy Foundation Symposium XXI, abstract 46.

33 Nelson JB, Nabulsi AA, Vogelzang NJ, et al. Suppression of prostate cancer induced bone remodeling by the endothelin receptor A antagonist atrasentan. J Urol 2003;169:1143-1149.

34 Dreicer R, Roth B, Petrylak D, et al. Bortezomib plus docetaxel in patients with advanced androgen-independent prostate cancer. A phase I/II study. Proc 2005 Prostate Cancer Symposium 2005; abstract 250.

35 Kantoff P. Recent progress in management of advanced prostate cancer. Oncology (Williston Park, NY) 2005;19:631-636.

36 Sternberg CN, Whelan P, Hetheringtom J, et al. Phase III Trial of Satraplatin, an oral platinum plus prednisone versus prednisone alone in patients with hormone-refractory prostate cancer. Oncology 2005;68:2-9.

The Economic Impact of Prostate Cancer Screening and Treatment

Rachael L. DiSantostefano, PhD, and John P. Lavelle, MB, BCh, FRCSI

Prostate cancer is a significant public health concern. Because of its high incidence and mortality and a lack of consensus on the recommended frequency of screening and the most appropriate treatments, prostate cancer is also characterized by high costs and uncertainty. As a result, there is perhaps no bigger debate in medicine today as far as whether or not there should be widespread screening for prostate cancer and if and/or how to treat early-detected cases.

"Whereas the increase in screening detects cancer early and at a potentially curable stage with aggressive treatment, it has also resulted in the overdiagnosis of latent disease and unnecessary biopsies for men with false-negative screening tests."

The corresponding economic costs of screening, diagnosis, treatment, and follow-up for prostate cancer are not trivial and are expected to increase with the aging of the population and a larger volume of screening. In 1990, the total annual costs to treat prostate cancer were estimated to range from $1.72 billion to $4.75 billion.[1] With the advent of prostate-specific antigen (PSA) screening in the early 1990s, the costs of treating prostate cancer in the United States likely far exceeded this amount, based on trends toward earlier detection and more aggressive treatment. Based on early estimates, the cost of screening increases prostate cancer expenditures by three-to-ten times.[1] The costs of treating prostate cancer in Sweden have been observed to fall within this range, increasing three-fold between 1991 and 2002 (20 million to 65 million euros).[2]

The exponential increase in the volume of prostate cancer screening adds to healthcare costs via the cost of the screening test, follow-up biopsies for positive tests, and treatment (or long-term monitoring) for confirmed prostate cancers. For example, the use of PSA tests increased seven fold, and radical prostatectomies increased six fold between 1991 and 2002 in Sweden.[2] Radiation therapy increased ten fold from 1997-2002.[2] In the United States, similar trends were likely. Between 1989 and 2002, there was a 234% increase in radical prostatectomy in the United States.[1] In 2003, there were 90,328 hospital discharges with the diagnosis of prostate cancer and associated costs of $673 million.[3] While treatment for prostate cancer is expensive, the overuse and/or inappropriate use of diagnostic tests in a manner inconsistent with treatment guidelines significantly inflates costs for disease management.[2] According to the Medicare Current Beneficiary Survey (2002), nearly two thirds of the 17.6 million Medicare beneficiaries received prostate cancer screening.[4] If all Medicare beneficiaries or all men older than 50 (34.7 million in 2000) sought screening, annual costs for the PSA screening test for

Rachael L. DiSantostefano, MS, PhD, is an Assistant Director of Epidemiology at GlaxoSmithKline, where she studies the epidemiology of respiratory diseases. Prior to accepting a position at GlaxoSmithKline, Dr. DiSantostefano was a doctoral student in the Department of Health Policy and Administration, School of Public Health at the University of North Carolina at Chapel Hill, where she studied cost-effectiveness of prostatic diseases. She can be reached at rdisantostefano@nc.rr.com or 104 Ironwood Place, Chapel Hill, NC 27514. Telephone: 919-544-4230.

John P. Lavelle, MB, BCh, FRCSI, is an Assistant Professor in the Division of Urology, School of Medicine at the University of North Carolina at Chapel Hill. Dr. Lavelle can be reached at Lavelle@med.unc.edu and CB# 7235, Chapel Hill, NC 27599-7235. Telephone: 919-966-2571.

one year would approach ~$2 billion assuming Medicare reimbursement (~$50 per test).[5] With costs in the range of a few billion dollars per year (screening, treatment, disease management, monitoring, etc.), costs of a population-based screening program, including disease management, could easily exceed $20 billion within five-to-seven years.

The biggest controversy in prostate cancer research is in the lack of consensus on the value of prostate cancer screening given the test's performance at diagnosing cancer and the inconsistent demonstration of effectiveness of early intervention at improving patient outcomes, including reductions in mortality. Although the existing evidence of effectiveness has improved in recent years, and cost-effectiveness analyses have been increasingly performed, uncertainty about the benefits of treatments in improving patient outcomes remains. A recent systematic review demonstrated that it was difficult to draw conclusions without uncertainty on the benefits of treatment alternatives due to lack of randomized clinical trials. Newer technologies, in particular, were hardest to evaluate given a lack of evidence of effectiveness and a lack of comparison with standard treatment alternatives.[6] Although radical prostatectomy and radiation rapidly replaced watchful waiting for early disease detection with the advent of PSA, there was weak and inconsistent evidence regarding any benefits in terms of improved patient outcomes (including mortality) during this period.[2] One recent study demonstrated lower mortality using radical prostatectomy versus watchful waiting in early-stage disease,[7] but evidence is otherwise weak or inconsistent from other trials, including those with long follow-up.

The lack of consistent or compelling evidence about early detection of prostate cancer showing an improvement in survivorship has not stopped numerous treatments from being rapidly diffused, including aggressive treatments in relatively young men. This is problematic in that aggressive treatments themselves have consequences. For example, after 18 months of follow-up, patients receiving radical prostatectomy in one study experienced significant erectile dysfunction (59.9%) and urinary incontinence (8.4%).[8] Other treatment alternatives result in co-morbidities affecting sexual and urinary function. If these patients experience a long survival period, they must face the psychosocial consequences of treatment-related adverse effects that might not have been necessary if their underlying disease was latent or extremely slow in progressing.

Whereas the increase in screening detects cancer early and at a *potentially* curable stage with aggressive treatment, it has also resulted in the overdiagnosis of latent disease and unnecessary biopsies for men with false-negative screening tests.[9] False positive screening has financial and psychological costs, with about half of men with suspicious screening test results and subsequent negative biopsies reporting worrying "a lot" or "some of the time" about prostate cancer.[10] For men with confirmed prostate cancer, those choosing either watchful waiting or aggressive intervention for early-stage disease must address the implications of their choices, which can result in anxiety, decreased activity level, decreased quality-of-life, adverse effects of treatment, etc. [11]

From an economic perspective, the value of a screening test can be determined by estimating the relative costs and benefits, where benefits of screening can be measured in terms of test performance, unnecessary biopsies, and/or formal cost-effectiveness analyses. Studies that evaluate prostate cancer screening focus primarily on the PSA test. One recent study found that complexed PSA (cPSA)[a] (threshold 2.2 ng/ml) was a better test than total PSA (tPSA) (2.5 ng/ml), with higher sensitivity and specificity and fewer unnecessary biopsies.[12] A cost-benefit study looking at five screening strategies found that cPSA (3.8 ng/ml) was dominant (more costly and less effective), with a threshold of 3.0 ng/ml identifying a similar number of cancers with fewer biopsies than tPSA (4.0 ng/ml).[13]

Using simulations including Markov modeling that simulate the progression of disease to determine the most efficient PSA screening algorithm, the benefits of prostate screening vary by age and were not recommended above age 70, where the competing risk of mortality outweighs the benefit.[14,15] In their Markov model, Ross and colleagues conclude that annual PSA screening (4.0 ng/ml threshold) starting at 50 years of age is dominant (i.e., more costly and less effective) by a biennial screening strategy after tests at 40 and 45 years of age.[16] Screening beyond age 70 required more treatments (and significant additional costs) per person-year of life saved.[14] A second computer model supports screening every two years (4.0 ng/ml threshold), which reduces false-positive and overdiagnosis rates sharply, while catching most cases relative to the more traditional annual screening without any age-specific thresholds.[17] Clearly, additional research to determine the best thresholds for PSA measures (tPSA, cPSA, PSA velocity,[b] etc.) and to determine the utility of other biomarkers in detecting aggressive prostate cancer is critical. If future screening tests can better distinguish latent disease from aggressive disease and minimize false positives, they offer great potential to lower unnecessary expenditures for prostate cancer.

The utility of prostate cancer screening and treatment will be debated for the foreseeable future, especially with the advent of new treatments and the absence of randomized clinical trials. The most common treatments, radiation and radical prostatectomy, might never be compared in a randomized trial for a variety or reasons. PSA is the only real biomarker available today to detect prostate cancer, and it is imperfect. Based on the current economic evidence, routine prostate cancer screening using PSA and subsequent treatment for early-stage disease do not appear to be cost-effective until improvement in patient outcomes, including

a Complexed PSA is a test measuring the level of PSA that has been complexed or bound with a certain protein (alpha-1-antichymotrypsin) in a patient's blood sample.

b PSA velocity is the rate of change in the PSA level over time.

mortality, have been demonstrated. Methods calculating the expected value of perfect information (EPVI is a measure of the cost of making an incorrect decision due to uncertainty) should also be factored into decisions about prostate cancer screening.[18]

Despite its shortcomings, PSA will continue to be used to detect prostate cancer in the absence of a more accurate biomarker. Furthermore, we will continue to treat early-stage prostate cancer aggressively if a patient prefers this to watchful waiting. However, healthcare administrators might give more scrutiny to screening and treatment programs as costs continue to escalate with the aging of the population. With this increased scrutiny, cost containment might include a prostate cancer screening schedule tailored to individuals based on prognostic factors that are still being identified. **NCMedJ**

REFERENCES

1 Saigal CS, Litwin MS. The economic costs of early stage prostate cancer. Pharmacoeconomics 2002;20(13):869-878.

2 Sennfält K, Carlsson P, Varenhorst E. Diffusion and Economic Consequences of Health Technologies in Prostate Cancer Care in Sweden, 1991-2002. Eur Urol 2006 Jan 6; [Epub] (in press).

3 HCUPnet [on-line], Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/HCUPnet. Accessed March 10, 2005.

4 The Henry J. Kaiser Family Foundation, Medicare Chart Book, Medicare Policy Project, Publication Number 7284, 2005. Available at: www.kff.org. Accessed April 17, 2006.

5 United States Census Bureau. Available at: www.census.gov. Accessed April 15, 2006.

6 Hummel S, Paisley S, Morgan A, Currie E, Brewer N. Clinical and cost-effectiveness of new and emerging technologies for early localized prostate cancer: a systematic review. Health Technol Assess. 2003;7(33):iii, ix-x, 1-157.

7 Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, Spangberg A, et al. Scandinavian Prostate Cancer Group Study No. 4. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005 May 12;352(19):1977-1984.

8 Fowler FJ Jr, McNaughton Collins M, Albertsen PC, Zietman A, Elliott DB, Barry MJ. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. JAMA 2000 Jun 28;283(24):3217-3222.

9 Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schroder FH, de Koning HJ. Lead times and overdetection due to prostate-specific antigen screening: Estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003;95(12):868-878.

10 McNaughton-Collins M, Fowler FJ Jr, Caubet JF, Bates DW, Lee JM, Hauser A, Barry MJ. Psychological effects of a suspicious prostate cancer screening test followed by a benign biopsy result. Am J Med 2004;117(10):719-725.

11 Weber BA, Sherwill-Navarro P. Psychosocial consequences of prostate cancer: 30 years of research. Geriatr Nurs 2005;26(3):166-175.

12 Babaian RJ, Naya Y, Cheli C, Fritsche HA. The detection and potential economic value of complexed prostate-specific antigen as a first line test. J Urol 2006;175(3 Pt 1):897-901; discussion 901.

13 Ellison L, Cheli CD, Bright S, Veltri RW, Partin AW. Cost-benefit analysis of total, free/total, and complexed prostate-specific antigen for prostate cancer screening. Urology 2002;60(4 Suppl 1):42-46.

14 Howard DH. Life expectancy and the value of early detection. J Health Econ 2005;24(5):891-906. Epub 2005 Apr 19.

15 Ross KS, Guess HA, Carter HB. Estimation of treatment benefits when PSA screening for prostate cancer is discontinued at different ages. Urology 2005;66(5):1038-1042.

16 Ross KS, Carter HB, Pearson JD, Guess HA. Comparative efficiency of prostate-specific antigen screening strategies forprostate cancer detection. JAMA 2000;284(11):1399-1405.

17 Etzioni R, Cha R, Cowen ME. Serial prostate-specific antigen screening for prostate cancer: A computer model evaluates competing strategies. J Urol 1999;162(3 Pt 1):741-748.

18 Sculpher M, Claxton K. Establishing the cost-effectiveness of new pharmaceuticals under conditions of uncertainty—when is there sufficient evidence? Value Health 2005;8(4):433-446.

Horse-Related Injuries and Deaths in North Carolina, 1995-1999

Doris M. Bixby-Hammett, MD

Nationally, accidents are the leading cause of death for those under 35 years of age and the fifth leading cause of death among all age groups.[1] Injuries are a serious public health problem, which takes a toll on the health of the population and imposes social and economic costs on society. If the medical community is to prevent injuries and deaths, each activity should be individually evaluated.

This data presented here are based on a study is of equestrian accidents in North Carolina resulting in injury or death. North Carolina has a horse population of 256,270 equines,[2] and many North Carolina citizens use horses for recreation and employment. There are an estimated 70,000 horseback riders in North Carolina. This study compared data from three sources for the years 1995 through 1999: the National Electronic Injury Surveillance System (NEISS)[3] (records for North Carolina), North Carolina Trauma Registry (NCTR),[4] and the North Carolina Medical Examiner's Database (NCME).[5] Records in the NCTR were selected with Ecodes indicating injuries caused by animals.

The age group at greatest risk for all injuries (NEISS), severe injuries (NCTR), and deaths (NCME) are equestrians between the ages of 25 and 44 years of age. Equestrians age 45-65 years are the second highest group at risk of injury. The largest percent of injuries among this age group can be seen in the NCME data, with smaller percentages in the NCTR and the NEISS data. It has been suggested that experience would decrease the number of accidents, but one would expect the equestrians age 25-64 years would have more experience in horse-related activities than younger equestrians.

Fractures represent the highest percent of injury type in the NEISS and NCTR data. The second most common injury in NEISS is contusion and abrasion, but in NCTR, it is laceration. Neurological head injury is the most common cause of death, the third most common injury in the NCTR data, and the fourth most common injury in the NEISS data.

According to the NEISS data, the extremities are the most commonly injured body parts, while the NCTR and NCME data rank the head as the most commonly injured. The trunk ranks second in all three databases.

Conclusions

The North Carolina data correspond with national medical studies of horse-related activities in that head injury is the leading injury. Head injuries are the most severe of the injuries in North Carolina, causing 56% of all horse-related deaths. Head injuries can be prevented or reduced in severity by wearing properly fitted and secured American Society for Testing and Materials (ASTM) equestrian standard/Safety Equipment Institute (SEI) certification protective headgear. Other factors that can play a role in injury prevention include: horse selection at the level of the rider, horse and rider conditioning for the activity, instruction from a qualified teacher, no use of alcohol while riding, and proper attire for the activity.

Table 1.
Age Groups from NEISS, NCTR, and NCME Databases, 1995-1999

	NEISS (NC subset)		NC Trauma Registry		NC Medical Examiner	
Age	Count	Percent	Count	Percent	Count	Percent
0-4	2	0.5%	16	3.1%	3	12%
5-14	61	16.4%	68	13.3%	1	4%
15-24	59	15.8%	85	16.6%	1	4%
25-44	172	46.1%	211	41.2%	11	44%
45-64	70	18.8%	104	20.3%	7	28%
64+	9	2.4%	28	5.5%	2	8%
Unknown	0	0%	0	0%	0	0%
Total	373	100%	512	100%	25	100%

Doris M. Bixby-Hammett, MD, is Board of Director emeritus of the American Medical Equestrian Association/Safe Riders Foundation and a past member and chairman of the Safety Committee, United States Pony Clubs. Dr. Bixby-Hammett lives in Asheville, NC and can be reached at dbhammett@yahoo.com or 828-285-2361.

Table 2.
Comparison of Diagnosis Categories from NEISS, NCTR, and NCME Databases, 1995-1999

	NEISS (NC subset)		NC Trauma Registry		NC Medical Examiner	
Injury Type	Count	Percent	Count	Percent	Count	Percent
Fracture	129	34.6%	428	35.5%	2	8.0%
Contusion/Abrasion	118	31.6%	75	6.2%	0	0%
Strain/Sprain	36	9.7%	14	1.2%	0	0%
Laceration	31	8.3%	188	15.6%	0	0%
Neurological Head	31	8.3%	160	13.3%	14	56%
Internal Injury	0	0%	153	12.7%	0	0%
Other	23	6.2%	89	7.4%	6	24%
Spine	0	0%	81	6.7%	2	8.0%
Dislocation	5	1.3%	18	1.5%	0	0%
Perinatal*	0	0%	0	0%	1	4.0%
Total	373	100%	1,206	100%	25	100%

* Mother was kicked by horse resulting in premature delivery and death of baby.

Table 3.
Injured Body Region from NEISS, NCTR, and NCME Databases, 1995-1999

	NEISS (NC subset)		NC Trauma Registry		NC Medical Examiner	
Injured Body Region	Count	Percent	Count	Percent	Count	Percent
Head (including brain and face)	68	18.2%	360	33.6%	14	56%
Trunk	109	29.2%	319	29.8%	6	24%
Extremity	186	49.9%	273	25.5%	0	0%
Spine	0	0.0%	81	7.6%	0	0%
Neck	9	2.4%	0	0	2	8.0%
25-50% of Body	1	0.3%	0	0	2	8.0%
Perinatal	0	0	0	0	1	4.0%
Unspecified	0	0	38	3.5%	0	0%
Total	373	100%	1,206	100%	25	100%

REFERENCES

1 Centers for Disease Control and Prevention, National Center for Health Statistics. Deaths: Final Data for 2003. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/finaldeaths03/finaldeaths03.htm. Accessed February 27, 2006.

2 American Horse Council, Deloite-Touche survey, Washington, DC. As reported by the NC Horse Council, 2005.

3 National Electronic Injury Surveillance System, US Consumer Product Safety Commission, National Injury Information Clearing House, Office of Information Services, Vicky B. Leonard, vleonard@cpsc.gov. 2000.

4 University of North Carolina at Chapel Hill North Carolina. Department of Surgery, Trauma Registry. 2004.

5 North Carolina Medical Examiner's Database. Chapel Hill, NC. 2000.

Running the Numbers

A Periodic Feature to Inform North Carolina Healthcare Professionals about Current Topics in Health Statistics

From the State Center for Health Statistics, North Carolina Department of Health and Human Services
www.schs.state.nc.us/SCHS

Recent Trends in Prostate Cancer in North Carolina

Prostate cancer is the most frequently diagnosed cancer in men in North Carolina and in the nation. The objectives of this analysis are to examine recent trends in prostate cancer incidence, mortality, and staging; to examine racial differences in incidence, mortality, and staging; and to compare North Carolina statistics to national data.

North Carolina incidence and mortality data were provided by the State Center for Health Statistics. Incidence rates (cases per 100,000 population) and mortality rates (deaths per 100,000 population) are presented. The rates were age-adjusted to the 2000 United States population by five-year age groups. The incidence and mortality rates were calculated as overlapping three-year rates. For comparison, national incidence (Surveillance Epidemiology and End Results Program, or SEER) and mortality rates (National Center for Health Statistics) are presented.

Figure 1.
Age-Adjusted Incidence Rate (per 100,000)

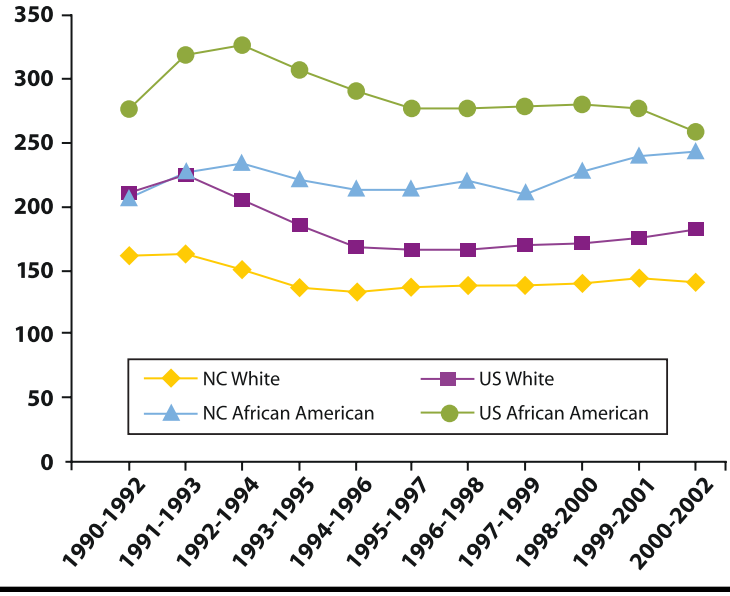
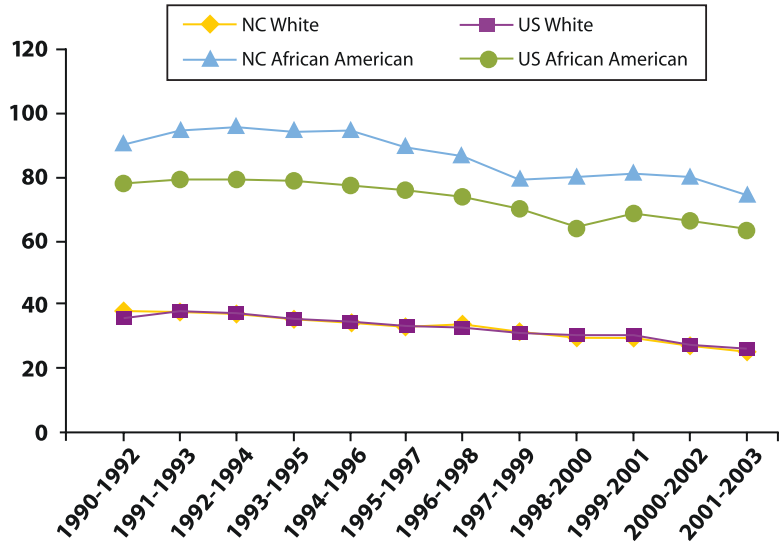


Figure 1 displays trends in prostate cancer incidence. In the last decade, the incidence of prostate cancer in North Carolina has been stable overall. Incidence rates in North Carolina for both whites and African Americans are lower than the SEER national rates. However, according to a second data source, the National Program of Cancer Registries, which includes most of the United States population and, therefore, is more representative of national rates than SEER, in 2002 only North Carolina whites and not North Carolina African Americans had an incidence rate statistically different from the respective national rate. In North Carolina, the incidence for African Americans is approximately 70% higher than for whites (during 2000-2002, 239 per 100,000 versus 139 per 100,000).

Figure 2 displays trends in prostate cancer mortality. In the last decade, North Carolina mortality rates have been declining. Overall, the North Carolina rate is higher than the national rate. Although whites in North Carolina have the same mortality rate as whites in the United States, African Americans in North Carolina have a higher mortality rate than African Americans in the United States. In North Carolina, the mortality rate for African Americans is almost three times as high as that for whites (during 2000-2002, 74 per 100,000 versus 25 per 100,000).

Figure 2.
Age-Adjusted Death Rate (per 100,000)



There are substantial differences in stage at diagnosis between whites and African Americans in North Carolina. Eighty-two percent of white men are diagnosed with local stage disease, compared to 74% of African Americans. These two groups are equally likely to be diagnosed with regional disease (9%), but African Americans are more likely to be diagnosed with distant disease (7% versus 3%) or for the stage to be unstaged or unknown (9% versus 5%). Later diagnosis contributes to higher mortality.

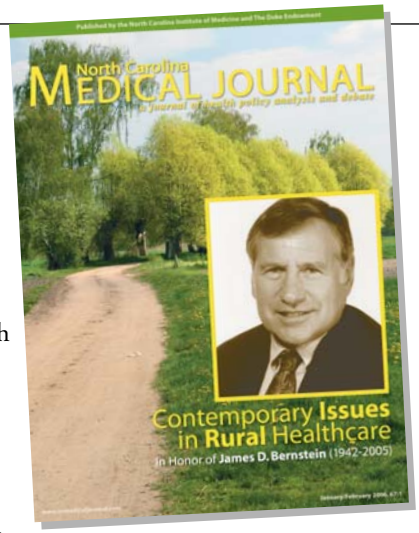
Interpretation of the incidence data is affected by the introduction and dissemination of prostate-specific antigen (PSA) testing. The advent of this diagnostic tool in the 1980s resulted in an overall increase in incidence rates, followed by a period of stability. Future changes in the use of PSA and other methods of diagnosis will impact trends and differences in the incidence data.

North Carolina African Americans have much higher prostate cancer incidence rates than whites, similar to the pattern seen at the national level. It is unlikely that differences in testing for prostate cancer contribute to this racial difference in incidence, since recent data from the Behavioral Risk Factor Surveillance System (BRFSS), a state-based telephone survey, suggest that North Carolina African Americans and whites have similar rates of PSA testing ever or in the last year.

Declining trends in prostate cancer mortality in North Carolina are encouraging and could be related to earlier detection of cancers by PSA testing or improvements in treatment. The three-fold disparity in mortality between whites and African Americans suggests differences in tumor biology, stage at diagnosis, access to healthcare, or treatment. The prostate cancer incidence rates in North Carolina are lower than those for the United States, while the mortality rates in North Carolina are higher overall than for the nation. This pattern could be due to differences between North Carolina and the nation in case reporting, stage at diagnosis, access to healthcare, or treatment.

Contributed by Deborah Porterfield, MD, MPH, Chronic Disease and Injury Section and Karen Knight, MS, Central Cancer Registry, North Carolina Division of Public Health

Readers' Forum



To The Editor:

I have greatly enjoyed my issues of the *North Carolina Medical Journal*, but none more than the January/February 2006 issue that honored James Bernstein. He was a remarkable man, and I found Donald Madison's article, in particular, both moving and informative.

The mention in Don's article of the Global Community Health Fellows Program, the brainchild of Bill Stewart, MD, when he was serving as Surgeon General of the United States Public Health Service, brought back memories of that remarkable group of individuals who were selected for the program. My closest contacts among the fellows were Steve Joseph, MD, who later became Health Commissioner of New York City, the Dean of the School of Public Health at Minnesota, and the Assistant Secretary of Defense for Health and Medical/Department of Defense; Merve Silverman, MD, who later became Director of Public Health for the City and County of San Francisco and a national and international leader on HIV/AIDS; and Jim Brown, MD, who was the Director of Student Health Services at the University of California Berkley (UC Berkeley) and one of the founders of the Joint Medical Program at UC Berkeley and the University of California San Francisco. All remarkable individuals and contributors as was Jim Bernstein. Jim was what Tom Oliver and others have called "policy entrepreneurs" who could link problems to solutions to the political process, and do it effectively. That is a rare skill.

Leadership is something a lot of people write about, but few practice with the understanding that Jim had for all the elements of leadership. In Don's article, he describes what we might call "Bernstein's principles" on page 35. Very informative.

The January/February 2006 issue was special because of my high regard for Jim and because Don's article triggered so many thoughts about the evolution of rural health service over the past 40 years, including the critical role played by Jim and his colleagues in North Carolina.

Phillip R. Lee, MD
Program in Human Biology
Stanford University

Editor's Note: Dr. Lee served as Assistant Secretary for Health under both Presidents Lyndon Johnson and Bill Clinton

How to Reach Us

LETTERS TO THE EDITOR

- Our e-mail address is NCMedJ@nciom.org
- Our fax number is 919-401-6899
- Or you can send your letter to: *North Carolina Medical Journal*, Letters, 5501 Fortunes Ridge Drive, Suite E, Durham, NC 27713
- Please include the writer's full name, address, and daytime phone number. Letters may be edited for clarity or space.

SUBSCRIPTIONS AND GIFTS

- Customer services for subscriptions or gifts can be accessed via e-mail NCMedJ@nciom.org or by calling the North Carolina Medical Journal's business and advertising manager, Adrienne R. Parker, at 919-401-6599 ext. 28

SUBMITTING PEER-REVIEWED ARTICLES

- For instructions on how to submit an article to the *North Carolina Medical Journal*, please visit www.ncmedicaljournal.com/guideline.htm
- Please send your articles via e-mail NCMedJ@nciom.org or mail to: *North Carolina Medical Journal,* Submissions, 5501 Fortunes Ridge Drive, Suite E, Durham, NC 27713

CHANGE OF ADDRESS

- Please send your change of address via e-mail NCMedJ@nciom.org or by calling the North Carolina Medical Journal's business and advertising manager, Adrienne R. Parker, at 919-401-6599 ext. 28

REPRINTS AND PERMISSIONS

- Information is available at the website www.ncmedicaljournal.com/reprints
- To request photocopy permission or content licensing, e-mail NCMedJ@nciom.org

ADVERTISING

- For advertising information visit www.ncmedicaljournal.com/media.htm or contact the North Carolina Medical Journal's business and advertising manager, Adrienne R. Parker, at 919-401-6599 ext. 28; adrienne_parker@nciom.org

North Carolina MEDICAL JOURNAL

Classified Ads

Pediatrician needed for full service Hispanic Pediatric practice in Burlington, NC. Must be bilingual, competitive salary and benefits. Phone: 336-570-0010, Fax: 336-570-0012, lnfamclin@bellsouth.net.

Specialty practice interested in sharing our office space and staff with another physician. Excellent location in North Raleigh. Near major hospital. Please contact Cathey Kerr for details if interested. Phone: 919-873-0002, fax 919-873-0006.

PT/FT Physician needed for Internal Medicine, Pediatrics or Family Practice. Competitive salary and benefits. Send or fax CV to 704-225-0428 Attn: Benedict Okwara, MD. First Care Medical Clinic. Email: bokwara@aol.com.

PT/FT Physician Assistant (PAC) needed for Internal Medicine, Pediatrics or Family Practice. Competitive salary and benefits. Send or fax CV to 704-225-0428 Attn: Benedict Okwara, MD. First Care Medical Clinic. Email: bokwara@aol.com.

North Carolina MEDICAL JOURNAL

CLASSIFIED ADS: RATES AND SPECIFICATIONS

The Journal welcomes classified advertisements but reserves the right to refuse inappropriate subject matter. Cost per placement is $60 for the first 25 words and $1/word thereafter.

Submit copy to:
ncmedj@nciom.org
fax: 919-401-6899
mail: North Carolina Medical Journal
5501 Fortunes Ridge, Suite E, Durham, NC 27713

Include phone number and billing address, and indicate number of placements, if known.

Index of Advertisers

Introducing a New Level of Cardiovascular Care for Southeastern North Carolina

When heart disease affects one person in our community, it affects us all—families, loved ones—our neighbors. Here in Robeson and surrounding counties, we have a high incidence of heart disease. And in the past, treatment options often required traveling outside our community, adding to the stress of an already difficult situation. But now Southeastern Regional Medical Center has teamed up with Duke University Health System to offer a new level of cardiovascular care, right here at home.

Owned by SRMC and managed by Duke, one of the world's most respected names in healthcare, the new Southeastern Heart Center will offer open-heart surgery, cardiac intensive care, and complete cardiac cath and interventional services, all provided in a state-of-the-art equipped facility by a team of highly trained SRMC and Duke physicians.

At Southeastern, we take the health of our community to heart. So we're bringing Robeson and surrounding counties the high standards of Duke, without the drive.

Neighbors caring for neighbors. That's Southeastern Regional.

SOUTHEASTERN HEART CENTER

managed by

DUKE UNIVERSITY HEALTH SYSTEM

Your Heart Deserves a Great Team

WWW.SRMC.ORG | 910-671-5000 | LUMBERTON, NC

Opening May 2006

It's your reputation and assets at risk. Entrust them to only the strongest.

Only Medical Protective.

Protecting more of the nation's healthcare providers than any other insurance carrier by delivering:

- **Strength** – the highest-rated medmal insurance with "AAA" S&P and "A+" A.M. Best ratings
- **Defense** – the nation's most proactive winning defense
- **Solutions** – the foremost continuous risk management expertise
- **Since 1899** – the commitment to the medical malpractice field, three times longer than our nearest competitor

For more information on how you may qualify to obtain the nation's best coverage call us at 800-4MEDPRO, visit us online at medpro.com or contact your Medical Protective appointed agent.

MEDICAL PROTECTIVE

Strength. Defense. Solutions. Since 1899.