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2018 Prostate Cancer Review



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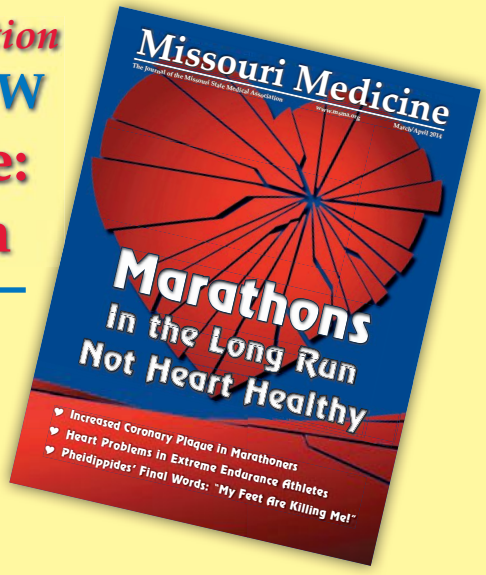
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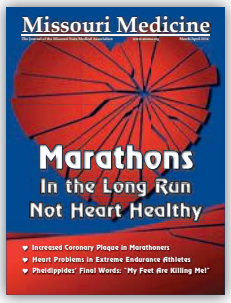
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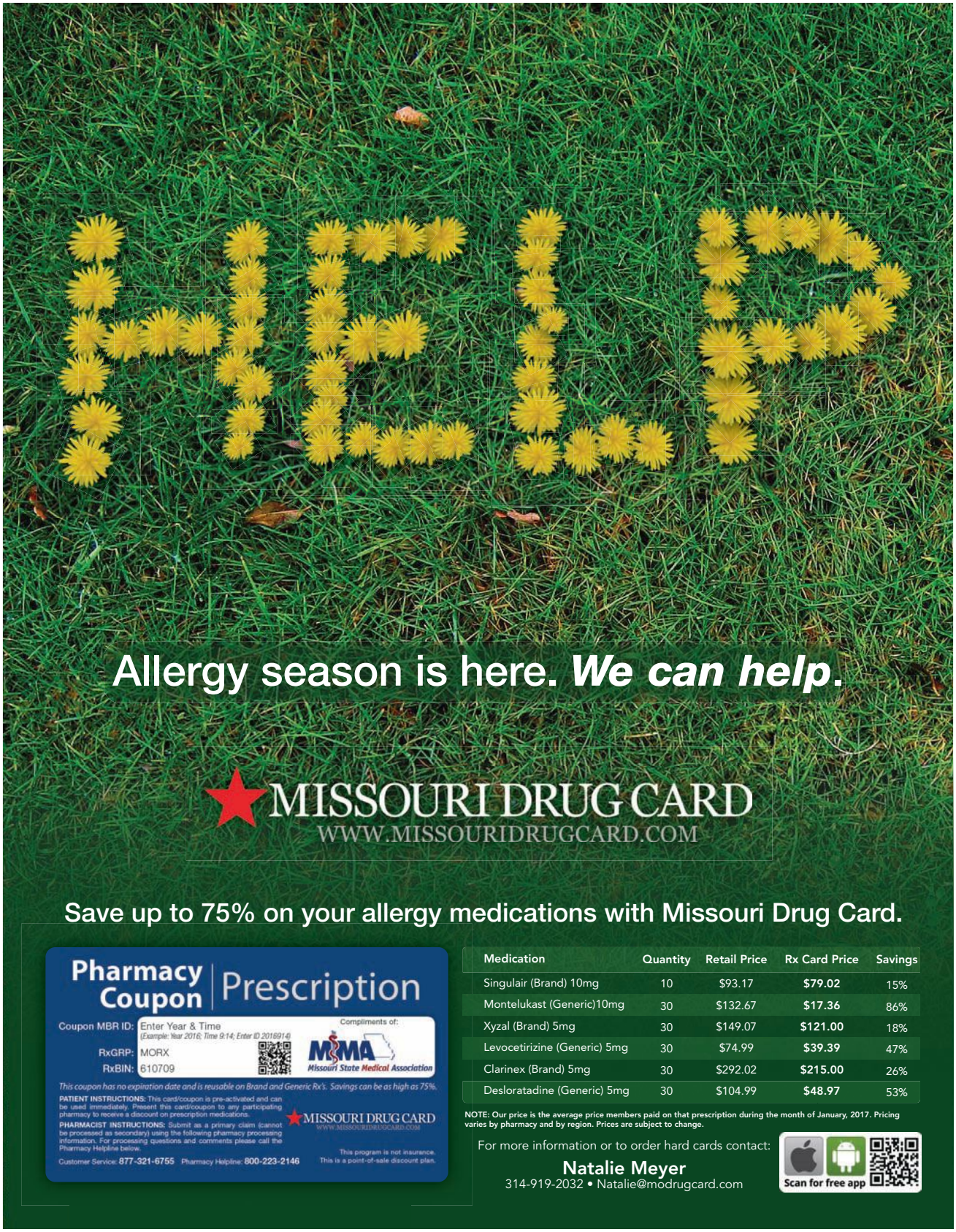
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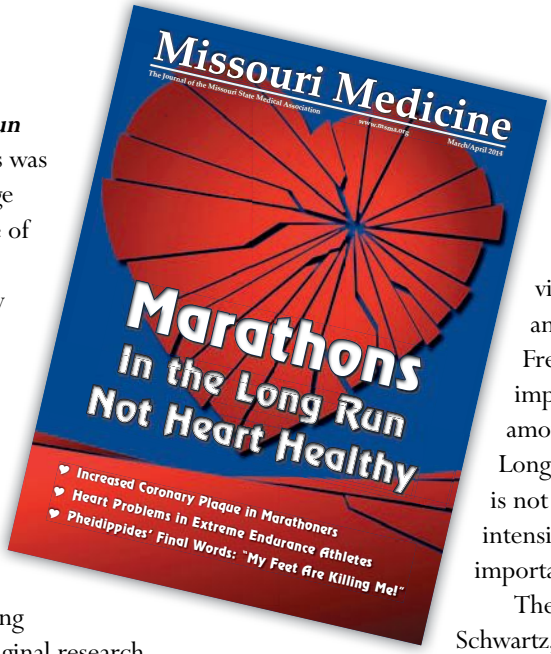
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Marathon Running: An Unhealthy Addiction!

by John C. Hagan, III, MD



***Marathons: In the Long Run Not Heart Healthy*!** This was our call-out cover message in the notable March/April 2014 issue of *Missouri Medicine.*[1] With the passage of time - four years to be exact - it's now apparent *Missouri Medicine* authors got it right. Their naysayers got it wrong. The research paper by Robert S. Schwartz, MD, et al., an editorial review by eminent cardiologists Carl J. Lavie, MD, and Peter A. McCullough, MD, and the editorial outlining my 'heart of stone' from over three decades of marathon running remain our most widely publicized original research. They were noted and quoted in the *Wall Street Journal, New York Times,* and *Runner's World* to modestly name only a few.

In this current 2018 editorial and in the following scientific article, "The Goldilocks Zone for Exercise: Not Too Little. Not Too Much," by James H. O'Keefe, MD, Evan L. O'Keefe, MS, and Carl J. Lavie, MD, (see page 98) *Missouri Medicine* updates subsequent research that has vindicated our earlier conclusions and assertions. New message: Frequent exercise is extremely important to health but in moderate amounts at low to moderate intensity. Long duration-high intensity exercise is not heart healthy. Moderation in intensity and duration is especially important after 40-45 years of age.

The primary 2014 conclusion by Schwartz, Kraus, O'Keefe et al.[1] was the finding that veteran marathon runners had higher coronary artery calcium scores (CACS) than age matched non-marathoner cohorts. CACS, determined by CT scanning, is a surrogate for coronary artery plaque burden. Normal value is 0 and values higher than 100 raise concerns for coronary artery heart disease and increased risk for cardiovascular events such as myocardia infarct, serious arrhythmias, and sudden death. All things most marathoners, myself included, thought they were running away from, not running towards, by full bore running many miles for many hours every week.

Subsequent studies have confirmed that marathon-type, excess exercising is associated with elevated CACS. At the most extreme end of excess exercising, CV events may even be more common than in non-exercisers. Many examples exist of what is essential and/or healthy in small or moderate amounts may be detrimental or even fatal in large amounts such as medication dosage, trace elements, water or alcohol ingestion. In their 2014 editorial overview, McCullough and Lavie also raised a cautionary note about excessive marathon-type exercise, posed excellent



Missouri Medicine Editor John C. Hagan, III, MD, was very confident that his long-distance running would guarantee a healthy heart. He now believes 45 years of maximum endurance exercising contributed to his atrial fibrillation and high coronary artery calcium score. Left, Dr. Hagan runs the Kansas City Hospital Hill Half Marathon in 1988.

Contact: jhagan@bizkc.rr.com

mechanisms by which hyper-exercise might damage the heart and its arteries and cause elevated CACS. They called for more research and wondered if the elevated CACS in marathon runners would carry the same increased risks of CV events as similar scores in non-exercisers with high CV risk factors (smoking, obesity, hypertension, diabetes, etc.).

While I certainly can be accused of having observational bias, my reading of the cardiovascular literature suggests that hyper-exercisers with otherwise few CV risk factors tend to form high calcium density, lower volume fibrous atheroma that are more stable and less prone to cause CV events than the low calcium density, high volume lipid-filled plaque that more commonly causes CV events. Newer techniques of coronary artery testing are able to determine which types of atheroma predominate.

In my 2014 editorial, "Pheidippides' Final Words: 'My Feet Are Killing Me!'" I outlined my personal health problems related to over 35 years of marathon running; the development of what was then called "lone" atrial fibrillation and a CACS of 1606, so high Dr. O'Keefe, my personal physician, called me at home and asked if my wife would drive me back to his office for more tests. (These turned out fine.) Subsequently I stopped running, lost a few pounds, made modest changes in my diet, went on low dose statin and aspirin, and do six days/week low intensity exercise such as walking, exercise bike, treadmill at the snail-like speed of 3.1 mph, or swim for about an hour. Thus far no more atrial fibrillation, no cardiovascular events, and I'm almost completely off blood pressure medication. I began marathon running in the belief it was healthy especially for my cardiovascular system. Had I known then what we now know about excess endurance exercise, I would have patterned my exercise program to match the O'Keefe-Lavie Goldilocks Zone recommendations.

That pretty much gets to the 'heart' of the matter. I am gratified for the role *Missouri Medicine* and this outstanding group of authors played in disabusing the belief that lifelong marathon running-type excessive exercise is beneficial. A prescription for frequent age-specific mild/moderate exercise should be one of the first prescriptions every physician writes for their patients ... and themselves.

References

1. Missouri Medicine, March/April 2014;111(2): 89-101

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The Goldilocks Zone for Exercise: Not Too Little, Not Too Much

by James H. O'Keefe, MD, Evan L. O'Keefe, MS & Carl J. Lavie, MD

In an attempt to promote lifestyles marked by well-being and longevity, it is our hope that people are gravitating towards what we choose to call the Goldilocks Zone of exercise as they become aware of the potential liabilities of excessive endurance efforts. From a pure health standpoint, it is unnecessary to perform vigorous exercise for more than 40-60 minutes.







Clockwise, James H. O'Keefe, MD, MSMA member since 2003, is at Saint Luke's Mid America Heart Institute, Kansas City, Missouri. Evan L. O'Keefe, MS, is in the Ochsner Clinical School, University of Queensland School of Medicine, New Orleans, Louisiana. Carl J. Lavie, MD, FACC, is in the Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, University of Queensland School of Medicine, New Orleans, Louisiana.
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Abstract

Homo sapiens **are evolutionarily adapted to be very physically active throughout life, and thus habitual physical activity (PA) is essential for well-being and longevity. Never the less, middle-aged and older individuals engaging in excessive strenuous endurance exercise appear to be at increased risk for a variety of adverse cardiovascular (CV) effects including atrial fibrillation, myocardial fibrosis, and coronary atherosclerosis. An emerging body of evidence indicates U-shaped or reverse J-shaped curves whereby low doses and moderate doses of PA significantly reduce long-term risks for both total mortality and CV mortality, however, at very high doses of chronic strenuous exercise much of the protection against early mortality and CV disease is lost. The optimal dose, or what we term 'Goldilocks Zone,' of PA may be: at least 150 minutes per week of moderate-intensity aerobic exercise or 75 minutes per week of vigorous-intensity aerobic activity, but not more than four to five cumulative hours per week of vigorous (heart-pounding, sweat-producing) exercise, especially for those over 45 years of age. It is also important to take at least one day per week off from vigorous exercise. There appears to be no concerns about an upper threshold for safety for leisure-time low-to-moderate intensity activities such as walking at a comfortable pace, housework, gardening, etc. After every 30 consecutive minutes spent sitting, stand up and move, ideally walking briskly for about five minutes.**

Introduction

Exercise may be best understood as a medicine with potent benefits, particularly for the CV system. As with any powerful drug, establishing the ideal therapeutic window is of crucial importance. An ineffectively low dose will not impart full benefits, whereas the adverse effects stemming from an excessively high dose may overshadow potential benefits and introduce detriments. A lifelong habit of incorporating PA into one's daily routine is essential to a lifestyle ideal for conferring well-being and longevity.[1] Middle-aged and older individuals engaging in excessive strenuous endurance exercise appear to be at increased risk for a variety of adverse effects—mostly CV in nature.[1-18]

These adverse CV consequences of chronic excessive endurance exercise have been noted in humans as well as in animal models.[19, 20]

Exercise for Longevity

A broad range of PA has salutary effects on many CV risk factors, including lowering resting heart rate and blood pressure (BP), improving lipids and glucose, normalizing body mass index (BMI), reducing emotional stress, improving sleep, and encouraging other healthy lifestyle choices, such as following a nutritious diet and avoiding tobacco.[12, 13, 17] Daily exercise and cardiorespiratory fitness (CRF) are also linked to lower inflammatory markers.[21]

Large long-term epidemiological studies have consistently reported that regularly undertaking PA and maintaining good physical fitness are among the most effective habits for improving life expectancy.[5-11, 14, 18] The consensus emerging from an extensive body of observational data indicates that a routine of regular exercise is associated with an increase in life expectancy by up to six years.[5, 9-13, 15-17] By comparison, if medical science discovered how to cure and/or prevent all cancer, the average life expectancy in the United States (US) would rise about 3.5 years.[22] If scientists were able to eliminate all CV deaths, life expectancy would rise approximately seven years.[22] Thus, a lifelong habit of effective PA is clearly one of the most effective approaches for enhancing longevity and public health.[23-26]

In the past five years, a number of large and scientifically rigorous observational studies have reported that performing as little as 50 minutes per week of strenuous exercise, such as jogging, will bestow near maximal improvement in life expectancy related to PA.[5-7, 9-12, 15-17] The improvement in longevity plateaus with running one to two times per week for a cumulative distance of five to six miles.[9, 15] Paradoxically, running distances longer than approximately 30 miles per week appears to significantly attenuate the boost in life expectancy noted with more moderate doses of exercise.[14, 17, 18, 24, 27, 28]

The U-Curves of Strenuous Endurance Exercise

The lion's share of studies focusing on the topic of exercise dose and life expectancy report U-shaped or reverse J-shaped associations for vigorous PA and risk

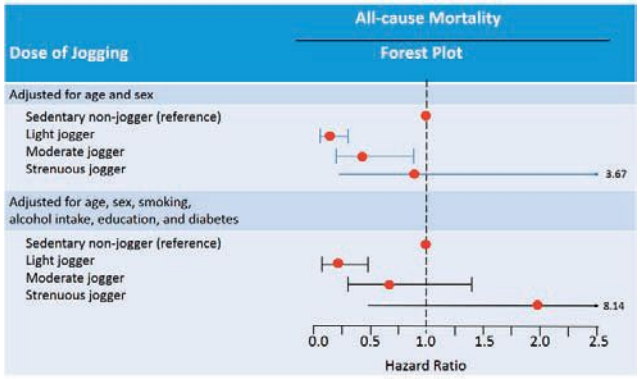


Figure 1. Forest plot indicating all-cause mortality in light, moderate, and strenuous joggers compared with sedentary nonjoggers.[17]

of mortality during follow up.[29] The recurring pattern is that low doses and moderate doses of vigorous exercise significantly reduce long-term risks for both total mortality and CV mortality.[5-7, 9-11, 13-18] The majority of high-quality prospective epidemiological studies on this issue report that the cohort of people who chronically log very high doses of vigorous PA appear to lose most or all of the protection against early mortality and CV disease that was apparent in cohorts attaining low or moderate doses of vigorous exercise.[5-11, 13-18, 24, 25, 27, 28]

Cardiac overuse injury is an insidious syndrome in which excessive strenuous exercise can progressively precipitate CV damage. Many long-term endurance athletes have personal experience with orthopedic overuse injuries—stress fractures, patellar chondromalacia, Achilles tendonitis, shin splints, plantar fasciitis, etc. Correspondingly, endurance athletes can also develop cardiac overuse injuries such as atrial fibrillation (AF), ventricular ectopy, severe bradycardia, coronary atherosclerosis, premature aging of the heart, fibrosis of the atrial and ventricular walls, and rarely even sudden cardiac death (SCD).[2-4]

Data generated from the long-term prospective Copenhagen City Heart Study found that both male and female runners have life expectancies that are approximately six years longer than physically inactive non-runners.[15-17] Yet the individuals subjecting themselves to the highest doses of running, typically more than three running sessions per week, at a faster pace, for a longer duration of time (mean of > 4 hours of running per week), lost the improvement in life expectancy that was observed in the groups doing low or moderate doses of running (Figure 1).[16, 17]

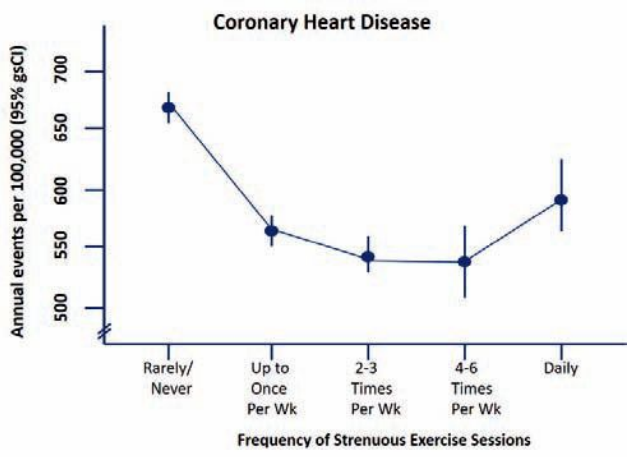


Figure 2. Absolute risks and 95% confidence intervals for CV events.[6]

Similarly, the Million Women Study[6] reported that among a sizeable cohort of adult females from the United Kingdom (UK), those women who regularly completed a heart-pounding, sweat-producing workout one or more times per week had significantly reduced risks for coronary heart disease (CHD) events, venous thromboembolism, and cerebrovascular disease.[6] However, the cohort of females who did take one or more days off each week from strenuous exercise lost a substantial degree of conferred protection against CV diseases (Figure 2).[6] Another massive epidemiological study[5] reported that PA markedly reduced the mortality among those doing moderate doses of exercise, with the familiar reverse J-curve indicating partial loss of protection among the cohort doing the highest dose of exercise.

The small sample size of the cohort performing the very high doses exercise typically causes the upturn at the far end of the reverse J-curve or U-curve to be not statistically significantly different from the nadir. Tellingly, this partial or complete loss of long-term health benefit tends to be statistically significant in studies comprised of very large numbers of study participants. For instance, among the 1.1 million females in the UK study, there were 35,000 women (3.2%) who performed strenuous exercise seven days each week; their risks of CHD, stroke, and venous thromboembolism were statistically significantly higher than the females in the study who each week took one or more days off during which they abstained from vigorous exercise.[6] In studies comprised of populations at higher risk, such as those with known CHD disease at baseline, the exercise-related benefits in life expectancy and CV health were again significantly decreased among the very high-dose PA cohort compared to the moderate-dose PA cohort (Figure 3).[18]

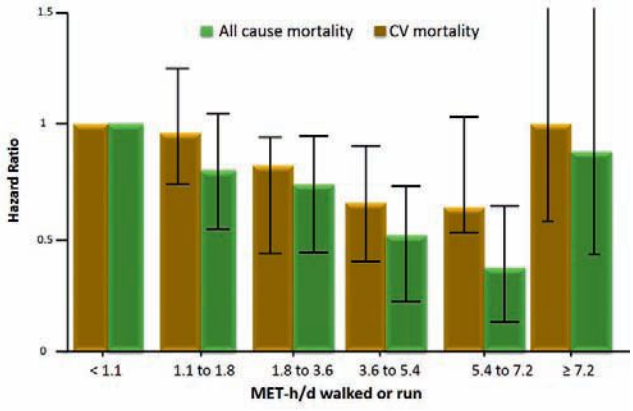


Figure 3. For patients after a cardiac event, running and/or walking reduce risks for all-cause mortality and CV mortality, however these benefits are lost at the highest levels of exercise, which is equivalent to running: more than 7.1 km/day or walking briskly more than 10.7 km/day.[18]

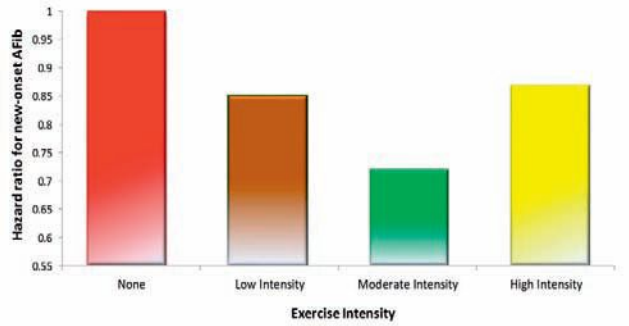


Figure 4. Relative risk of new-onset AFIB among men > 65 years old. The exercise-induced reduction in AFIB was attenuated in the cohort doing chronic strenuous exercise.[31]

Veteran endurance athletes have approximately a five-fold higher incidence of AF compared with sedentary individuals.[30] Despite solid evidence that a routine of moderate exercise decreases risk of AF,[31] with excessive strenuous exercise the AF risk rises dramatically, particularly for persons older than age 45 years (Figure 4).[31]

The Physical Activity Guidelines (PAG) for Americans, published by the Center for Disease Control (CDC), advise at least 150 minutes per week of moderate-intensity aerobic exercise, or 75 minutes per week of vigorous-intensity aerobic activity; at least half (and perhaps as high as 70-80%) of the US adult population fails to reach this exercise goal.[2-4, 12] On the other hand, only 2.5% of the population appears to be overdoing exercise.[13, 14] To put this problem in perspective, approximately 20 people are not meeting the CDC PAG for every one person who is excessively exercising.[2, 12]

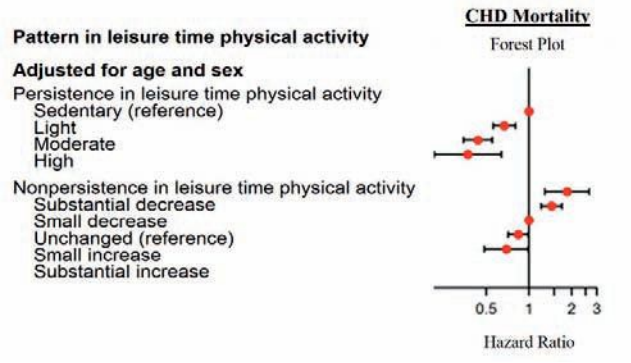


Figure 5. Persistence and non-persistence in leisure time physical activity for the 12,314 CCHS participants. Risk of all-cause mortality in fully adjusted Cox proportional hazards regression analysis.[1]

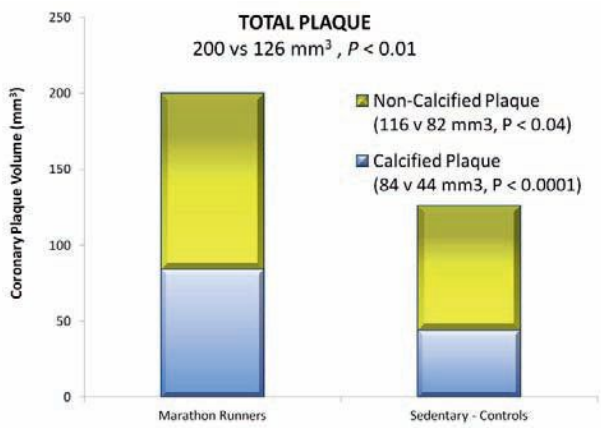


Figure 6. The quantitative volumes of both calcified and non-calcified coronary plaques were higher in the marathoners than in sedentary controls.[38]

No U-curves for Light and Moderate Leisure Time PA (LTPA)

Recent studies of tribes still following the indigenous hunger-gatherer lifestyles demonstrate high levels of activity throughout the day, with individuals often sitting for just two to three hours during their waking daytime routines.[21, 32] These people typically reach 16,000 steps per day—roughly three times the average number of steps taken daily by American adults. The activity levels of these native people is nearly all done in light and moderate ranges of intensity.[21, 32, 33] These individuals following our ancestral lifestyle stayed physically active into middle age and beyond, with the 70-year-old elders often moving as much as the adolescent tribes-people. Notably, both of these modern day hunter-gatherer tribes had remarkably robust health, and virtually no CV disease.[21, 32]

In contrast, studies show that typical US adults sit about 10 hours out of an average 16 waking hours per day. A recent methodologically rigorous study reported that multivariate-adjusted risk of death increased in proportionally with total sitting time.[34] Both the total amount of sitting time and its accumulation in sustained uninterrupted bouts were significantly correlated with total mortality. Individuals who sat for less than 30 minutes at a time had the lowest risk of premature mortality.[34]

The Copenhagen City Heart Study recently reported that LTPA reduces both total mortality and CHD mortality (Figure 5).[1, 25] Compared to the sedentary cohort, mean life expectancy gains were: 2.8 years for the light PA cohort, 4.5 years among the moderate PA cohort, and 5.5 years for the high PA cohort. The highest level of overall PA in that study still paled in comparison to the excessive strenuous activity range noted in above-mentioned studies (which were mostly comprised of runners), thus no evidence for a U-shaped relationship was seen in the study of leisure time activities.[5-11, 13-18] In other words, more is better when it comes to staying active in leisure time with light and/or moderate PA, such as gardening, walking, or housework, and active play such as golf, racquet sports, bowling and dancing.

Regular exercise increases life expectancy in part by improving physical fitness, especially CRF. In fact, the level of cardiorespiratory fitness predicts survival better than does the amount of exercise performed.[35, 36] Similarly, for overweight or obese individuals, physical fitness is an important predictor of longevity, whereas weight loss is not.[37] Maintaining a physically active lifestyle during leisure time improves fitness and bolsters emotional and physical wellbeing for all age cohorts.[1]

Excessive Endurance Exercise and Coronary Atherosclerosis

In collaboration with Robert Schwartz, MD, et al., we studied the association of decades-long marathon training/racing with quantitative coronary artery plaque volume as assessed by computed tomography (CT) coronary angiography.[38] We found that long-term marathon running in men was associated with increased coronary artery plaque development, with significantly greater amounts of both soft (non-calcified) and hard (calcified) coronary artery plaques compared to sedentary controls (Figure 6).

Other studies show that male marathon runners as compared to sedentary controls have larger amounts of calcified coronary artery plaque as quantitated by CT coronary artery calcium (CAC) scoring.[39] The recent CARDIA study, a 25-year long prospective cohort study

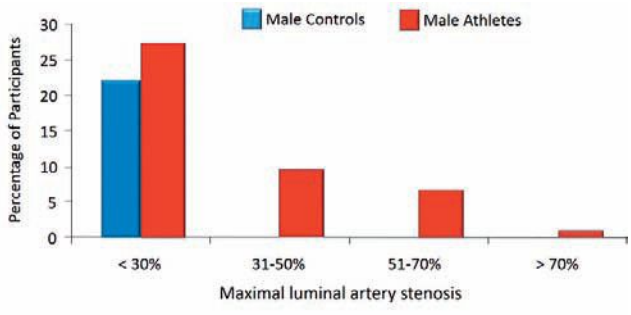


Figure 7. Luminal stenoses in male athletes and sedentary male controls.[41]

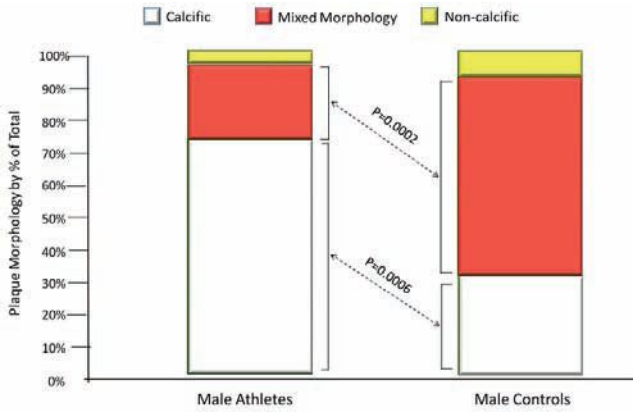


Figure 8. Plaque morphology in male athletes and relatively sedentary male controls.[41]

involving 3,175 individuals, reported that white individuals chronically attaining at least three-fold the exercise suggested by the CDC PAG, as compared to a cohort not meeting the minimum CDC recommended exercise goal, were 75% more likely to have CAC on CT scans.[40] In other words, during a quarter century of follow up the individuals performing at least three times the recommended amount of exercise had significantly higher odds of developing subclinical coronary atherosclerosis during middle age than physically inactive individuals.

A recent prospective comprehensive case-control study assessed 152 masters athletes (77% were runners), mean age of 54 years with average of 31 years performing chronic endurance exercise, and compared them to 92 controls matched for age and gender and Framingham 10-year coronary artery disease risk scores.[41] Despite a paucity of traditional CHD risk factors in both groups, male endurance athletes were twice as likely as male controls to have a substantial amount of coronary plaque (44% vs 22% of individuals, respectively) (Figure 7). Additionally, the coronary plaques were predominantly calcified in the athletes, as compared to plaques of mostly mixed morphology—with calcified and non-calcified components—in the sedentary men (Figure 8). Whether or not these high exercisers may have stable plaque that is less likely to rupture causing acute CV events is unknown. Notwithstanding, significant myocardial fibrosis as assessed by cardiac magnetic resonance imaging was appreciated in the left ventricle in 15 (14.2%) of the male athletes as compared to none of the male controls ($P=0.004$).[41] Other studies have raised concern about this.[42, 43] At present, we agree with Levine's recent review/editorial that these risks are not substantial enough to justify over-frightening athletes about these risks.[44]

The mechanical and metabolic stresses produced by excessive strenuous exercise could play a causal role in accelerated atherosclerosis. Individuals who train and race over very long-distances experience prolonged elevations in heart rate, BP, cardiac output, and atrial and ventricular volumes for up to several hours per day. Strenuous exercise produces large quantities of free radicals, which deplete the buffering capacity of the system after about 50 to 60 minutes of continuous intense exercise.[3, 4] Thus, oxidative stress can become problematic after one hour of sustained strenuous exercise, triggering increased atherogenic modification of cholesterol particles, and predisposing to endothelial dysfunction.[20] Ultra-endurance exercise also generates a multitude of additional circulatory system stresses including protracted elevations of catecholamines and resultant coronary vasoconstriction, lactic acidosis, prolonged sinus tachycardia that reduces the diastolic filling time of the coronary arteries, alterations in free fatty acid metabolism, and other metabolic derangements.[3, 4]

These effects noted among some veteran ultra-endurance athletes are likely to be playing a causal role in other features of cardiac overuse injury including: myocardial fibrosis, increased stiffness and thickness of the walls of the great vessels as well as the cardiac chambers. A recent study reported that young (< 30 years of age) male amateur runners showed transient stiffening of the aorta and other great vessels immediately following a half-marathon race.[41] Strenuous and protracted endurance exercise may also precipitate supply-demand mismatch and demand ischemia, and rarely this can result in myocardial infarction and SCD.[41, 45, 46]

Conclusions

We *Homo sapiens* are evolutionarily adapted to have high PA throughout life. Even so, our indigenous lifestyle called for mostly light and moderate PA for most of our waking



Figure 9. Annual number of individuals (in millions) who completed running competitions in the US over the past quarter-century.[47]

hours, with only occasional bursts of more strenuous exercise. Low doses and moderate doses of vigorous exercise significantly reduce long-term risks for both total mortality and CV mortality. Of concern, excessive strenuous exercise has been shown in many studies to be associated with increased CV risk for myocardial fibrosis and scarring, potentially dangerous arrhythmias, and accelerated coronary atherosclerosis,[3, 4] along with attenuation of longevity benefits noted with less excessive doses of strenuous PA. Accordingly, we suspect that when considering the cumulative PA dose as a spectrum from completely inactive to extremely active, those individuals located on either end of the continuum (sedentary people and those logging excessive doses of strenuous exercise) would reap long-term health dividends by changing their daily routines to get a moderate dose of PA. With respect to cardiac overuse injury, there is likely a large amount of person-to-person variability, with synergistic risk resulting from multiple factors, such as advancing age, genetics, excessive alcohol intake, poor sleep, suboptimal diet, and elevated blood pressure.

Perhaps in part due to accumulating evidence about the potential health risks of excessive exercise, the number of individuals participating in marathons and other strenuous endurance events, after rising dramatically for 40 years, has trended lower over the past six years (Figure 9).[47] This downturn coincided with the first publications by us and others about the potential risks of excessive exercise.[2-18] In an attempt to promote lifestyles marked by well-being and longevity, it is our hope that people are gravitating towards what we choose to call the *Goldilocks Zone* of exercise as they become aware of the potential liabilities of excessive endurance efforts. From a pure health standpoint, it is unnecessary to perform vigorous exercise for more than 40-60 minutes. We recognize that some people exercise longer and more intensely than needed for health benefits their motivation including competition, improving sports performance, ego, fun, and camaraderie. Although we try to emphasize the huge health benefits and minimal risks of low and moderate PA/exercise doses, the risks of excessive exercise, although present, may not be high enough to cause competitive athletes or high-dose athletes to abandon their behaviors despite these risks.[44]

The Goldilocks Zone for Physical Activity or Physicians Exercise Prescription

- Aim for the CDC Physical Activity Guideline 150 minutes per week of moderate-intensity aerobic exercise or 75 minutes per week of vigorous-intensity aerobic activity
- Try to limit doses of vigorous (heart-pounding, sweat-producing) exercise to not more than 4 to 5 cumulative hours per week, especially for those over 45 years of age.
- After 30 consecutive minutes spent sitting, stand up and move, ideally walking briskly for about 5 minutes. Consider a standing desk to reduce prolonged sitting.
- Changing from a completely sedentary lifestyle to one that incorporates even a modest amount of PA will confer substantial benefits to mental and physical health.
- For individuals performing doses of strenuous exercise above recommended levels, consider substituting less aerobically demanding PA, such as walking, yoga, stability exercises, strength training, etc.
- There appears to be no concerns about an upper threshold for safety when performing leisure-time low-to-moderate intensity activities, such as walking at a comfortable pace, housework, gardening, baseball or softball, bowling, volleyball, golf, doubles tennis (and other racquet sports), dancing, croquet, etc.
- Take at least 1 day per week off from vigorous exercise.
- For very high exercisers over 50 years of age, consideration should be given to some cardiac testing (e.g. CT scanning for CAC, or exercise testing and /or echocardiography.)

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Disclosure

None reported.

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Residency: Training for Burnout

by Charles W. Van Way, III, MD

Don't talk to me about adjusting. I don't want to become adjusted to a bad system.

-Paraphrase of remark by Barbara McAneny, President-Elect, AMA, 2017

There is much current hand-wringing about physician burnout. We now have task forces, committees, surveys, and learned articles. We don't have Congressional investigations, but that's coming, as sure as taxes. And yet, we all know the source of our frustration. It's our toxic work environment. There's only so much we can do to adapt to 12-minute clinic visits, excessive paperwork, intrusive oversight, and execrable technology. The word "execrable," by the way, stems from the Latin word for "putting under a curse." Right on.

But what about our residents? Those wonderful young folks, who are helping us today, and will be putting us out to pasture tomorrow? Are they going to bring fresh blood into the system, and re-invigorate American medicine? We're training them to be our successors, to be sure. Are we training them to be our salvation?

Well, no. In fact, we aren't even training them to tolerate the system we've got. Perhaps that's why so many students and residents are all up for single-payer medicine. Compared with what they have to live with, even Canada looks better and better. Or so they think. But I digress.

Let us begin with students. There are at least four problems. First, medical school has always been high pressure. Tragically, my own medical school class had a suicide within two weeks. Medical students still kill themselves.[1] Second, medical students are high achievers, driven by their parents and themselves to succeed. Even small failures can be devastating. Third, we don't let up. Grade point average. Three USMLE exams. Residency match. Abusive residents. Grumpy faculty. And fourth, money, money, money. The average student graduates with $200,000 debt. They've acquired a mortgage, but they don't have a house to live in.

And then, they get to be residents. At least, they're now doctors. OK, residency has always been challenging. But I recall vividly, looking back on my intern year and commenting that I'd rather do that for four years than be a medical student again. Remember, this was in the day of 110-hour weeks. It was still highly rewarding, no matter how much work it was. Since 2003, residents have been limited to 80-hour work weeks. With less frequent call! Still rewarding, but much more livable, eh? Well … sort of.

The 80-hour work week has indeed solved some problems. Residents have fewer nights on call, and get more sleep. Some of them even have a social life. Back in the day, there were programs in which residents were on call, at home, or in the hospital, all the time. Every other night was considered pretty reasonable. No longer. Even every third night call, although "legal," will exceed the 80-hour limit. The most demanding surgical programs are every fourth night, with some exceptions. However, the lighter call schedule means fewer residents to cover the service each night. When a resident is on call, he or she works the whole night. Then, there is the dreaded hand-off. Residents not on call must leave their patients under someone else's care. Handing patients off to another resident for the night or the weekend introduces its own stresses, on both physicians. Also, it affects patient care. In surgical programs, fewer nights on call may mean fewer operations and less experience. Residents often reach the end of the program feeling they need more training. Before the work hour limits, 25% of general surgery graduates took post-residency fellowships. Now, 75% do so.

Residents share the same sort of harassment that plagues all physicians. The electronic health record is still execrable (hey, when I find a good word, I use it). In multihospital programs, residents may have to learn three or four execrable EHRs (see?). Oversight is still intrusive. Residents have to limit their work hours, and they frequently have to do so by compromising patient care.



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Or else they just lie on their timesheets. Did I mention that? Yes, residents have to fill out timesheets. Every week. In detail. In some places, they have to "card" in and out of the hospital. Sounds like we're telling them that they're really factory workers.



Like a factory worker, a resident might be fired. From a faculty standpoint, it's very hard to fire residents. But from a resident's standpoint, the risk is always there. It's a terrible threat, because the consequences are devastating. Even a 1% possibility is demoralizing and stressful.

And examinations. Everyone has to take yearly "in-training" examinations. These are supposed to be for "evaluation." Except that if scores are too low, a resident may be kicked out of the program. All of this leads up to the very high-stakes Board exam(s) at the end of training. You thought exams were over with that M.D.? Think again.

Many residents take further fellowships. That means applications, interviews, competitive matches. Maybe moving the family to another city. That's if the resident is foolish enough, or brave enough, to start a family. Consider. You're $200 grand in debt, you're working 80 hours a week, you're making $10-$15 an hour, and your employment status is year-to-year. Who wouldn't want to get married and start a family? Did you fall in love with another resident? Then the two of you can be $400 grand in debt when you start out! And remember, the interest accumulates.

Of course, residents are supposed to be "resilient." Now, resilience is a very good quality in a healthy personality. The sort of individual who gets through college and medical school usually has that quality in spades. But even the stoutest rubber band will break if it's stretched far enough. And we do a whole lot of stretching. If the resident seeks mental health services, will that affect their later career? Licensing? Employment? Better to tough it out.

Burnout among medical residents is not a terribly well-studied problem. There have been a few studies. A Dutch review from 2007 found 19 articles in the literature, of which five were of moderately good quality. The reported rate of burnout symptoms ranged from 18% to 82%.[2] In a 2002 survey of 415 American internal medicine residencies, Collier et al. found depression symptoms in 35% of residents, with indicators such as dehumanization and cynicism in still others.[3] Goebert et al., in a study of residents and students at six centers, found depressive symptoms in 21% of residents.[4] A French survey of general surgery residents published in 2017 indicated a 52% rate of burnout symptoms.[5] Yes, burnout is a problem in Europe, as well as in the U.S. We can conclude that both medical and surgical residents are subject to burnout, perhaps about as much as physicians in general. Putting it more harshly, our training programs are failing to protect residents from burnout and depression.

There have been a fair number of articles from individual centers promoting this or that coping strategy. Most of these papers say their strategy works. Or appears to work. In general, if a program recognizes and tries to deal with the problem, the residents will benefit. However, there is little consensus on best practices. The truth is, if we don't know how to manage burnout in practicing physicians, then we probably don't know how to manage stress in residents.

We're still training competent residents. We are not, as has been suggested, training future workers in the medical factory. But we are getting somewhat closer to that than we may find comfortable. One thing is certain. Our current medical students and residents will be the core of the profession in the next 10 to 15 years. The more we can keep them happy and mentally healthy, the better our profession will become. And right now, we're not doing that very well. Among nearly all specialties, we need to begin a serious conversation on how we can stop burning out our residents even before they get into practice.

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We Need to Reflame the Fire Before It Burns Out

by J. Collins Corder, MD

Loss of control over work, EHR burdens, and hours at work, all contribute to spike in physician burnout.

As physicians we are faced with challenges in patient care that involve making many decisions in a concentrated time frame and interacting with our peers to give appropriate care to our patients. We expect this as we have been trained to diagnose difficult problems and work long hours that lead to stress between our work and personal lives. The physician selection process is rigorous and eliminates those unable or unwilling to accept this lifestyle. Most physicians are altruistic and committed to their profession. They are taught to address complex problems and to embrace challenges, including grueling training, ongoing night calls and long work hours.

A Public Health Care Crisis

An escalating problem which is beginning to receive much-needed attention from health care leaders is physician burnout. Burnout is a long-term stress reaction characterized by depersonalization, including cynical or negative attitudes toward patients, emotional exhaustion, a feeling of decreased personal achievement and a lack of empathy for patients. The rate of physician burnout ranges from 30-65% across medical specialties, with the highest rates among physicians in the front line of care including emergency medicine and general internal medicine. We must address burnout among physicians as a national imperative as health care reform necessitates greater reliance on primary care.

The Quadruple Aim recognizes that a healthy, energized, engaged and resilient physician workforce is essential to achieve the national health goals of higher quality, more affordable care and better health for populations we serve. Studies continue to show more than half of physicians report at least one symptom of burnout, a substantial increase over previous years. This indicates that burnout among physicians has become a national health crisis that CEOs of institutions are recognizing. They are stating their commitment to address the root causes of burnout and reposition the health care work force for the future.[1]

We will address this scope of burnout and ways in which this is being dealt with in the medical community.

The Scope of the Crisis

Physicians from 27 specialties graded the severity of their burnout on a scale of one to seven in a recent Medscape survey—one being that it does not interfere, and seven indicating thoughts of leaving medicine. All but one specialty selected a four or higher. The most affected specialty? Emergency medicine, with nearly 60 percent of ED physicians saying they feel burned out, up from half in 2013. How can the rising prevalence and severity of burnout be addressed? Regulatory, systemic and practice environment issues appear to be key.

More than 14,000 physicians surveyed designated four concerns of too many bureaucratic tasks, spending too many hours at work, feeling like you're just a "cog in a wheel," and increased computerization of practice.[2] "Today's medical practice environment is destroying the altruism and commitment of our physicians," said Tait Shanafelt, MD, a hematologist and physician-burnout researcher at the Mayo Clinic, in a presentation at a NEJM Catalyst event last June. He also stated that "We need to stop blaming individuals and treat physician burnout as a system issue … If it affects half our physicians, it is indirectly affecting half our patients."[3] In any other business this would call for immediate assignment of a team of system engineers, physicians and administrators to correct this catastrophic problem that affects quality of care, limits access to care, and is eroding patient satisfaction.

Issues of burnout get in the way of physicians' ability



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to provide care to a patient. This primarily relates to the physician's professional spirit of life, involving individuals who work in intense interaction with people. A physician's present daily activity is a double-edged sword: what makes doctors great also drives burnout![4]

The quality and safety of patient care, and indeed the very vitality of our health care systems, depend heavily on high-functioning physicians. In light of this compelling evidence that burnout negatively affects patient care, health care leaders are rightly alarmed and are searching for answers.

Burnout is a term that many professions both medical and non-medical experience on a daily basis. Does the physician burnout rate differ from that of the general working population? The AMA and the Mayo Clinic study published in the Mayo Clinic Proceedings found that physicians work a median of 10 hours more per week, display higher rates of emotional exhaustion and report lower satisfaction with work-life balance. This clearly is driving increases in physician burnout at a higher rate compared to the general U.S. population.[5]

Sources of Burnout ... The Flame Will Flicker

Studies clearly show that the more satisfied physicians are, the less likely they are to leave their practices. Physicians who have tried a go-at-it-alone approach have found they were impacted negatively. We must find ways to relieve this burden through team-based care.

As physicians we entered medicine to help patients. Obstacles that get in the way of patient care which are systemic or environmental should be the focus of change. The EHR system requires half of the physician work day to be devoted to entering data and performing other administrative desk work. The AMA and Dartmouth-Hitchcock Health Care System Time Motion Study found that only 27 percent of physicians' time is spent on direct clinical care. They also found that for every hour of face-to-face time with patients, physicians spend two additional hours on their EHR and clerical desk work.[2]

This spike in burnout is directly related to lost control over work, increased performance measurement, escalating complexity of medical care and EHR burdens and waste, all leading to altered workflows and changed patient interaction. The end result is that many previously well-adjusted physicians are prompted to retire early, give up teaching and mentoring young physicians, go into "nonclinical" business, or leave the profession altogether.

As a physician, I find a very trying problem is the "challenging patient." I do not mean patients who challenge my clinical expertise or that of my colleagues. I am referring to the patients whose circumstances make it impossible to arrive at a satisfactory therapeutic plan.

The example I will give is the 88-year-old who lives with her frail husband. Their children live in another state, their friends are no longer living or able to help, and they have difficulties finding transportation to office visits. She was stabilized in her recent hospitalization and sent out doing well, only to return as a readmission within the next 30 days. She refuses to be placed in a nursing home or assisted living facility. Since the social work team rates her as mentally competent, she is sent home from the hospital. She refuses home health services, saying she "does not need them." The medical team knows at the time of discharge and her follow-up visit in the office, that it will be only a matter of time before she will land in the ER as a readmission.

As the population ages, we will see more of these types of patients. We must find ways to deal with these situations in case management and public assistance to enable them to live independently. I am thankful for the many patients who do not fall into this category of the aging-challenging patient, but their number is increasing and that is very concerning.

Another problem I see in the "new" health care delivery reimbursement system is the primary care providers (both the physician and hospital) are the ones that have to bear the costs of these types of patients who are readmitted due to reasons beyond the provider's control. This creates a large amount of stress on the providers because the new value-based payment systems require the providers to pay back the system for something they cannot control. Yes, we as physicians are responsible to an extent, but we should not bear the burden for those who are incapable of caring for themselves or those patients who are irresponsible and non-compliant as they continue to smoke, not follow directions to change lifestyle, and/or do not take their medications.

Another primary care physician stress I have experienced is inheriting a patient in an advantage risk plan who has not been adequately worked up for a previous problem by their prior risk-participating physician who "gained" by not ordering certain tests. As the unhappy and undiagnosed patient then changes his care to another physician in the risk plan, the new physician and hospital system then become responsible for the high costs to treat that patient. Examples can include aortic valve replacement, defibrillator placement, or long-needed back surgery/intervention. This new physician and provider network

may have to pay back the system if the limited funds for treatment are exceeded. Since the risk is now on the physician assuming care, he or she becomes a "victim" of this system. Unfortunately, the patient is caught as the victim as well. These are the added new stressors that make a physician look at early retirement and shorten a career which one thought would continue until we eventually "push up the daisies."

The experience from Atrius Health suggests that replacing a physician who retires early or leaves to pursue other career opportunities can cost between $500,000 and $1 million due to recruitment, training and lost revenue. All of this is in addition to the significant toll, sometimes with tragic consequences, that burnout exacts on physicians and their loved ones.[1]

Changing the Flicker to a Flame … Solutions and Help

I am sure that those reading this are not surprised by these results which are undercutting the patient-physician relationship. These problems take up the majority of our work day. Kevin Hopkins, MD, a family physician at the Cleveland Clinic, was staring at his computer screen rather than looking at his patient, when he concluded that if he did not have to do this documentation he would really like his work. His team developed templates for health maintenance reminders and he has made workplace modifications such as curtains to allow medical assistants to remain in the exam room to document while maintaining "privacy" for his patients. Multi-tasking skills have been developed for his MAs to be more engaged in patient care than they have ever been and they enjoy their work. Utilizing the MAs can give a big return on investment and achieve a real sense of team work resulting in better satisfaction for both the physician and the patient.[6]

Another suggestion is reducing the work time outside office hours, since physicians spend another one to two hours of personal time each night doing clerical work related to EHRs. (I have frequently referred to this as more "bean-counting work as we click!") By getting documentation support either through dictation or documentation assistant services, we may be able to increase direct clinical face time with patients and reduce "home office clerical hours."

Ways to Reflame the Fire

A very good collection of practice improvement start strategies can be found in the AMA Steps Forward Module as it relates to bringing team documentation to your practice. The collection offers several models to help physician relieve the burden of current EHR in deficiencies as well as aiding EHR software selection, purchase and implementation.

An excellent local source is the Missouri Physicians Health Program which is sponsored by MSMA and local medical societies along with other health care systems. Sharing office space with SLMMS, MPHP is available to help physicians in many areas of mental health. They "know more than just substances abuse" as they address physician problems with mental health which include stress, burnout, depression and suicidal thoughts. Their other areas of professional assistance are numerous.

Another source of assistance can be found in the article, "10 Bold Steps to Prevent Burnout in General Internal Medicine,"[4] which was initially presented at the annual meeting of the Society of General Internal Medicine in 2013:

Institutional Metrics

1. Make clinician satisfaction and well-being quality indicators.
2. Incorporate mindfulness and teamwork into practice.
3. Decrease stress from electronic health records.

Work Conditions

4. Allocate needed resources to primary care clinics to reduce health care disparities.
5. Hire physician floats to cover predictable life events.
6. Promote physician control of the work environment.
7. Maintain manageable primary care practice sizes and enhanced staffing ratios.

Career Development

8. Preserve physician "career fit" with protected time for meaningful activities.
9. Promote part-time careers and job sharing.

Self-Care

10. Make self-care a part of medical professionalism.

These 10 steps are presented to identify stress at its earlier stages and choose programs to prevent it. Institutional success must include physician satisfaction and well-being. It also incorporates mindfulness and teamwork for training practicing clinicians. Mindfulness, a known stress reducer, is a means for internally accommodating external stress orders. Teamwork is critically important for burnout prevention through sharing and support of clinician workload. The patient-centered medical home is an example of this.

CEOs of health care institutions have a vital role; their attention is paramount to help in easing this problem of physician burnout. To further this objective, the CEOs of 10 leading health care delivery organizations held a summit meeting aat AMA headquarters in Chicago in September 2016. They concluded leaders must recognize burnout in the physician/health care worker and work in areas of burnout prevention and restoring the joy in medicine. Boards should hold CEOs accountable to implement these approaches to address physician burnout.[1]

The strength of the physician's immediate supervisor's leadership has been shown to matter. Each one-point increase (on a five-point scale) in leadership decreases the odds of the physician burnout by 3.3 percent and increases satisfaction by 9 percent. Successful leaders hold career development conversations with their physicians, inspire and empower their physicians to do their job well, and recognize the physician for a job well done.[1]

This meeting came to the consensus that addressing burnout is a matter of urgency. A local hospital is addressing low patient satisfaction scores and is having mandatory physician meetings to improve scores in the future. They must address "physician burnout" as a source and contributor to these low patient satisfaction scores and how to constructively deal with this problem.

Volunteering

Last but not least, giving back to the community "recharges a doctor's battery" and provides new motivation as a full reset for physicians. It reminds us of why we chose medicine as our calling. Physicians deal with problems that have no easy fixes, including increased scrutiny, more administrative hassle, and rising costs and responsibility for controlling these costs—all while we are trying to give the best of care to our patients. Volunteering has its own rewards and the research bears that out. After adjusting for socio-demographic factors, multiple studies have shown that adults who volunteer enjoy better mental and physical health and have lower mortality rates. There are additional benefits for physicians as volunteering can serve as inoculation against physician burnout even to causes unrelated to medicine, according to Gail Gazelle, MD, hospice and palliative care physician in Boston, who provides executive coaching for physicians and physician leaders.[7]

Volunteering can be done in the form of serving the medical community or the nonmedical community. Since the early 1990s, I have found this to be very beneficial as I have served in a homeless center and coordinate one night a month in serving a group of 15-20 homeless people in our community. When I watch the impact on their lives and see their faces, sometimes the tears and hugs, it humbles me and makes me recognize that what I do has a lot of value. We can truly make a world of difference for people. It is true that I am tired on that Friday evening after working in the office as "I may drag into the door of the homeless shelter but on the next morning I am skipping out." My office staff volunteers to help; they have prepared food and worked with these homeless that we serve. It is a great team builder and I feel has helped bond our office. This has been an opportunity to help someone else and get our busy minds off of ourselves and the "hassle" of running an office

Thoughts Overall on Turning Up the Flame

We need comprehensive, systematic and sustained efforts to improve physician well-being. The drivers of physician well-being must be addressed from the three reciprocally related areas: practice efficiency, a culture of wellness and personal resilience. A balanced approach is necessary to build this platform to drive sustained improvements in physician well-being and our health care performance. All of us in the health care system owe it to ourselves, to our patients and to generations to come, to work together for improvement in all areas of health care delivery.

Our patients deserve care from a compassionate, competent, caring, engaged and resilient physician. We must be committed to work with our patients, EHR vendors, medical leaders of our institutions, insurance companies, pharmaceutical companies, hospital CEOs, physician health programs, and last but not least our physician/health care colleagues and assist them in their daily dance with the crisis of burnout.

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The Private Physician Practice's Early Planning Considerations Under the New Tax Law

by Albert Lin, JD

The implementation of Pub. L. No. 155-97, referred to as the Tax Cut and Jobs Act of 2017 (the "Tax Act") on December 22, 2017 represents one of the most fundamental shifts in the taxation landscape since 1986, the last major recodification of the Internal Revenue Code of 1986, as amended (the "Code"). How quickly the Tax Act became law surprised many, and left tax advisors scrambling during the holiday season, answering questions from curious clients while still having to deal with last minute 2017 tax planning and spring 2017 tax due dates under the old regime.

With the lowering of the federal corporate income tax rate to 21%, for example, a majority of physician practices (typically structured as "pass-through") entities questioned whether they should direct their tax advisors to convert to a "C" corporation for federal income tax purposes. For better or for worse, larger non-service providing corporations stand to receive the most tax savings under the Tax Act, while larger specialty physician practices benefit less.

In response to the common refrain that physicians should hear from qualified tax advisors this early in the lifetime of the Tax Act, in general, major restructurings of private physician practices should be avoided until their tax advisors can carefully evaluate the new laws in the context of their specific clients' practices. One major caveat is that as of the date of this article, beyond the text of the Tax Act, administrative guidance is only now trickling in on various Tax Act provisions that sorely need guidance. Newly defined terms within the Tax Act, for example, have only general definitions that the Internal Revenue Service ("IRS") will almost certainly further refine, expand, or limit, in subsequent administrative rulings and notices.

For these reasons, quickly changing the form of the physician practice should be avoided. There will be no "one size fits all" structuring solution for an existing physician practice. What is important is that physician practices be aware of the new concepts created by the Tax Act that will have impact on their final tax bill. This article seeks to introduce physician practices to key provisions[1] under the Act, maximizing awareness when consulting with tax advisors for tax planning.

New Tax Rate Considerations

1. Individual Rates

Clearly the major accomplishment of the Tax Act was the overall reduction in tax rates; which take effect now in 2018, and expire after 2025. Already as of the date of this article, payroll withholding is being adjusted to take into account reduced individual tax rates. The following chart shows the individual rate brackets in effect for 2018. On an annual basis, the IRS will use the Consumer Price Index (CPI) to adjust the rate bracket's income amounts to account for inflation.

See Table 1 for the 2018 federal individual tax rate table (which would apply to physicians structured as sole proprietorships, as well as non-capital gain distributions and "pass through" ordinary income from physician practices, with taxable wages.[2]).

2. Corporate Rates

The new "C" corporation tax rate is now a flat 21 percent, with no graduated corporate tax rate schedule and, importantly, no flat 35 percent "personal service corporation" tax rate that would apply to physician practices structured as "C" corporations under the rules in place prior to the Tax Act.[4]

This rate would apply to any net income of a "C" corporation that remains after paying practice expenses, including compensation. The emphasis here is that the



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Table 1. **Individual Tax Brackets and Rates, 2018[3]**

Rate	For Unmarried Individuals, Taxable Income Over	For Married Individuals Filing Joint Returns, Taxable Income Over	For Heads of Households, Taxable Income Over
10%	$0	$0	$0
12%	$9,525	$19,050	$13,600
22%	$38,700	$77,400	$51,800
24%	$82,500	$165,000	$82,500
32%	$157,500	$315,000	$157,500
35%	$200,000	$400,000	$200,000
37%	$500,000	$600,000	$500,000

21% rate applies to "net income" of the "C" corporation – there still must be salary and other compensation paid to the physician before arriving at net income. The salary and other compensation (such as bonuses) will be taxed at the higher individual tax rates even aid within a "C" corporation. Historically physician practices structured as "C" corporations would zero out net income anyway by maximizing the compensation deduction. So, while in concept the 21% tax rate for "C" corporations is attractive, the actual benefits may be limited for many physician practices already structured as "C" corporations.

Moreover, the traditional disadvantages of the "C" corporation remain. There is still double taxation of any net income paid out as dividends; and, for any early stage business, net losses are trapped in a "C" corporation (rendering any pass-through of losses to shareholders impossible except through sale or liquidation).

New Tax Deduction for "Pass-Through" Entities (non-"C" corporation entities and sole proprietorships).

Since "C" corporations have a major reduction in the tax rate to 21 percent (down from the previous highest marginal rate of 35 percent), the Tax Act implemented a new 20 percent "qualified business income" deduction, or the "QBI deduction."[5] In principle, at least, the QBI deduction was intended help put on a more equal standing, tax-wise, the sole proprietorships, partnerships and limited liability companies ("LLCs") and "S" corporations (called "pass-through" entities") which do not have benefit of the low 21 percent tax rate applicable to "C" corporations. Generally, pass-through entities can take this new QBI deduction against their taxable net income (although not, unfortunately, against their net income for self-employment tax purposes). As will be seen below, while the new QBI deduction is a consideration for the physician practice, its utility is still in doubt.

1. QBI Caveat #1 – Difficulty in QBI Deduction Calculation

While the principle of the QBI deduction is commendable; its application is not because the mechanics, limitations, thresholds, and definitions surrounding the QBI deduction are not simple and will create headaches for tax compliance, as well as challenges for the IRS in its administration. If simplification was a goal for the Tax Act, that goal was missed. As will be seen in the discussion below, the majority of larger private physician practices will be unable to use the QBI deduction for the medical service-providing aspect of their business.

The QBI deduction is calculated, very generally, as the lesser of (i) 20 percent of a taxpayer's "qualified business income" from the pass-through entity (including a sole proprietorship); or (ii) the greater of (a) 50% of W-2 wages or (b) 25% of W-2 wages plus 2.5% of the "unadjusted basis of the taxpayer's assets." These amounts are determined, in the case of a taxpayer that is a part owner, with reference to the allocable share of such amounts (not the whole).[6]

The "qualified business income is trade or business income, and is intended to exclude investment income such as dividends and capital gains. Moreover, "trade or business income" does not include W-2 wages paid to an owner as an employee (which is usually seen in the context of "S" corporations). And the QBI deduction cannot exceed 50 percent of the total W-2 wages paid by the business.[7]

2. QBI Caveat #2 – Physician Practices Generally Excluded

The emphasis here on the above QBI deduction explanation, is "very generally." The actual QBI deduction is more complicated than in the brief description above, and even once the calculation is nailed down, the QBI deduction is not going to be available to most physician practices! This is because of a key exclusion (with its own exceptions). The QBI deduction is not available to more profitable physician practices because "specified service trade or businesses" are excluded from taking it. These "specified service trade or businesses" include the performance of services in the fields of health, law . . . accounting, actuarial science, performing arts, brokerage services, or "any trade or business where the principal asset of such trade or business is the reputation or skill of 1 or more of it employees."[8] As such, physician practices, where medical services are performed, are largely ineligible to take the QBI deduction. The rationale here is that such service providers, if able to easily take the QBI deduction, would simply be able to convert wages that they would otherwise get as an employee (taxed at the higher individual rates) into essentially the tax-favored corporate rates.

As a concession to smaller family and rural practices, however, the QBI deduction is still available for even owners of specified service trade or business if their taxable income is less than $315,000 (for joint filers) or $157,500 (for single filers).[9] Those practices (typically small sole proprietorships or disregarded professional limited liability companies) should have their tax advisors pay particular attention to the QBI deduction. There is a phase-out as the taxable income exceeds those thresholds, such that the QBI deduction is completely phased out at $415,000 for joint filers or $207,500 for a single filer.

3. QBI Caveat #3 – Clarifying Regulations that May Close Loopholes May be Forthcoming; Consider Non-Tax Reasons for Any Restructuring

Now, given the complexity of the QBI deduction, what are the practical aspects that the private physician practice should focus on? A caveat is that because no clarifying regulations have been issued, the IRS may see early proposed strategies as loopholes and shut them off. Some options make sense from a non-tax, liability protection standpoint, so to the extent a physician practice contains fixed assets of significant value, such assets, such as real estate or investment property, would be better off in a non-practice entity. The physician practices should balance the additional complexity created by separation of entities (especially with multiple owners and governing documents) and decide whether some tax savings and liability separation is worth the considerable administrative expense.

A. Consider separation of any non-medical practice components of the physician practice into separate entities. Larger physician practices may have sources of revenue that are not tied to the provision of physician services. Development of intellectual property, teaching/writing, surgery center development, real estate, equipment purchase/leasing, might be considered as activities that should be separated out from the physician practice businesses to take advantage of a potential QBI deduction. Naturally, there are liability reasons to do this as well, if not already done.

B. To the extent that the income level of a physician may be under the $415,000/$207,500 thresholds described above, pay particular attention to the timing of deduction and recognition of income to ensure the benefits of the QBI deduction will be taken. Invest in quality tax professionals to ensure the correct calculations are made in obtaining this QBI deduction. Particularly in the case of solo family practitioners which may purchase its own real estate and pay a fair market rental value to a wholly-owned real estate entity.

Specific New Provisions of Interest to the Physician Practice

1. Cash Method Changes

A key change that will impact many larger private physician practices is the ability to use the cash method of accounting for its practice. Previously, corporations, partnerships and LLCs must use the accrual method of accounting if they exceed $5 million in average gross receipts for the prior 3 taxable years. That $5 million threshold has been increased considerably to $25 million; moreover, this rule applies regardless of entity structure or industry.[10] Practices with significant timing issues between billing and actual receipt may consider whether deferral of income tax recognition to cash will be worthwhile (keeping in mind accrued expenses may not be currently deducted under the cash method). Changes in accounting method require a formal request be made with the IRS, via "Form 3115."

2. Completed Contract Method of Accounting

The Tax Act contains a bit of a windfall for some smaller construction industry taxpayers, which will also indirectly impact physicians engaged in construction

projects with surgery centers and hospitals. Construction contractors who engage in projects that may take several years to complete will be able to defer recognition until a project is completed (using the "completion method of accounting") as opposed to recognizing revenue over time (the "percentage of completion" method). The threshold for construction contractors to use the "completion method" was previously $10 million in annual gross receipts or under; that number has increased to $25 million.[11]

3. Increased Section 179 Expensing

A significant boon for all business taxpayers is the ability to take a 100% "Section 179" immediate expense deduction, up to $1 million of eligible new property placed in service before January 1, 2023 (the previous limit was $500,000). Also, where previously, the Section 179 expense deduction "phase-out" threshold was $2 million (after which the Section 179 expense ability is reduced dollar for dollar) was increased to $2.5 million. In addition, certain improvements to non-residential real property, such as roofs, heating, ventilation, air conditioning, and fire and alarm projection now qualify for Section 179 expensing.[12] These all help reduce the cost of equipment and key property improvements for the physician practice.

4. Elimination of Non-Meal Entertainment Expenses/ Limitation on Deductible Staff Awards

A tax break previously afforded to larger physician practices was the 50% deduction for entertainment costs for entertaining clients; this deduction was substantially rolled back and the only amount that may be deducted now is 50% of the costs for meals.[13] This eliminates the ability to write off costs of sporting events, event tickets, and club dues. Office holiday parties may continue (no word on whether you can combine a party with a client event).

Staff fringe benefit rules are adjusted as well; employee achievement awards must be in the form of tangible personal property and not cash, gift cards, tickets, meals, lodging, or stocks and bonds.[14] Practices with significant write-offs for staff awards may want to review its policies going forward.

Businesses may no longer deduct the cost of employee parking and transit passes, although employees who still receive the benefit do not have to recognize the cost as income.[15]

5. Litigation-Related Tax Changes

No physician practice ever wants to be hit with regulatory violations; however, in the event of such an unfortunate occurrence, the Tax Act has new provisions that the practice counsel should be aware of in structuring settlements. Previously, while fines and penalties paid to a governmental entity for any violation were not tax-deductible (punitive payments), compensatory payments, including False Claims Act and environmental remediation penalties, were deductible. Now, under the Tax Act, there is a general prohibition of tax deductions for any payments made to or at the direction of a government, governmental entity, or regulatory entity in connection with a violation of law or an investigation into a violation.[16]

The narrow exception for tax deductions that remain are for payments that constitute "restitution (including remediation of property) for damage or harm related to the violation or potential violation of law.[17] Amounts paid for the costs of the investigation or litigation are not deductible. The amounts that constitute "restitution" must be identified in the relevant court order or settlement agreement, and the governmental entity or regulatory agency must file an information return with the IRS reporting the deductible amounts.

And in response to the #MeToo movement, the Tax Act prohibits any deduction for amounts paid for any settlement or payment relating to sexual harassment or sexual abuse, or any attorney's fees related to any settlement or payment if such settlement or payment is subject to a confidentiality or nondisclosure agreement.[18]

Conclusion

The common refrain that the physician practice will hear from qualified tax advisors, following the passage of the Tax Act, should be to avoid major restructurings without careful consideration of all aspects of the practice. The most common question will be whether the more favorable "C" corporation tax rates will justify a change from pass-through status to that of a "C" corporation; but since the rates will generally only apply to income after payment of a reasonable salary, the benefits are not as clear cut as a straight up reduction. There is an old lesson in tax law classes – the "C" corporation is like a lobster trap – easy to get into, nearly impossible to get out of. Pass-throughs still contain more flexibility in operations and liquidation transactions, so currently, are still favored.

The QBI deduction is new, so most commentary suggests awaiting further analysis and IRS regulatory guidance before any major restructuring is done to attempt to take advantage of the new deduction (if at all possible). That being said, private practices with income that falls under the $415,000 joint filer/$207,500 single

filer thresholds should take care to ensure their tax return preparers take into account this deduction when the 2018 returns are filed next year.

Finally, numerous other provisions discussed in this article will impact the physician practices to some extent, particularly with respect to the increased Section 179 expensing amount. This benefit will permit younger physicians to jump-start their practices by permitting significant capital investment with less of a tax burden than in prior years. While tax considerations are only one factor driving the business decisions of a physician practice, a good awareness of its changes will help physicians make appropriate decisions through 2018 and beyond.

References

1. A thorough discussion of all changes impacting individuals, as opposed to entities, is beyond the scope of this article. These many individual changes include, but are not limited to, the doubling of the standard deduction and repeal of the personal exemption, increases in alternative minimum tax ("AMT") exemption amounts, the limitations on the residential mortgage interest deduction, the elimination of alimony as a tax deduction, and the doubling of the federal estate tax exclusion amount. All of these changes will have bearing on the tax advisor's overall analysis of specific physician practice clients.
2. There is no change to the self-employment tax regime, so sole proprietor physicians and physicians receiving ordinary income for services rendered as "pass-through" income from partnerships will still be subject to the 15.3% self-employment tax.
3. Tax Act § 11001, 11002; I.R.C. § 1, 15, 62(c)(2)(A).
4. Tax Act § 13001, 13002; I.R.C. § 11.
5. Tax Act § 11011; I.R.C. § 199A.
6. Id. The actual calculation is more complex, with adjustments based on net capital gain and certain "qualified cooperative dividends" that likely would not be too relevant to the physician practice.
7. Id.
8. As an example of the confusing Tax Act structure, "engineering and architecture" are excluded from the statutory definition of a "specified service trade or business" for purposes of the QBI deduction, arguably since their work generates capital investment, more so than physicians, lawyers, and accountants. Id.; I.R.C. § 199A(d)(2).
9. Id.; I.R.C. 199A(b)(3).
10. Tax Act § 13102; I.R.C. § 448, 447.
11. Tax Act. § 13102; I.R.C. § 460.
12. Id.; I.R.C. § 179(f)(2).
13. Tax Act § 13304; I.R.C. § 274.
14. Tax Act § 13310; I.R.C. § 74, § 274.
15. Id.
16. Tax Act § 13306; I.R.C. 162; § 6050X.
17. I.R.C. 162(f)(2)(A)(i).
18. Tax Act § 13307; I.R.C. § 162(g).

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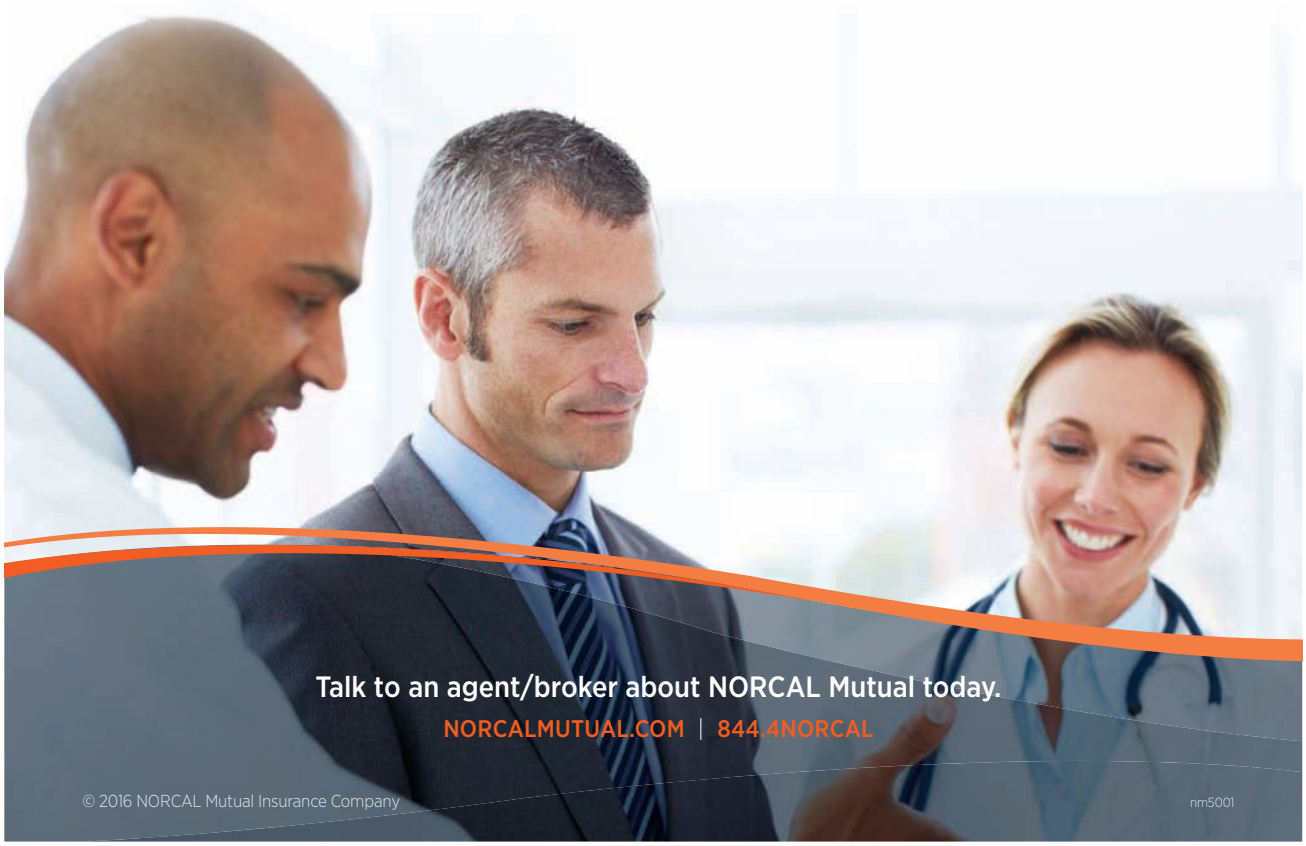
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Be Involved!

by Warren C. Lovinger, Jr., MD



Dr. Lovinger visits medical students at AT Still Kirksville College of Osteopathic Medicine.

As busy physicians and physicians in training, it is tempting to focus exclusively on the demands of our busy schedule, while neglecting other opportunities for growth and fellowship. However, if we prioritize involvement in activities and organizations that enhance personal and professional development, we will be happier and more effective in what we do. A great opportunity for medical students, residents/fellows, and graduate physicians to interact with peers is to be an active member of the Missouri State Medical Association and its components.

Involvement can take many forms, and may include local, regional, and national connections. MSMA sponsors active groups at all six of Missouri's allopathic and osteopathic schools. Student participants have the opportunity to attend statewide and national meetings, such as legislative advocacy days, the annual MSMA state meeting, and AMA meetings. Relationships developed at these events can lead to lifetime friendships and peer support.

The growing Mentor Program, piloted this year at MU-Columbia, pairs medical students with graduate physicians across the state. Residents and Fellows in Missouri's several training programs are urged to connect with peers in their growing and enthusiastically led MSMA caucus. Nationally, residents and fellows are very effective in influencing the policies of the American Medical Association.

For those of us who are now in practice—whether employed or independent—it is crucial that we stay connected to our peers locally, statewide, and nationally.



Drs. Ravi Johar and Lovinger help launch the MU Medical Student-Mentor program.

The Missouri State Medical Association exists to provide this professional umbrella. MSMA membership provides ready access to a myriad of participative, advocacy, and learning opportunities. In my home area, the West Central Missouri Medical Society brings together physicians from five rural counties. Our meetings are wonderful opportunities for fellowship, and networking—and are always heavily attended.

At a state level, MSMA has ten districts that each have at least two councilors/vice councilors who attend quarterly meetings in Jefferson City. There is no better way to feel the pulse of Missouri's healthcare community than to participate in these gatherings. It is also invigorating to get to know so many wonderful, motivated people. The MSMA staff is very effective in facilitating our organization's many activities, and constantly reaches out to Missouri students, residents/fellows, and practicing physicians.

For some MSMA leaders, the opportunity to represent Missouri nationally at the meetings of the American Medical Association provides an awesome experience.



Warren C. Lovinger, Jr., MD, MACP, MSMA member since 1979, and President for 2017-2018, is an Internal Medicine physician, Nevada, Missouri.
Contact: wclovinger@gmail.com



Right, members at the West Central component society.

We are especially fortunate this year to have a Missourian—David Barbe, MD, of Mountain Grove—as the AMA President. He presents our state and profession exceptionally well, as was readily apparent during our recent visit to Washington, D.C. and the Missouri congressional delegation during the National Advocacy Conference.

Perhaps the greatest involvement opportunity available to all of us—physicians and physicians in training – is the annual Missouri State Medical Association Annual Convention. It alternates between Kansas City and St. Louis—this year held at the St. Louis Renaissance Hotel from March 23 to 25, 2018. Not only is there fellowship with physicians, students, residents, and fellows from across the state, but there are numerous CME programs (free to MSMA members), discussion of MSMA positions and proposals in the coming year, and recognition of many leaders in our state. The value of your MSMA dues is easily recouped by simply attending this meeting.

In summary, membership in the Missouri State Medical Association and its components opens the door to a wide variety of opportunities for personal and professional growth and satisfaction. I hope that you will take this invitation to Be Involved!



Above, your MSMA Council.



Your Missouri Delegation to the American Medical Association.

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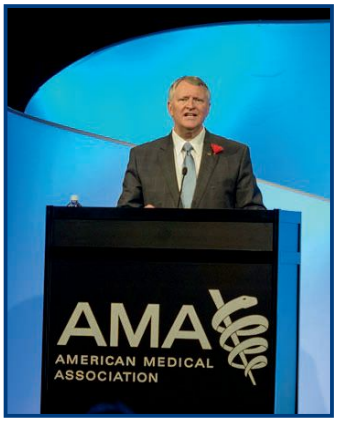
Missouri Physicians Keep Our Local Economy Healthy

by David O. Barbe, MD

As physicians, we carry tremendous responsibility as trusted confidants, patient advocates and leaders of the health care team. But our positive impact extends far beyond the exam room. We keep the economy healthy too.

This year, the American Medical Association (AMA) published a study that demonstrates the huge economic impact of physicians nationally and in their home states. The 2018 AMA Economic Impact Study (EIS) shows that America's physicians play a vital role in local economies by supporting jobs, purchasing goods and services, and generating tax revenue. For example, the findings show that Missouri's nearly 14,000 physicians contribute:

- Jobs: Physicians' economic investment supports 173,905 jobs across the Show Me State – an average of 12.6 for each physician.
- Economic activity: Physicians generate $29.2 billion in economic output – the value of the goods and services provided– and help other businesses grow through their own, and their employees' purchasing. Physicians' economic activity, and that which they have generated, comprises about 10 percent of Missouri's total economy.



David O. Barbe, MD, MHA, MSMA member since 1985, is the American Medical Association President and a Family Physician from Mountain Grove, Missouri.
Contact: dbarbe_md@yahoo.com
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- Wages & benefits: Physicians contribute $13.8 billion in total wages and benefits paid to workers across the state, empowering a high quality, sustainable workforce.
- State and local tax revenue: Physicians' contributions to the economy generate more than $1 billion in state and local tax revenue for their communities ($74,263 per physician), enabling essential investments.
- Ripple effect: Nationally, every dollar applied to physician services supports an additional $1.84 in other business activity. Nearly 11 additional sector jobs are supported for each one million dollars of revenue generated by a physician's practice, because physician offices support other businesses by purchasing supplies, equipment and services. Additionally, physicians and their employees are individual consumers, too, further supporting the economy.

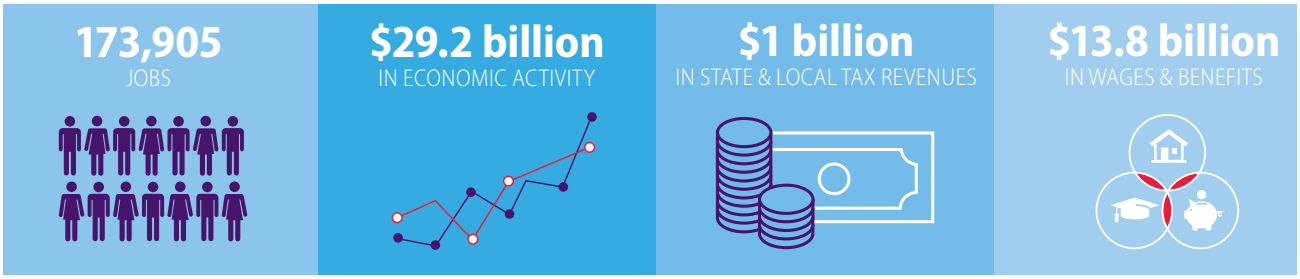
The study also shows physicians' comparative strength among other economic actors in the community. At the national level, physicians support greater economic output than legal services, home health care, higher education, or nursing home and residential care.

The EIS is a critical tool for educating lawmakers on the economic value of physicians' practices to states and the nation. The findings make the compelling case that our interests in economic matters are to be taken just as seriously as in clinical matters. It is critical to protect and fortify the programs and policies that help support physicians and allow their practices to thrive.

- For example, to maintain economic competitiveness, it is imperative for legislators to enact laws that foster a positive practice environment and support a strong and vibrant physician workforce

Physicians bring economic health to our communities.

The **2018 AMA Economic Impact Study** demonstrates how physicians contribute mightily to the health of Missouri's economy.



Physicians' impact is felt far beyond the exam room, reaching through local communities, producing a network of jobs and spurring local investment.

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AMA AMERICAN MEDICAL ASSOCIATION

MSMA Missouri State Medical Association

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that helps grow the economy. Particularly in rural areas, cultivating a productive practice environment can play a key role in fostering community development, because the physician-supported workforce grows the local economy and may even attracts investment from outside the community.

- The 2018 AMA Economic Impact Study underscores the need for state legislators to support tomorrow's physicians, too, by championing medical school loan repayment programs, financing medical school and residency programs, and creating tax incentives to train, recruit, and keep physicians in the state.

Using this powerful data, we can demonstrate that investment in the physician workforce is an investment in economic development. The EIS data is a powerful advocacy tool on a range of issues – from medical liability reform to unfair payer practices to Medicaid reimbursement. To help physician advocates put the data to good use the AMA has developed a number of tools:

- You can view an interactive map, full national report, individual reports for all 50 states and Washington, D.C., and data by specialty at www.physicianseconomicimpact.org.
- Find one-page summaries for each state and a toolkit to help physician advocates incorporate the study's findings in communication with policymakers to illustrate how their state tangibly benefits when they support physicians.
- The AMA also has customized social media infographics and ads available to you. Contact the AMA Advocacy Resource Center for more information about these resources.

The EIS is the only 50-state and national study of its kind, providing data on how physicians impact their state and local economies. And the study again underscores how access to high-quality medical is a key economic driver in Missouri and in communities across the country.

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MSMA
Missouri State Medical Association
Actions from 2018 Legislative Session
Anthem Policies
MSMA solidifies sponsorship for legislation that would prohibit recent Anthem policies regarding ED claims and modifier 25 payment reductions.
Low-Dose Mammography
MSMA requests the legislature include low-dose mammography in the state's insurance coverage mandates.
Youth Skin-Cancer Prevention
MSMA announces support of statewide effort to prohibit young people from using indoor tanning beds.
Vaccinations by Pharmacists
MSMA amends language that would have allowed pharmacists to give vaccinations to patients of all ages.
Legislation on Anthem Introduced
With MSMA's suggested language, Missouri became the first state to introduce legislation to fight unfair Anthem policies.
Assistant Physician Licensure
MSMA voices support for efforts to streamline the assistant physician licensure.
Telehealth Regulations
MSMA testifies against onerous telehealth regulations promulgated by the Department of Health.
Substance-Abuse Treatment
MSMA testifies in favor of extending MO HealthNet substance abuse treatment benefits for women up to two years postpartum.
Diabetes Awareness
MSMA offers support for the creation of Diabetes Awareness Week in Missouri.
Meetings on Capitol Hill
MSMA leaders and staff attend AMA's National Advocacy Conference in Washington, D.C., to discuss policy with elected officials.
Chiropractors in MO HealthNet
MSMA opposes allowing chiropractors to participate in MO HealthNet, fighting claims chiropractic care will reduce unnecessary surgeries and save millions of dollars for MO HealthNet.
APRN Proximity Rules
In an effort to increase rural access, MSMA agrees to extend the advanced practice registered nurse proximity rule to 75 miles and allow physicians to collaborate with up to six APRNs, if necessary.
Claims Denials
MSMA testifies for legislation that would punish insurers for inappropriately denying claims throughout the appeals process.
Texting While Driving
MSMA testifies in favor of extending the state's ban on texting-and-driving to all persons. Missouri is one of three states without an outright ban.
Drug Takeback Program
MSMA voices support for a statewide drug takeback program that would help properly dispose of unused controlled substances.
Board of Healing Arts
In a House subcommittee on appropriations, MSMA fights efforts to steal board of healing arts funding needed to police the practice of medicine.

Actions from 2018 Legislative Session

Missouri State Medical Association

Athletic Trainers Laws Updates MSMA staff meets with officers from the Missouri Athletic Trainers Association to discuss the possibility of amending the athletic trainers laws during the 2019 legislative session.	**Opioid Prescribers** MSMA attends meeting of Departments of Health, Social Services, and Mental Health to learn more about their new efforts to identify outlier opioid prescribers.
Mandatory CME on Opioids MSMA fights off efforts that mandate physicians take opioid-related CME in order to have their licenses renewed.	**Scope-of-Practice for APRNs** MSMA testifies in opposition to independent practice and increased scope of practice changes for advanced practice registered nurses.
Short-Term Insurance Policies In order to educate potential patients about the perils of short-term medical policies, MSMA adds consumer protection disclaimer language to legislation that would extend the term of those policies from three months to a year.	**Claims Against Physicians** MSMA pushes for higher standards of proof when plaintiff's attorneys try to prove punitive damage claims against physicians.
BoHA Policy Decisions MSMA attends meeting of Board for the Registration of Healing Arts in St. Louis to monitor policy decisions, and listen to licensure and regulatory updates that affect MSMA members.	**State Funding Issues** MSMA monitors the state budget process and protects funding for items affecting medical education, public health, and MO HealthNet.
Changes in Tort Laws MSMA voices support for comprehensive changes to Missouri tort laws.	**Surprise Billing** MSMA supports commonsense effort to end surprise billing of patients, and replace it with a fair reimbursement from the patient's insurer.
Motorcycle Helmets MSMA fights efforts to repeal the state's motorcycle helmet requirement.	**CBD Oil Treatment Immunity** MSMA fights for civil immunity for physicians who recommend CBD oil treatment for patients with serious medical conditions.
Modifier 25 Edits Due to MSMA's first-in-the-country legislation, and pressure from the AMA, Anthem rescinds its modifier 25 payment reduction program a week before its scheduled release.	**Organ Donation Services** MSMA pushes for more educational outreach for organ donation services.

MSMA Members in the News

Did you make the news? Submit your success story and photo to hwansing@msma.org.



Missouri Medicine announces a new member of our Editorial Board. Board members are selected on the basis of exceptional professional accomplishment and expertise in their specialty.

Joshua E. Petrikin, MD, MSMA member since 2010, new Editorial Board Member position in Neonatology, is Assistant Professor of Pediatrics, Staff Neonatologist, Department of Pediatrics, Division of Neonatology, Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City School of Medicine.



MSMA is grateful to have Betty Drees, MD, as District Seven Councilor and for her membership since 2000. Congratulations on being appointed President of the Graduate School of the Stowers Institute for Medical Research.

Sol Dubin, MD, MSMA member since 1977, is now seeing patients at Lafayette Regional Health Center's Outpatient Specialty Clinic.



Congratulations, Richard Hellman, MD, MSMA member since 1976, for receiving the 2017 Lifetime Achievement Award from Kansas City Medical Society.



KCMS President Joshua M.V. Mammen, MD, PhD, MSMA member since 2016, has been appointed to the board of directors of the American Board of Surgery.



Michael Mumert, MD, is now seeing patients at the Cox Monett Visiting Physicians Clinic. Thank you for continuing your membership in MSMA since joining in 2016.



MSMA member since 1964, William Sasser, MD, was recognized by J. Collins Corder, MD, member since 1980, at the Annual SLMMS Gala and Installation Ceremony with a certificate for his 50 years of membership in SLMMS.

Laura Voss, DO, recently opened New Springs Clinic, a free medical clinic in Lee's Summit. She's been a member of MSMA since 2015.



Richard Wolkowitz, MD, MSMA member since 2003, is now seeing patients in Memphis, Mo., at Scotland County Hospital, in addition to Columbia, Mo.



John C. Hagan, III, MD, Editor of *Missouri Medicine* and the book, "The Science of Near Death Experiences," presented at Grand Rounds at Santa Barbara Cottage Hospital, on "Tunnel Vision: The Common Medical Syndrome of Near-Death Experiences," in February. Above with Dr. Hagan is Stephen Hosea, MD, Chief of Medical Education and Head of Infectious Diseases at the hospital. Dr. Hagan also addressed the Santa Barbara International Association for Near-Death Studies. The lecture was based on the NDE book.

EDITORIAL BOARD OPENING: ANESTHESIOLOGY

Missouri Medicine has an opening on its Editorial Board for an anesthesiologist. Applicants must be board certified and a member in good standing of MSMA. Membership in state and national anesthesia organizations is highly desirable. Duties will include peer-review of papers within the field of anesthesia. This generally will not occur more than once/year. There are no meetings but approximately once every other year editorial board members may be asked to either author a paper or help procure willing authors on specific subjects within anesthesia. Candidates that have published extensively or who are involved in research, education, or who have academic appointments are given special consideration. Appointments are for one calendar year and are annually evaluated by the Editorial Board. Please submit your CV to Liz Fleenor (lfleenor@msma.org) by May 1, 2018.

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FDA Approves Direct-to-Consumer Cancer Genomics

The US Food and Drug Administration (FDA) recently made 23andMe the first and only direct-to-consumer genomics company authorized to test for cancer risk without a prescription. The FDA authorized testing for three mutations found to be associated with increased cancer risk in persons of Ashkenazi Jewish ancestry. A 1997 study published in the *New England Journal of Medicine*[1] showed that by the age of 70 women carrying any of these three alleles have a 40-73% chance of having breast cancer and a 6-28% chance of having ovarian cancer, while men carrying any of these alleles have a 4-30% chance of having prostate cancer.

23andMe already provides personalized genomics information without the intermediation of a physician, raising important ethical concerns that I discussed in my article "Direct-to-consumer genomics: harmful or empowering?" published in the 2017 January/February issue of *Missouri Medicine*.[2] In the current instance, there are two concerns:

- A consumer who gets a report indicating that they carry one of the mutant alleles may over-react. While the odds of certain cancers are clearly much higher in such individuals, they are far from 100%. A decision to, e.g., seek prophylactic bilateral mastectomy should be weighed against the merits of simply getting more frequent mammograms and other screening. Other factors, such as other genetic factors, diet, weight and other environmental factors clearly influence the risk for any given individual.
- A consumer who gets a report indicating that they don't carry any of the mutant alleles currently authorized for testing may conclude that their risk of cancer is negligible, even if they have first-degree relatives who had cancers. There are thousands of mutations described in hundreds of genes that are associated with elevated cancer risk. Regular screening (skin exams, colonoscopy, mammograms) is still indicated, particularly for individuals with a family history of cancer. The prognosis is always better with early detection.

Undoubtedly, many more cancer-predisposition alleles will be authorized for testing by 23andMe, as well as other companies. As I stressed in my 2017 *Missouri Medicine* article, the democratization of medical information comes with the burden of understanding what information is actionable and what action is appropriate. The amount of genomic information available to consumers without physician intermediation will only increase; so, too, will the burden of being responsible and informed consumers. Physicians—both primary care and specialists—must be prepared for the tidal wave of patient concerns awakened by this brave new world.

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2. Eissenberg JC. Direct-to-consumer genomics: harmful or empowering? Missouri Med 2017; 114: 26-32.

Joel C. Eissenberg, PhD
Associate Dean for Research
Professor of Biochemistry and Molecular Biology
Saint Louis University School of Medicine
St. Louis, Missouri

The Future of the American Health Care System

Yogi Berra said, "It's tough to make predictions, especially about the future." We are not making predictions but we do have a few suggestions. We are attempting to address three issues: cost of health care (national), affordability, and availability.

Our healthcare system which is Medicare plus Medicaid plus private insurance is not working well. Health care is the largest industry in America consuming ~17% of GDP. Many patients are still uncovered and the "Obamacare" Affordable Care Act (ACA) mosaic of private plans is clumsy and inefficient. The Congressional Budget Office has found that Medicare administrative costs are~3% compared to ~10% for private insurance for similar populations.

Senator Bernie Sanders has proposed "medicare for all" as a solution to health care availability. He proposes to do away with Medicare as we know it and institute a new single payer national health insurance system. He would abolish our most efficient health care program. We are opposed to a single payer system as inefficient and unaffordable.

We recommend continuing Medicare as a fee for service system. Over age 65, no changes. Under age 65, $10,000 deductible. Medicare supplement insurance rates under 65 would probably run from $100 to $700 per month depending on age. Those who chose not to buy a supplement would have "catastrophic health insurance."

There would be no uninsured. For those under the poverty level, Medicaid would cover the deductible. ACA changes in Medicaid would be rolled back. Deductibles are essential to control costs.

This program would cost less than private insurance based ACA. Current medicare reimbursements are modest but few physicians have opted out of the program. 54% of physicians favor increasing Medicare coverage to lower age groups. Medicare is our most cost effective system and we should take advantage of it. Changes here are incremental and feasible compared to single payer.

Yogi said, "You've got to be very careful if you don't know where you're going because you might not get there."

George Bohigian, MD
Past President St. Louis Metropolitan Medical Society 1979
Terence Klingele, MD
Past President St Clair County Illinois Medical Society 1985

Project Apache and Pediatric Care

My family is indirectly mentioned in the September/October 2017 *Missouri Medicine* article, "Project Apache: Bringing Pediatric Care to an Arizona Reservation circa 1972".

I served at the White Mountain Apache Indian Health Service (IHS) Hospital as Chief Pharmacist and Pharmacist Practitioner from March 1973 to March 1977. Due to the geographic and social isolation, in addition to the youthful "can do" professional clinical staff, this duty station opened my eyes to serve for over two decades within the IHS on a variety of reservations.

My wife, Jeanne, and I saw the birth of our premature boy-girl twins at the Whiteriver Hospital on May 29, 1973. Both of the twins were med-evacuated out to the Phoenix neonatal intensive care unit, as described in Dr. Ranney's article. Our son was given a 5% chance of survival, the most critical the NICU had experienced up to that time, but today is 20+ years into a career as a law enforcement officer. Our daughter is an excellent mother with a wonderful family and a college degree. Dr. Ranney and Dr. Fukuchi were our pediatric doctors and guided us through our twin's well baby check-ups and illness, including a bout of hepatitis with our son. (See photo).

Bobbette was, and continues today, to be not only an excellent clinical physician, but is musically talented, academically gifted, a lover of everything outdoors, and an individual who has lived her life providing care and comfort for those in need.



When the Stottlemyer twins were born, an Apache named Molly Colelay made two cradle boards for the children. During the days they often slept in their snugly tied cradle boards. Above is a photo of the twins being held by their Mom and Dad on the rim of the Grand Canyon, October 1973.

Frank Stottlemyer
United State Public Service Clinical Pharmacist (Retired)

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Missouri State

Missouri State University is accepting applications for PHYSICIAN, MEDICAL STAFF in the Missouri State University Health and Wellness Center. Responsibilities include providing quality health care for the University community in an out-patient, clinic type setting located in the Missouri State University Health and Wellness Center; functional responsibilities include the diagnosis and treatment of patients using the most current medical knowledge and techniques.

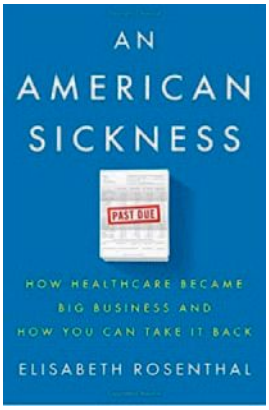
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An American Sickness: How Health Care Became Big Business and How You Can Take It Back

by Elisabeth Rosenthal, MD

Reviewed by Arthur Gale, MD

Penguin Press
Hardcover. 416 pp.
ISBN-10: 1594206759
ISBN-13: 978-1594206757A



A new book titled "An American Sickness How Health Care Became Big Business and How You Can Take it Back" by Elisabeth Rosenthal, MD, is the most up to date and comprehensive description of our current dysfunctional health care system.

Rosenthal is a graduate of Harvard Medical School. She is board certified in internal medicine and worked as an emergency room physician. She then worked for 22 years as a reporter, correspondent, and senior writer for the *New York Times*. She is now editor in chief of Kaiser Health News, an independent journalism news room which focuses on health and health policy. Kaiser Health News has no connection to Kaiser Permanente-the large staff model HMO based in California.

The book focuses on the high cost of health care and covers all the major drivers of high health care costs including hospitals, insurance, and drug and device companies. In the interest of brevity this article will focus on the role of hospitals as a major cause of high health care costs.

How Consultants Caused Hospital Costs To Spiral Out Of Control

In the 1990s I practiced internal medicine at the Jewish Hospital of St. Louis. Jewish Hospital was a well respected teaching hospital and community hospital. It always operated in the black. Many of the doctors held teaching positions at Washington University School of Medicine. There was high morale among the medical and nursing staffs. It had a large dedicated volunteer staff.

One day the Jewish Hospital Board of Trustees told the medical staff that there was to be a merger of Barnes and Jewish Hospitals. The reasons we were told was that the merger would increase efficiency and produce "economies of scale." "Integration and coordination" would be achieved to produce a "seamless" system of health care delivery that was necessary to lower health care costs.

As noted above Jewish Hospital, at that time when health care costs were nowhere near as high as they are today, operated efficiently and profitably. Although many physicians opposed the merger it nevertheless did occur. Eventually the merger between Barnes and Jewish hospitals morphed into BJC the largest hospital network in Missouri. The merger was backed by the business community.

The Board of Directors told the medical staff that "consultants" had advised them that such mergers were necessary. At that time consultants visited just about every hospital in America and told their respective boards of trustees essentially the same story. If the boards followed their advice the hospitals would prosper and overall health care costs would drop. Twenty-five years later half of the consultants' prediction is true. Half is false. The hospitals prospered enormously while costs to the public have skyrocketed.

Until I read "An American Sickness" I never knew who the consultants were and precisely what they told hospital boards of directors. That information was kept secret from the American public and physicians. Rosenthal writes that before the business consultants from Deloitte and Touche arrived the hospitals ran on such thin margins that consultants had to offer a pay for results model.

Rosenthal quotes a consultant from Deloitte and Touche: "We came to them with this proposal that with little up-front cost you can increase the amount you bring in just by manipulating how you bill. This is called strategic pricing. Deloitte advised hospitals to stop billing for items like gauze rolls which insurers rarely or never reimburse, and to boost charges for billing like O.R. time, oxygen therapy, and prescription drugs…you can increase the amount you bring in just by manipulating how you bill."

The consultants' advice basically was all about increasing hospital profits not reducing health care costs Rosenthal records a few absurdities of strategic pricing.

"Everyone knows about the $17 Tylenol pill. In one instance a family was billed $21,000 after the father had a heart attack in the living room of his home. He was driven by relatives to the hospital only to be declared dead in the lobby before a single test was done."

A surgeon who stuck himself with a needle during an operation as per protocol went to the emergency room for a blood test for HIV and hepatitis. [He] received a bill for $3,400 including $1,137 from the ER doctor and $2,198 for hospital services. The surgeon said, "What is written down and what is charged bear little relation. The net charges are just dissociated from reality. All I needed was a blood draw, nothing else. I have discussed this with the ER docs and with the Hospital Administration but they stand by their practices."

Rosenthal then discusses the "up coding" that hospitals engaged in. She describes how doctors were advised to up code their patient visits to levels 4 and 5 before Medicare began to crack down on this practice. She describes the outrageous charges for "facility fees" that did not even exist two decades ago.

She describes hospital billing using the chargemaster which has no relation to actual costs and varies according to the payer. She discusses the inflated multimillion dollar salaries of hospital CEOs. She writes about the actual amount of money hospitals spend on charity care which is no more than for profit hospitals. She describes how cities such as Pittsburg which have tried in vain to have the University of Pittsburg Medical Center with its 60,000 employees pay property taxes. The government places this tax advantage at $24.6 billion 2011.

Hospitals care for large numbers of low income people but they purchase their pharmaceuticals at a discount through a federal program. Medicare gives them "disproportionate share" payments which are essentially bonuses for treating poor people. Rosenthal cites one study that concluded that 196 hospitals received $3.3 billion in state and federal tax exemptions and actually spent only $1.4 billion on charity care.

The author relates how hospitals profit from observation status. When a patient is admitted on observation status hospitals can charge patients and Medicare much more than when they are admitted on the regular service. Patients are then stuck with higher out of pocket bills. Hospital consultants soon homed in on observation status with articles like "How Your Hospital Can Succeed Under the Two Midnight Rule."

In the remainder of the book Rosenthal gives examples of real people coping with huge bills from the other major players in the medical industrial complex- the insurance and pharmaceutical and medical device industries. She describes how the business consultants have shown these entities how to improve profits through strategic pricing just as they did with the hospitals.

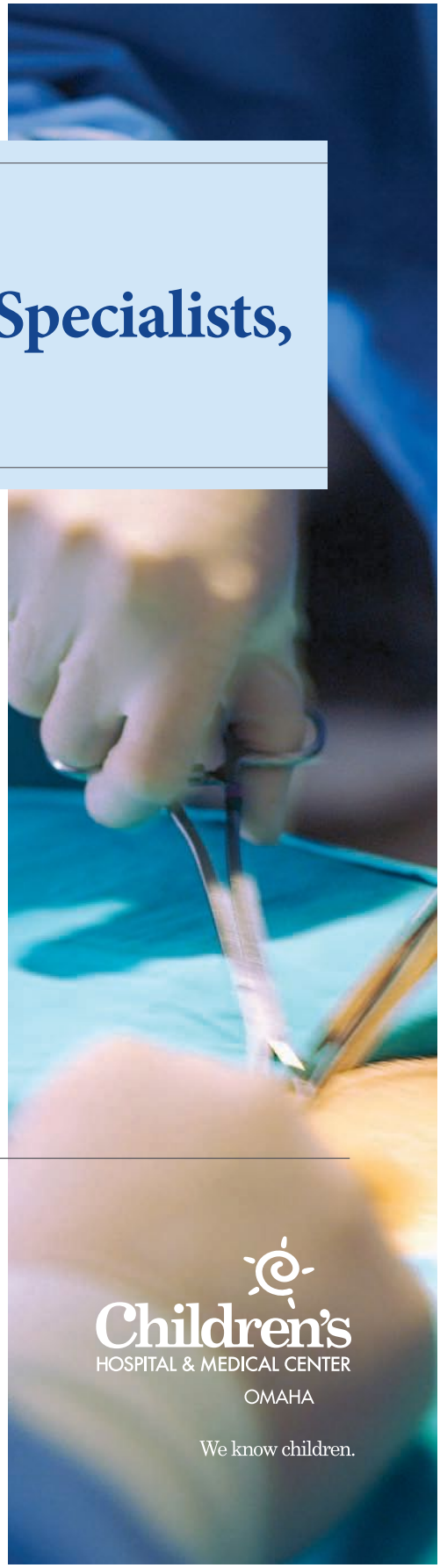
Although Rosenthal offers some specific advice to persons coping with health care financial issues she does not recommend any general solution although she does briefly mention how other countries have dealt with high health care costs.

For years there has been much hand wringing about high health care costs. The experts and policy makers have been promoting various solutions most of which boil down to a form of capitation. Current proposals are Accountable Care Organizations (ACOs), Value Based Care (VBCs), Population Health Management, clinical outcomes, etc. Most of these proposals have been tried in the past in one form or another and have failed to result in any significant effect in lowering costs. Nor in my view will they ever have any success in the future. Competition and transparency were supposed to control health care costs. There is very little of either in hospital networks. Instead these networks have often become powerful monopolies.

What the Washington policy wonks and bureaucrats won't admit and won't address is that a significant source of high hospital costs (and also for that matter the high costs engendered by all of the members of the medical industrial complex) is strategic pricing or simply put over charging for services. The ACOs and other capitation schemes place the blame for high health care primarily on doctors who are convenient scapegoats. It is easier to blame doctors than hospitals. Doctors are an easy target. It is not politically feasible to take on the powerful health care lobby at the present time

In my estimation the most informative section of the book is the short section on the business consultants who showed the boards of directors how to use strategic pricing and increase hospital profits. Strategic pricing made hospitals very wealthy. It is also in large part responsible for giving Americans the most expensive health care system in the world. That's not what the consultants and hospital boards told the public and physicians when they began their merger mania in the 1990s. **MM**

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Prostate Cancer Review

by Eric H. Kim, MD & Gerald L. Andriole, MD

Although widespread screening and aggressive treatment has led to an improved survival rates, "overtreatment" and treatment-related side effects have had a drastic impact on the quality of life of survivors.



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With nearly one in every seven men diagnosed during their lifetime, prostate cancer (PCa) is a common disease in the United States. Although widespread screening and aggressive treatment has led to an improved survival rates, "overtreatment" and treatment-related side effects have had a drastic impact on the quality of life of survivors. As a result, the diagnosis and management of PCa has come under considerable controversy over the last decade. The many medical specialities involved in the treatment of PCa—the primary care provider, the urologist, the radiation oncologist, the pathologist, the radiologist, and the medical oncologist—have been left with key questions to answer. Which patients should be screened? How do we best diagnose PCa? Can we minimize the detection of indolent PCa? Which men with PCa need treatment? For those that require treatment, what can we do to improve the unintended side effects of intervention? Finally, for the men we are unable to cure, how can we improve survival and quality of life?

Washington University School of Medicine has leaders in PCa research across multiple sub-specialties. For this review, we have gathered faculty members to highlight the "state of the art" for their field.

Robert Grubb, III, MD, discusses the key PCa screening trials, summarizes the current guidelines for the early detection of PCa, and discusses new tests designed to improve risk discrimination for clinically significant PCa prior to biopsy.

Joseph Ippolito, MD, and colleagues discuss the newest innovations in imaging for both localized and metastatic disease, specifically focusing on the growing role of multiparametric magnetic resonance imaging.

Eric Kim, MD, and Arnold Bullock, MD, discuss the role of surgery in the management of PCa, for both early and advanced disease, as well as the emerging role for focal therapy.

Hiram Gay, MD, and Jeff Michalski, MD, discuss the role of radiation therapy in the management of PCa, focusing on the improvements made to reduce the side effects of treatment.

Jennifer Sehn, MD, discusses the most recent updates in histopathologic grading of PCa, which have a tremendous impact on PCa care.

Theodore Thomas, MD, and Russell Pachynski, MDreview the role of hormone deprivation and chemotherapy for advanced PCa, discuss the newest FDA approved medications for metastatic castrate resistant PCa, and the ongoing investigation of immunotherapy in PCa.

We hope that this review provides all practitioners important insights into the contemporary diagnosis and management of PCa. **MM**

Prostate Cancer: Update on Early Detection and New Biomarkers

by Robert L. Grubb, III, MD

The future of screening will likely remain PSA-based, but will also involve an increasing use of adjuvant testing to avoid biopsies and minimize overdiagnosis of indolent cancers.



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Abstract

Screening and early treatment of prostate cancer (PCa) has recently come under scrutiny due to the rates of overdiagnosis of low risk cancer. Randomized trials, including ERSPC and PLCO, have informed our understanding of the survival benefit provided by systematic PCa screening with serum prostate-specific antigen (PSA). To reduce the number of patients diagnosed with indolent disease, new adjuvant risk stratification tests have become available.

Introduction

Prostate cancer (PCa) is the most common cancer diagnosed in males in the United States, with an estimated 161,360 new cases and causing 26,730 deaths in 2017.[1] This high incidence to mortality ratio is strongly linked to the introduction of prostate-specific antigen (PSA) as a screening test in the 1980s, which facilitated detection of PCa over pre-existing methods.[2] Patterns of PSA-based screening have evolved as the results of randomized screening trials have become available, and professional organizations have incorporated these findings into their recommendations. Although a powerful marker for the early detection of cancer, PSA has been associated with the over detection of many indolent cancers. New urine and blood-based biomarkers have been developed to improve the identification of clinically significant cancers, while minimizing the detection of less aggressive cancers. This article will review the current state of PSA-based early detection of PCa, focusing on the seminal screening studies and current guidelines for early detection. Additionally, the use of new urine and blood based early detection biomarkers will be discussed.

PSA Screening

Randomized trials have demonstrated a reduction in PCa-specific mortality rates attributable to PSA-based screening for PCa.[3-5] The largest of these is the European Randomized Study of Screening for Prostate Cancer (ERSPC), which randomized 182,160 men to a screening arm or control group across seven European countries.[3] The screening regimen was not uniform across all centers, but a PSA of 3.0 ng/mL was most commonly used as the threshold for a biopsy. Digital rectal exam was omitted from the screening process. No difference in overall mortality was noted (RR 0.99, 95% CI [0.97-1.01]),[3] but for the pre-defined core group of men aged 55-69 years (n=162,243), there was a 21% reduction in PCa-specific mortality (RR 0.79, 95% CI [0.68-0.91]) at 11-year median follow-up. This corresponded to an absolute mortality risk reduction of 1.07 deaths per 1,000 men. When the ERSPC was updated at 13-year median follow-up, the 20% reduction in PCa-specific mortality was maintained. Importantly, the number needed to screen in order to prevent

one death dropped from over 1,000 to 781.[6] Further, the cumulative risk of metastatic disease at 9 to 11 years of follow-up was 31% to 33% lower in the screened arm compared to the control arm of ERSPC.

Another significant population-based PSA screening trial was performed in Göteborg, Sweden; in this trial, 19,904 men aged 50-64 years were randomized to either a screening or control group.[5] Screening was performed with a PSA every two years, with additional evaluation (consisting of DRE and biopsy) performed for an elevated PSA. The PSA cutoff changed over the course of the study. A PSA cutoff of 3.4 ng/mL was used at the beginning of the study, but this was later lowered to 2.5 ng/mL. After a median follow-up of 14 years, a significant 44% decrease in PCa mortality was noted in the group randomized to screening (RR 0.56, 95% CI [0.39-0.82]), with a 56% risk reduction noted in the group of men who actually attended screening (RR 0.44, 95% CI [0.28-0.68]). Based on the observed risk reduction, in order to prevent one PCa death, the number needed to screen was 293. Even in this strongly positive trial in favor of PSA screening, 1,000 men would need to be screened for 14 years, and 120 men would have been diagnosed and treated, in order to avert 5 PCa deaths.[7]

In contrast to the ERSPC and the Göteborg trial, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial did not show improved PCa-specific mortality with PSA-based screening.[4] In the PLCO trial, 76,685 men were randomized to screening or usual medical care across ten sites in the United States. The screening regimen consisted of an annual PSA for six years and an annual DRE for four years. All screened men and their primary care providers received PSA results; those with a PSA above 4.0 ng/mL were advised to seek further diagnostic evaluation. After 13 years of follow-up, no difference in PCa-specific mortality (RR 1.09, 95% CI [0.87-1.36]) was observed between the groups. In the updated 15-year follow-up results, there is still no significant difference in PCa-specific mortality between the intervention (screened) and control groups.[8]

Criticisms of the PLCO study are well-documented, mainly relating to the high rates of PSA screening that occurred in the control group (3 in 4 men underwent at least one test), as well as the level of PSA screening prior to trial enrollment (up to 40%).[9] A recent evaluation of PLCO data suggested that men in the control group underwent more intense PSA screening through the follow-up period (study years 6-12).[10] Although these findings have been refuted by PLCO investigators, as the incidence of PCa was higher in the intervention group,[11] the above mentioned study limitations and the fact that only 85% of men in the intervention group underwent PSA screening may have affected the power of the trial to detect a beneficial effect from PSA screening.[12] While the PLCO trial failed to demonstrate a survival benefit to screening as a whole, a secondary analysis of men with minimal comorbidity found a 44% reduction in PCa-specific mortality (hazard ratio [HR], 0.56, 95% CI [0.33-0.95], p=0.03).[13] Moreover, the number needed to treat to prevent one PCa death at ten years in this subgroup was five. This analysis demonstrates the importance of clinical judgement and weighing competing risks of mortality when considering PSA screening and PCa management.

Taken together, the results of these large randomized screening trials demonstrate that PSA screening confers a modest reduction in PCa-specific mortality at the cost of significant overdiagnosis and overtreatment, with attendant economic and quality of life costs. As a result, many organizations have changed their PSA screening guidelines to emphasize the importance of a discussion of these risks.[14]

Current Guidelines in Early Detection

The American Urologic Association (AUA), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN) have modified their guidelines to reflect the limitations of PSA screening and provide a rational basis of screening that minimizes overdiagnosis.[14,15] The AUA, EAU and NCCN recommend shared decision-making, counselling men on potential risks and benefits of PSA screening. All three organizations recommend screening only men in the 45-75 year age group (AUA and EAU use 70 years as routine upper age limit); the AUA and EAU also limit screening to men with life expectancy > 10-15 years. Screening intervals of two or more years are also suggested as a way to decrease the risks of overdiagnosis. The EAU provides risk stratification and interval adjustment based on PSA levels, while the AUA does not provide any specific criteria on who may be offered an extended screening interval. Neither organization recommends PSA testing in men younger than 40 years of age. However, the EAU does imply that a baseline PSA at age 40 can be used to risk stratify those who should begin earlier routine screening (men with PSA >1.0 ng/mL at age 40).[16,17]

Use of Adjuvant Risk Stratification Tests

The NCCN guidelines were among the first to incorporate adjuvant testing into their screening recommendations. Men with persistently elevated PSA are

recommended to undergo adjuvant testing: blood tests such as percent free PSA, the 4K score (GenPath, Elmwood Park, NJ), and prostate health index (PHI) (Beckman Coulter, Brea, CA), or urine tests such as prostate cancer antigen-3 and Select MDx (MDx Health, Irvine CA). These adjuvant tests are designed to help reduce overdiagnosis by avoiding potentially unnecessary biopsies. As an example, using a PHI score of 24 as a cutoff for biopsy would avoid 36% of biopsies with no cancer and 24% of biopsies with indolent cancer; this strategy would miss only 4% of clinically significant PCa.[18] The 4K score uses a panel of four prostate specific kallikrein proteins related to PSA to improve the accuracy of diagnosis. As an example, using the 4K score with a cutoff of 6% risk of high grade PCa among participants in the PLCO trial would have eliminated unnecessary biopsies in 42% of men, while detecting 88% of high grade cancers.[19] While PHI and 4K score are blood tests, urine based diagnostics are also available to help improve PCa diagnostic accuracy. One such example is the Select MDx test, which measures the mRNA levels of HoxC6 and DLX1 in the urine and incorporates traditional clinical variables into a predictive model. In a testing and validation cohort study, Van Neste et al. determined that the Select MDx test could avoid 30% of negative biopsies while only missing 2% of aggressive cancers.[20]

Another major tool that has been increasingly utilized to improve diagnostic accuracy for PCa is multiparametric magnetic resonance imaging (MRI). MRI has most commonly been used for patients who have had at least one prior negative biopsy. When combined with ultrasound fusion biopsy technologies, MRI improves the diagnosis of high grade PCa without an increase in overdiagnosis of more indolent cancers. Prostate MRI is discussed in greater detail elsewhere in this issue.

Conclusions

PSA remains the most sensitive screening test available for the early detection of PCa. However, screening of all men has been shown to have only a modest benefit in PCa-specific mortality reduction, while introducing significant potential harms. While the ESRPC and PLCO trial did not provide a clear resolution to the issue of PSA screening, they more clearly defined its benefits and limitations. As a result, national and international organizations have altered their guidelines in recognition of the nuances of PSA screening in order to try to maximize the benefits while minimizing the harms. The future of screening will likely remain PSA based, but will also involve an increasing use of adjuvant testing to avoid biopsies and minimize overdiagnosis of indolent cancers. The exact role and sequence of adjuvant blood, urine, and imaging tests continues to evolve.

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Disclosure

None reported.

MM

Imaging in Prostate Cancer: Magnetic Resonance Imaging and Beyond

by Daniel R. Ludwig, MD, Tyler J. Fraum, MD, Kathryn J. Fowler, MD & Joseph E. Ippolito, MD

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Prostate mpMRI plays an important role in the management of patients with known or clinically suspected PCa, and its strength lies in its ability to detect and localize clinically significant cancers.



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Abstract

Imaging is becoming critical for guiding management decisions in prostate cancer (PCa) both at initial diagnosis and at recurrence. Multiparametric magnetic resonance imaging (mpMRI) and positron emission tomography (PET) of the prostate have proven valuable in the detection and localization of aggressive disease. Therefore, understanding the indications for mpMRI, imaging techniques and interpretation, limitations of current imaging approaches, and utility of PET and simultaneous PET/MRI has become increasingly important.

Indications for mpMRI

Screening for PCa is conventionally performed with serum prostate-specific antigen (PSA) testing and digital rectal exam (DRE), followed by transrectal ultrasound (TRUS)-guided biopsy, if indicated. In recent years, mpMRI has played a growing but primarily supportive role. Published guidelines from the European Association of Urology (EAU), American Urological Association (AUA), and National Comprehensive Cancer Network (NCCN) have made similar recommendations regarding the use of mpMRI for the diagnosis, initial staging, and detection of suspected recurrence of PCa. These guidelines are summarized in Table 1.[1-3]

At present, there is no evidence to support the use of mpMRI for population-based screening, and insufficient evidence to support its routine pre-biopsy use.[4] There may, however, be a role for mpMRI in risk stratification for biopsy-naïve patients with equivocal indications for biopsy. Indeed, the utility of mpMRI prior to initial biopsy is the focus of two ongoing large-scale clinical trials in the United Kingdom: Prostate MR Imaging Study (PROMIS)[5] and PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION).[6] Furthermore, there is strong evidence to support the use of mpMRI in patients with persistent clinical suspicion for PCa despite a negative systematic biopsy. In these patients, targeting of any suspicious lesion identified on mpMRI at the time of repeat systematic biopsy can improve the rate of diagnosis of clinically significant cancers (Gleason score ≥ 7).[7]

Several approaches have been established for targeting suspicious lesions identified on mpMRI. One approach relies on visual approximation, in which the clinician performing the biopsy reviews the pre-procedural mpMRI data and utilizes TRUS to target the expected location of the lesion.[8] Although this approach does not provide real-time feedback, it is easy to implement without much

modification to standard workflow. Another approach, which is currently utilized at our institution, employs MRI/TRUS fusion. In this technique, suspicious lesions are delineated on anatomic MRI data and projected onto real-time ultrasound images to assist in lesion targeting.[9] Registration is achieved by using the contour of the prostate gland, which is also delineated on the anatomic MRI data, as an internal fiducial marker. This approach has been shown to be more accurate for sampling smaller lesions and provides significantly more informative histologic results on the presence of cancer compared to visual targeting.[9] However, this MRI/TRUS fusion approach requires image acquisition and biopsy to be performed at the same institution to ensure accurate co-registration and targeting. Finally, real-time MRI-guided biopsy, which is performed within the MRI bore itself, has the potential to provide the most accurate targeting of suspicious lesions.[10] This approach, however, requires longer procedure times, more expensive equipment, and can be uncomfortable for the patient.

Table 1. Professional society guidelines for use of MRI in prostate cancer.

	Diagnosis	Staging	Recurrence
EAU[1] Year: 2016	"Before repeat biopsy, perform mpMRI when clinical suspicion of PCa persists in spite of negative biopsies." "During repeat biopsy include systematic biopsies and targeting of any mpMRI lesions seen."	"[In intermediate- and high-risk PCa], use prostate mpMRI for local staging. "In intermediate- and high-risk disease, use multiparametric MRI as a decision tool to select patients for nerve-sparing procedures."	"[In patients with PSA recurrence after radiation therapy], perform prostate mpMRI only in patients who are considered candidates for local salvage therapy, use mpMRI to localize abnormal areas and guide biopsies."
AUA[3] Year: 2017	"MRI [potentially allows] pre-biopsy risk stratification for individualized decision-making. [….] Its use may be considered in men for whom clinical indications for biopsy are uncertain." "[MRI] should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is undergoing a repeat biopsy."	"Staging patients with prostate cancer using MRI to evaluate for possible lymph node metastasis can be considered in selected patients (T3/T4 and T1/T2 patients with nomograms predicting the risk of lymph node metastasis >10%.)" "mpMRI/TRUS may offer valuable staging information when performed prior to definitive local therapy."	"It is possible that mpMRI may be useful for follow up evaluation of men treated with radical prostatectomy or in situ ablative therapies."
NCCN[2] Year: 2016	"Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative [in patients with expected survival >10 years]."	"mpMRI may be used to better risk stratify men who are considering active surveillance." "[Consider for] initial evaluation of high-risk patients [including those with] T3 or T4 disease [or those with] T1 or T2 disease and nomogram-indicated probability of lymph node involvement >10%".	"MRI may be considered in patients after RP when [PSA becomes detectable], or after RT for rising PSA or positive DRE if the patient is a candidate for additional local therapy."

EUA = European Assoication of Urology; AUA = American Urological Assocation; SAR = Society of Abdominal Radiology; NCCN = National Comprehensive Cancer Network; mpMRI = multiparametric magnetic resonance imaging; RT = radiation therapy; DRE = digital rectal examination; PSA = prostate-specific antigen; RP = radical prostatectomy.

Once a tissue diagnosis has been made, mpMRI has an established role in the initial staging of intermediate-risk and high-risk PCas. The added value of mpMRI in this setting derives from its ability to detect extraprostatic extension, seminal vesicle invasion, and locoregional lymph node involvement. Furthermore, there is moderate evidence to support the use of mpMRI in selecting candidates for nerve-sparing radical prostatectomy and identifying patients suitable for active surveillance.[11] In contrast, the role of mpMRI in detecting recurrent disease in treated patients is less clear. mpMRI should be considered for the evaluation of biochemical recurrence (BCR) after radiation therapy, in patients that are candidates for local salvage therapy. Similarly, mpMRI may help differentiate recurrence within the prostatectomy bed from nodal, osseous, or visceral metastatic disease in patients with rising PSA levels after radical prostatectomy, thereby guiding decisions regarding further treatment. Overall, additional research is still needed to define the proper role of mpMRI in the assessment of recurrent disease.

mpMRI Technique

The Prostate Imaging Reporting and Data System (PI-RADS) is a structured reporting system developed by the European Society of Urogenital Radiology (ESUR) in 2012 to standardize prostate MRI acquisition and interpretation. It was subsequently revised in 2015 (PI-RADS v2) by the American College of Radiology (ACR) and ESUR.[12]

PI-RADS v2 specifies that mpMRI should include T1-weighted (T1W) images, high-resolution T2-weighted (T2W) images, diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps, and dynamic contrast-enhanced (DCE) imaging.[12] When possible, DWI should include high b-value (≥1400 sec/mm^2) acquisitions. T1W images are most helpful for identifying intraprostatic hemorrhage and skeletal lesions. High-resolution T2W images are important for localizing tumors within the prostate gland and detecting extraprostatic extension (including seminal vesicle invasion). DWI is also valuable for tumor identification. Furthermore, the degree of diffusion restriction positively correlates with tumor aggressiveness and Gleason scores.[13] DCE imaging provides an assessment of lesion vascularity, which may aid in the detection of recurrent tumor after therapy.[14] However, the information provided by DCE is of limited impact in the most current diagnostic algorithm, especially in treatment-naïve patients.

Figure 1: Peripheral zone prostate adenocarcinoma. Within the right lateral peripheral zone in the mid-portion of the gland is an area of focal marked hyperintensity on high b-value DWI, corresponding to marked hypointensity on the ADC map and measuring greater than 1.5 cm in size (DWI score of 5; arrows). On the T2W images, there is a circumscribed, homogenously hypointense focus measuring greater than 1.5 cm and corresponding to the abnormality on DWI (T2W score of 5; arrow). This lesion demonstrates focal early hyperenhancement on DCE images (DCE positive; arrow). The overall PI-RADS score was 5, and biopsy demonstrated Gleason 4+5 adenocarcinoma. The patient was treated with radiation and hormonal therapy.

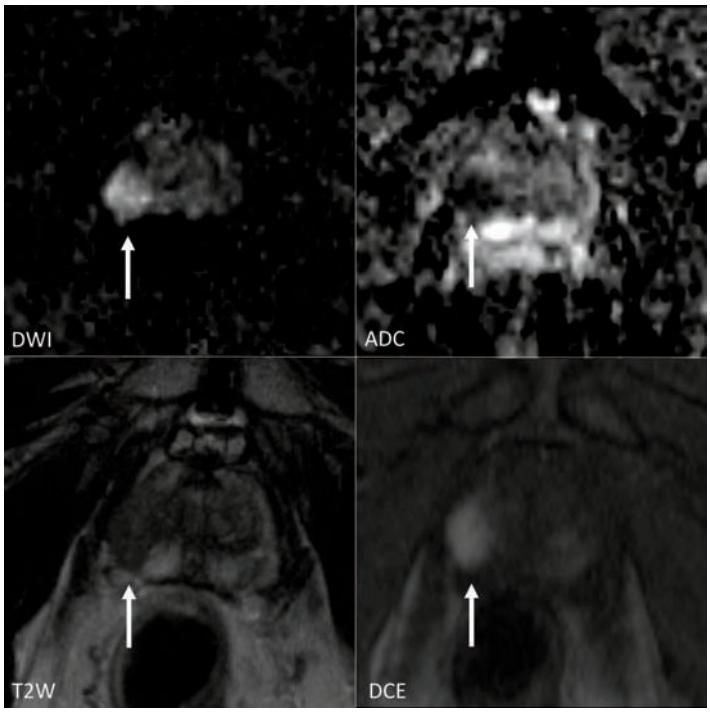
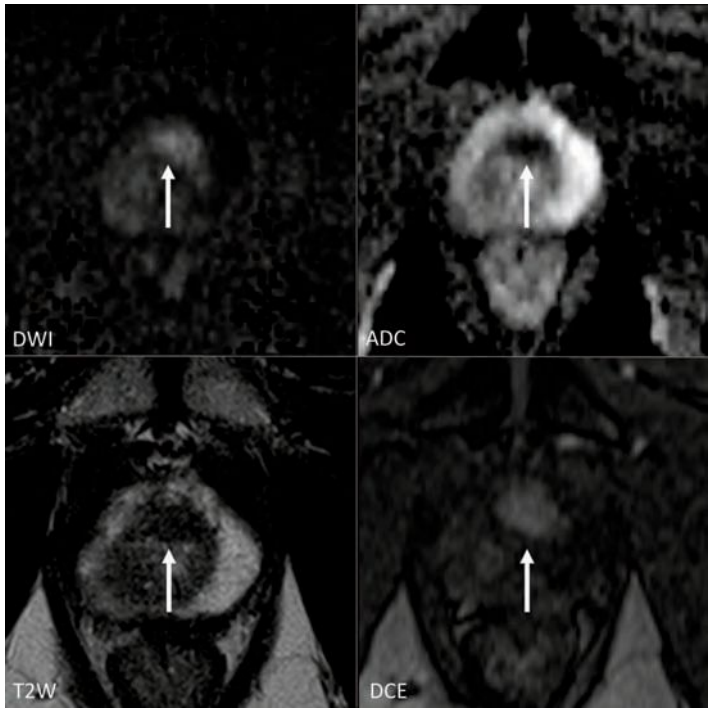


Figure 2: Transitional zone prostate adenocarcinoma. Within the central anterior transition zone in the mid-portion of the gland, there is a lentiform, homogenously hypointense focus on T2W images measuring greater than 1.5 cm, (T2W score of 5; arrow). There is a corresponding focal marked hyperintensity on high b-value DWI and a marked hypointensity on the ADC map measuring greater than 1.5 cm (DWI score of 5, arrows). DCE is positive (arrow). The overall PI-RADS score was 5. Biopsy revealed Gleason 4+4 disease, and the patient was treated with transurethral resection of the prostate.



Patient Considerations

Because hemorrhage in the post-biopsy setting may confound mpMRI assessment, an interval of at least 6 weeks between biopsy and mpMRI is advisable. Administration of an antiperistaltic agent (e.g., glucagon) prior to the study may reduce artifact related to rectal motility, especially when using an endorectal coil. To minimize artifacts related to gas in the rectum, a pre-procedural enema may be beneficial. Importantly, the use of high field strength MRI systems (i.e. 3 Tesla [3T]) is preferable to maximize the signal-to-noise ratio. However, in circumstances when it is necessary to image the patient at lower field strength (1.5T), use of an endorectal coil is essential. Such circumstances include the presence of hip arthroplasties, which can create significant artifacts, or certain implanted medical devices, which may not be safe for imaging at 3T. Direct discussions between the radiologist and referring clinician are advised in this setting.

Imaging Interpretation

The Prostate Imaging Reporting And Data System, Version 2 (PI-RADS v2) includes five assessment categories based on the probability that an individual lesion corresponds to a clinically significant cancer, defined as a tumor with Gleason score ≥7: PI-RADS 1 – very low; PI-RADS 2 – low; PI-RADS 3 – intermediate; PI-RADS 4 – high; and PI-RADS 5 – very high. The final PI-RADS category is determined by a composite of findings on DWI, DCE, and T2W images, with different emphases placed on specific sequences for the peripheral (PZ) versus transition zones (TZ). Up to four lesions with an assessment category of 3 or greater may be reported, and a standardized sector map should be utilized to assist in biopsy targeting. Reporting lesions with a PI-RADS score of 1 or 2 is optional.

PI-RADS v2 characterizes lesions in the PZ differently from lesions in the TZ. Assessment of lesions in the PZ relies

Table 2. PET Tracers for Prostate Cancer

PET tracer	Indications	Strengths	Weaknesses
[^{18}F]-NaF	Evaluation of known or suspected osseous metastatic disease [18]	Faster, higher resolution imaging than conventional bone scans, with better diagnostic accuracy [18]	Time intensive interpretation due to high sensitivity for benign processes (e.g., degenerative disease)
[^{11}C]-choline	Identification of recurrent disease in patients with rising PSA after completion of therapy [19]	Potential for detecting spread to bones, lymph nodes, and distant organs [19]	Prohibitively low disease detection rates for initial staging; uptake by other cancers and benign processes
[^{18}F]-fluciclovine	Same as [^{11}C]-choline	Same as [^{11}C]-choline, though with better recurrence detection rates [20]	Same as [^{11}C]-choline
[^{68}Ga]-PSMA-HBED-CC	To be determined; possible roles in initial staging, suspected disease recurrence, and treatment response assessment	Likely greater sensitivity and specificity for prostate cancer than [^{11}C]-choline or [^{18}F]-fluciclovine [21]	Not yet FDA-approved
[^{18}F]-DCFPyL	Same as [^{68}Ga]-PSMA-HBED-CC	Same as [^{68}Ga]-PSMA-HBED-CC, though with longer half-life and better spatial resolution [22]	Same as [^{68}Ga]-PSMA-HBED-CC

Abbreviations: PSA – prostate specific antigen; PSMA – prostate specific membrane antigen

almost entirely on its appearance on DWI. Contrast enhancement is useful for PZ lesions in cases where characterization of the lesion on DWI is equivocal. A PI-RADS 5 lesion in the PZ, which corresponded to histologic Gleason 4+5 prostate adenocarcinoma on biopsy, is shown in Figure 1. Conversely, assessment of lesions in the TZ relies predominantly on the T2W score. Contrast enhancement is not used for evaluation of TZ lesions; however, DWI can be used to further characterize equivocal TZ lesions. A PI-RADS 5 lesion in the TZ, which corresponded to histologic Gleason 4+4 prostate adenocarcinoma on biopsy, is shown in Figure 2. In general, PI-RADS 5 lesions in the PZ or TZ are characterized by either a minimum diameter of 1.5 cm or signs of invasive disease.

Staging information, including extraprostatic extension, involvement of adjacent structures (i.e., neurovascular bundles, external urethral sphincter, seminal vesicles, and bladder wall), enlargement of locoregional lymph nodes (>8 mm in the short axis), and suspicious osseous lesions, should be reported.

Limitations of Current Imaging Techniques

mpMRI has several important limitations. Notably, the sensitivity for detection of PCa in the TZ is limited by the intrinsically heterogeneous nature of the transitional zone in the setting of benign prostatic hyperplasia (BPH). BPH nodules can exhibit high cellularity, thus mimicking cancerous lesions on MRI sequences, specifically DWI.[15] Hence, morphologic features on T2W images are more reliable than DWI for TZ assessment, a concept reflected in the PI-RADS v2 scoring system. Various other benign and pre-malignant processes (e.g., granulomatous prostatitis, adenosis, prostatic intra-epithelial neoplasia) can also mimic PCa on mpMRI.[15] Furthermore, mpMRI is also limited by inter-observer variability. Although PI-RADS v2 was specifically developed to improve inter-observer reliability, sensitivity, and specificity, further revisions will likely be necessary to optimize agreement among different readers and to limit the use of subjectively applied features.[16] Additionally, the main determinant of the overall PI-RADS score in the PZ is DWI, which is intrinsically susceptible to artifact from rectal gas and metal implants. As previously mentioned, the ability to generate sufficient signal on high b-value DWI requires either imaging at 3T or use of an endorectal coil at 1.5T, both of which may be of limited availability in general radiology practices. Finally, mpMRI has a limited ability to discriminate between post-treatment change and local recurrence following prostatectomy, local ablative therapy, and/or radiation therapy.

New PET Radiopharmaceuticals

Oncologic PET/CT, most commonly performed with the glucose analogue [^{18}F]-fluorodeoxyglucose (FDG), has become standard of care for the initial staging and subsequent treatment response assessment for many different malignancies. However, FDG-PET/CT has a limited role in PCa imaging. Although FDG-PET/CT may be useful in the initial staging of tumors with aggressive features on pathology, many PCas are not FDG-avid.[17] Consequently, there is considerable

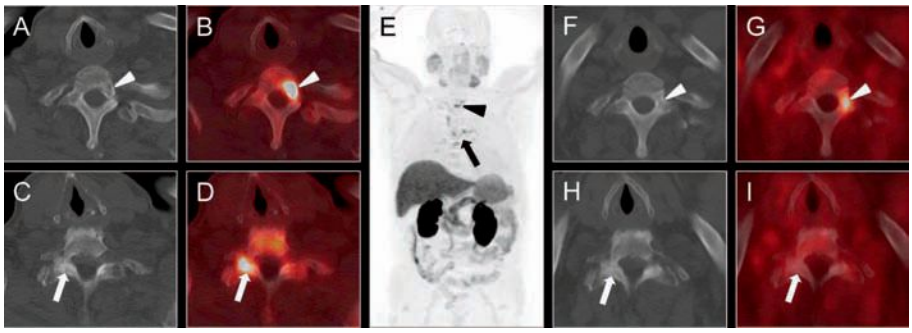


Figure 3. An 85-year-old man with prostate cancer treated with radiation therapy several years prior presented for ^{18}F-NaF-PET/CT (**A-D**) due to a rising PSA. Transaxial CT images (**A**, **C**) with PET fusion (**B**, **D**) showed a focus of tracer uptake in the left pedicle of T1 without a definite anatomic correlate (arrowheads). A similar focus of tracer uptake in the right lamina of T1 (arrows) corresponded to sclerosis on CT. These findings were interpreted as consistent with degenerative change, with no definite evidence of osseous metastatic disease. A ^{11}C-choline-PET/CT (**E-I**) was subsequently performed for localization of disease recurrence. A maximum intensity projection (**E**) demonstrated normal physiologic uptake in the liver, spleen, pancreas, kidneys, stomach/intestines, and salivary glands. However, a suspicious focus of activity was noted in the upper thoracic spine (arrowhead). Mild uptake in several mediastinal lymph nodes (arrow) was felt to be inflammatory in etiology. Transaxial CT images (**F**, **G**) with PET fusion (**G**, **I**) showed a focus of tracer uptake in the left pedicle of T1 (arrowhead) corresponding to the site of increased ^{18}F-NaF uptake, concerning for a prostate cancer metastasis (later confirmed by biopsy). In contrast, there was no abnormal uptake in the right lamina of T1, indicating that the tracer activity seen at this site on ^{18}F-NaF-PET/CT instead represented degenerative change. This case demonstrates that ^{18}F-NaF has excellent sensitivity but lower specificity for prostate cancer osseous metastasis and that the differentiation of metastasis from degenerative change can be challenging. Other PET tracers, such as ^{11}C-choline, may provide a higher level of specificity for osseous metastatic disease.

interest in non-FDG PET tracers with better diagnostic performance for detecting PCa metastases and localizing sites of disease in patients with biochemical recurrence. Furthermore, such PET tracers may have the ability to interrogate the biological pathways underlying PCa behavior, potentially influencing selection of treatment regimens.

There are three FDA-approved non-FDG PET tracers currently available for PCa imaging at Washington University in St. Louis/Barnes-Jewish Hospital ([^{18}F]-NaF, [^{11}C]-choline, [^{18}F]-fluciclovine). Additional PET tracers targeting the prostate specific membrane antigen (PSMA) are likely to enter clinical use in the near future. The mechanisms of targeting, imaging indications, strengths, and weaknesses of these agents are described in detail in Table 2. For imaging osseous metastatic disease, [^{18}F]-NaF-PET/CT outperforms conventional [^{99m}Tc]-methylene diphosphonate (MDP) SPECT bone scans although [^{11}C]-choline-PET/CT provides a greater degree of specificity for osseous metastatic disease (Figure 3).[18] [^{11}C]-choline-PET/CT and [^{18}F]-fluciclovine-PET/CT have the advantage of being able to image nodal and visceral metastatic disease in addition to osseous disease (Figure 4), with best diagnostic performance in the setting of biochemical recurrence.[19, 20]

Although not yet FDA-approved, the prostate specific membrane antigen (PSMA)-targeting PET tracers ([^{68}Ga]-PSMA-HBED-CC and [^{18}F]-DCFPyL) are likely more sensitive and specific for metastatic PCa than [^{11}C]-choline or [^{18}F]-fluciclovine.[21, 22] These PSMA-targeting PET tracers may also add diagnostic value in the setting of initial staging. Overall, though more research is needed to define their optimal clinical roles, these non-FDG PET tracers have already begun to revolutionize the imaging of PCa.

Combined PET/MRI

Simultaneous PET/MRI systems combine the respective advantages of PET and MRI into a single imaging study. These systems have been in use in the United States since 2011 and are currently available for clinical use at Washington University in St. Louis. In the context of PCa, PET is ideal for identifying locoregional nodal and distant metastatic disease, whereas mpMRI provides high-resolution images with excellent soft tissue contrast for lesion localization within the prostate and staging. The results of early studies evaluating simultaneous PET/MRI suggest benefits for preoperative tumor identification, treatment planning, and localizing suspected recurrence (Figure 5). Simultaneous [^{68}Ga]-PSMA-

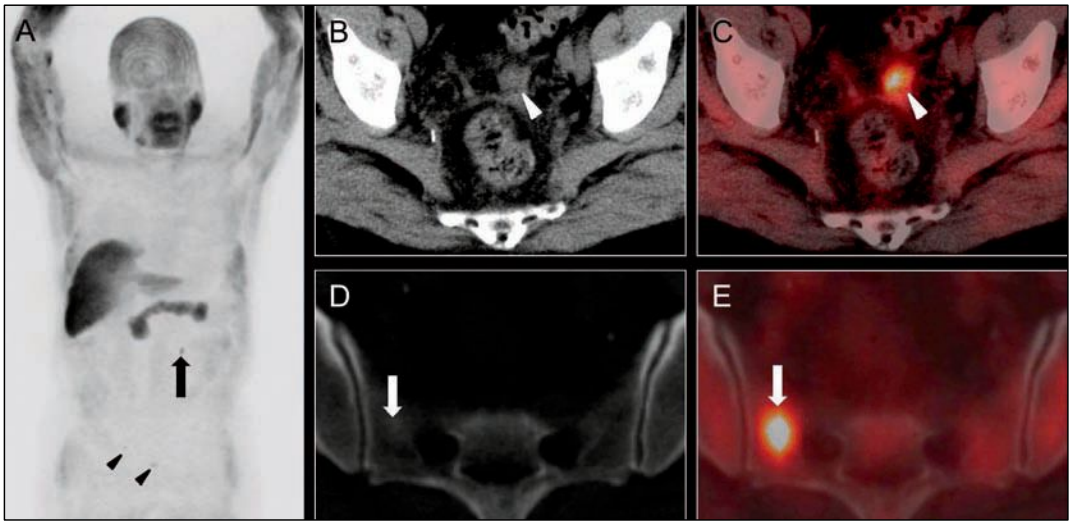


Figure 4. A 64-year-old man with prostate cancer (Gleason 5 + 4) presented for ^{18}F-fluciclovine-PET/CT due to rising PSA levels 8 months after radical prostatectomy. A maximum intensity projection (**A**) showed normal physiologic tracer activity in the salivary glands, liver, and pancreas, with a small amount of activity in the left renal pelvis (arrow) and several suspicious foci in the pelvis (arrowheads). Transaxial CT images (**B**) with PET fusion (**C**) near the prostatectomy bed revealed activity in a tissue lesion (arrowheads), consistent with local recurrence. Additionally, more superiorly, transaxial CT images (**D**) with PET fusion (**E**) demonstrated an intense focus of tracer avidity in the right sacrum corresponding to a subtle sclerotic lesion (arrows), suspicious for osseous metastatic disease. A conventional 99mTc-MDP bone scan 1 month prior had been normal (images not shown). Percutaneous biopsy of the sacral lesion confirmed metastatic prostate cancer. This case illustrates the benefits of ^{18}F-fluciclovine for localizing both osseous and non-osseous sites of recurrent disease.

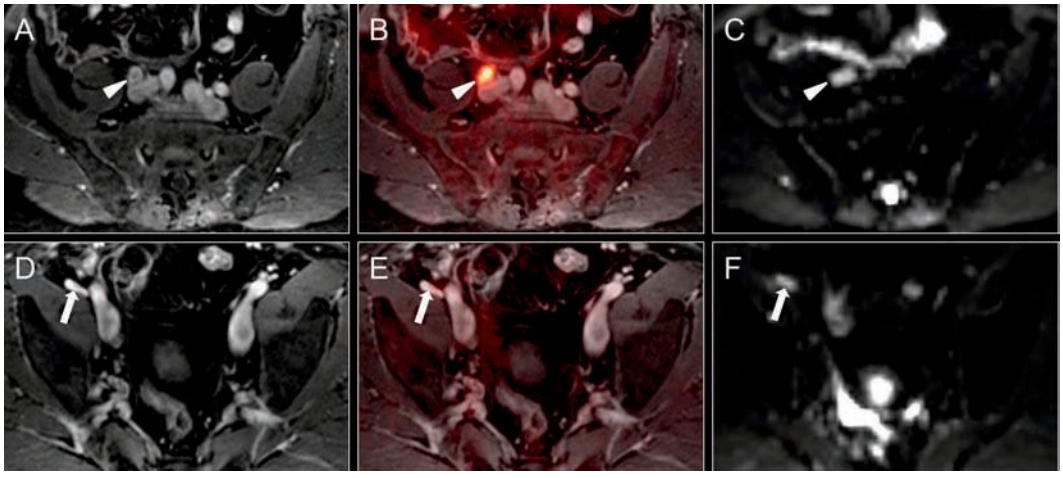


Figure 5. A 63-year-old man with prostate cancer (Gleason 3 + 4) status-post radical prostatectomy with subsequent recurrence in the surgical bed (treated with salvage radiation therapy) presented for a restaging ^{11}C-choline-PET due to a rising PSA. Given its superior soft tissue contrast and the patient's prior recurrence in the surgical bed, PET/MRI was selected instead of PET/CT. Contrast-enhanced transaxial T1-weight images (**A**, **D**) with PET fusion (**B**, **E**) and transaxial diffusion-weighted images (**C**, **F**) are provided. There was no abnormal enhancement, diffusion restriction, or tracer activity in the surgical bed (images not shown). A mildly enlarged right common iliac lymph node (arrowheads) and a prominent right external iliac lymph node (arrows) had similar enhancement (**A**, **D**) and diffusion (**C**, **F**) characteristics. However, the right common iliac lymph node demonstrated intense tracer uptake, whereas tracer activity in the right external iliac lymph node was similar to background. These findings were consistent with a right common iliac nodal recurrence, and the patient was empirically treated with radiation therapy to this area. This case demonstrates the value of the amino acid PET tracers for identifying nodal sites of recurrence, which can be challenging to differentiate from normal lymph nodes on MRI alone.

PET/MRI has been shown to improve both pre-prostatectomy tumor localization and diagnostic accuracy compared with either modality alone.[23] Likewise, simultaneous [^{18}F]-choline-PET/mpMRI outperformed mpMRI alone with respect to sensitivity and accuracy for the initial diagnosis of PCa.[24] In the setting of biochemical recurrence, [^{68}Ga]-PSMA-PET/MRI outperformed [^{68}Ga]-PSMA-PET/CT for the detection of local recurrence in the prostatectomy bed.[25] Bone-specific PET tracers (e.g., [^{18}F]-NaF) may improve the sensitivity of whole-body MRI for osseous metastatic disease. Overall, further work is needed to make novel PET tracers more readily available and to optimize PET/MRI workflows.

Conclusions

Prostate mpMRI plays an important role in the management of patients with known or clinically suspected PCa, and its strength lies in its ability to detect and localize clinically significant cancers. Current indications for mpMRI include persistent clinical suspicion for PCa despite negative systematic biopsy and initial staging of intermediate-risk and high-risk PCas. Multiple clinical trials are underway to assess the utility of mpMRI prior to initial prostate biopsy. Furthermore, mpMRI may play a role in identifying patients suitable for active surveillance. Although the role of mpMRI in biochemical recurrence is less clear, PET/CT and PET/MRI both show significant potential in localizing sites of active disease after initial treatment. Multiple promising PET tracers are already FDA-approved, though further work is needed to define their optimal roles in guiding clinical management.

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Disclosure

None reported.

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Surgical Management for Prostate Cancer

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As the results of large randomized trials have become available and technology continues to improve, the role of surgery in the management of PCa continues to evolve.



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Abstract

For prostate cancer, radical prostatectomy remains the gold standard for surgical management. Given the side effects associated with surgery, patients at low risk of prostate cancer-specific mortality should consider active surveillance under the guidance of a urologist to safely delay intervention. For patients with an intermediate risk of cancer-specific mortality and otherwise healthy life expectancy, radical prostatectomy has been demonstrated to improve survival. Finally, even for select patients with advanced prostate cancer—metastatic disease to the lymph nodes or distant sites—radical prostatectomy may provide a survival benefit.

Introduction

Although radical prostatectomy (RP) remains the gold standard for surgical management of prostate cancer (PCa), the role for RP and other surgical options have grown increasingly complex due to patient and tumor specific considerations that must be taken into account to balance morbidity with cure. For instance, the most appropriate management for a patient with low risk PCa may range from active surveillance (AS) to focal ablative therapy to RP, based on the overall health as well as preferences of the patient. On the other hand, for patients with high risk disease, multimodality treatment that includes RP should be considered. Importantly, the role of surgery in the management of PCa requires an informed discussion with the patient weighing the oncologic benefits against the potential risks to urinary and sexual function.

Active Surveillance

For patients with very low and low risk PCa, AS is the treatment of choice in order to reduce or delay the morbidity of RP. Patients on AS are not initially treated at the time of their PCa diagnosis and are instead followed closely with plans to intervene with evidence of disease progression. AS was conceived based on the natural history of PCa; in studies of men aged 55 to 74 years with localized PCa who did not receive RP, the 20-year PCa-specific mortality was greatly outweighed by non-PCa competing risks of mortality for patients with low risk disease (Gleason $\leq$ 6) across all age groups.[1] The specific criteria for AS candidacy vary from institution to institution. The most stringent criteria require prostate-specific antigen (PSA) less than 10 ng/mL,

Gleason $\leq$ 6 disease, 2 or less biopsy cores positive, and $\leq$ 20% involvement of the cores. The least strict criteria require PSA less than 15 ng/mL, Gleason $\leq$ 3+4=7 disease, and less than 50% of the biopsy cores to be positive. Importantly, the PCa-specific mortality for patients on various AS protocols across seven institutions remains very low (0-1%), while approximately one third of patients receive intervention at a median of 2.5 years of AS.[2] The institution with the most relaxed AS criteria also has the longest follow-up duration, and they report PCa specific survival rates of 99% and 97% at 5 and 10 years, respectively.[3] These longitudinal findings have been confirmed by a recent randomized study, ProtecT, in the United Kingdom, where patients were randomized to AS, RP, or radiation therapy. In this study of men aged 50 to 69 years with localized PCa, the 10-year PCa specific survival was nearly identical between AS and RP (98.8% versus 99.0%). Of note, more than half (approximately 53%) of the patients on AS received either RP or radiation therapy during the study period.[4] Finally, the advent of improved imaging (namely 3T multiparametric magnetic resonance imaging) as well as histopathologic genetic markers have allowed for even more careful selection of patients for AS, providing reductions in morbidity by safely delaying RP.[5]

Radical Prostatectomy for Localized Prostate Cancer

For patients with localized PCa, RP is a surgical treatment performed with curative intent, and has been demonstrated in a number of trials to provide a survival benefit. Conversely, alternative treatment options for localized PCa have not been studied in a controlled fashion. For patients with organ-confined disease who wish to preserve erectile function, a nerve-sparing retropubic approach to RP is the standard of care. With technologic advances, the traditional open retropubic RP has been mostly replaced by laparoscopic and robot-assisted laparoscopic approaches. Importantly, numerous studies have demonstrated that laparoscopic and robotic RP have similar functional and oncologic outcomes when compared to traditional open RP, while also decreasing perioperative morbidity.[6-8] Due to patient demand and perceived technical advantages, the robotic RP has become the standard surgical approach to RP in the United States, despite higher per case costs when compared to laparoscopic RP.[9] Regardless of the surgical approach (open, laparoscopic, or robotic), the anatomic principles of the retropubic RP remain the same, and thus the results of the following studies can be applied to all techniques.

In the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), RP was compared to watchful waiting (delayed hormonal therapy for metastatic disease) in a randomized fashion for men aged 75 years or less with at least a 10-year life expectancy who were diagnosed with clinically localized PCa. At 13.4 year median follow-up, a significant survival benefit was found for the men who were treated with RP, with PCa-specific mortality of 18% in the RP arm versus 29% in the watchful waiting arm. When the patients were sub-stratified by age, those who were less than 65 years derived the greatest benefit from RP, with a 26% reduction in overall mortality, 16% reduction in PCa-specific mortality, and 16% reduction in the development of metastatic disease. Additionally, patients with intermediate risk disease (PSA between 10 and 20 ng/mL or Gleason $\geq$ 7) derived the greatest benefit from RP, with a 15% reduction in overall mortality, 24% reduction in PCa-specific mortality, and a 20% reduction in the development of metastatic disease.[10]

In the Prostate Cancer Intervention Versus Observation Trial (PIVOT), RP was compared to watchful waiting in a randomized fashion for men aged 75 years of less, with PSA less than 50 ng/mL, with at least a 10-year life expectancy who were diagnosed with clinically localized PCa. An important consideration compared to SPCG-4 is that 50% of patients in PIVOT (versus 12% in SPCG-4) had non-palpable PCa. At 10 year median follow-up, no significant differences were found between the treatment groups for overall and cancer-specific survival. However, the patients who received RP had significantly less bone metastasis (5 versus 11%).[11] The recently published update of PIVOT confirms a statistically insignificant benefit in PCa-specific mortality for RP over observation (11.4 versus 7.4%, p=0.06).[12] The ProtecT study demonstrated a similar finding when comparing RP to AS—no significant differences in overall or cancer-specific mortality at median 10 year follow-up, but a significant reduction in the development of metastatic disease with RP.[4] In PIVOT, similar to SPCG-4, patients with intermediate

risk disease did experience a significant reduction in overall mortality with RP, 31% relative reduction and 13% absolute risk reduction.[11,12] Combining the findings from PIVOT and SPCG-4 suggests that RP provides a survival advantage in patients with intermediate risk disease, particularly those who are less than 65 years of age.

Radical Prostatectomy for Locally Advanced Prostate Cancer

Traditionally, surgical removal of the prostate was believed to provide no benefit to patients who had lymph node metastatic PCa. As the above trials determining the survival benefit of RP for patients with localized PCa were being performed, the role of surgery for patients with locally advanced PCa (with metastasis to the pelvic lymph nodes) was also being explored. In two retrospective studies of patients who received RP despite lymph node involvement, a minority of patients were found to have no evidence of disease at intermediate to long term follow-up. Examining patients from 1989 to 1999 in Switzerland, Bader et al. report approximately 25% (92/367) of patients receiving RP were found to have lymph node involvement. Of these patients, 24% (21/88) with available follow-up were found to have no evidence of disease recurrence at a median follow-up of 45 months.[13] Similarly in a study between 1972 to 1999 in the United States, Daneshmand et al. report approximately 12% (235/1936) of patients receiving RP were found to have disease that had spread to the lymph nodes. At 137 month median follow-up, the estimated recurrence-free survival was 80%, 65%, and 58% at 5, 10, and 15 years, respectively.[14] More important than the finding that a minority of patients with lymph node metastatic PCa have a durable cure after RP, Engel et al. found that survival for patients who had RP was significantly improved over patients who had RP aborted due to lymph node involvement. Using the Munich Cancer Registry between 1988 and 2007, they found that the 5 and 10 year estimated cancer-specific survival was 95% and 86% for RP but 70% and 40% with aborted RP.[15] As a result of these studies, the role of RP in locally advanced (lymph node metastatic) disease has been established as providing survival benefit to most patients, while providing cure to some.

Radical Prostatectomy for Metastatic Prostate Cancer

More recently, a role for RP in the treatment of patients with metastatic PCa has been proposed. Retrospective studies using the Munich Cancer Registry and the Surveillance Epidemiology and End Results (SEER) database have demonstrated a survival advantage of RP over radiation or no local therapy in patients with metastatic PCa. In the Munich Cancer Registry from 1998 to 2010, 5% (74/1538) of patients with newly diagnosed metastatic PCa received RP. Although these likely represent carefully selected patients, the survival advantage was significant— 5-year survival of 55% versus 21% for RP versus any other therapy (radiation or systemic therapy alone), respectively.[16] The same findings were echoed in the SEER based study from 2004 to 2010, where roughly 3% (245/8185) of patients underwent RP in the setting of metastatic PCa. For those who received RP, 5-year survival was 67%, while 5-year survival was 23% for patients receiving no therapy.[17] Based on these studies and others,[18] three prospective trials examining the role of RP in metastatic disease have been opened: 1) a multicenter United States randomized trial of best systemic therapy versus best systemic therapy plus local therapy (RP or radiation), 2) a United Kingdom randomized trial of RP plus usual therapy versus usual therapy alone in patients with bone only low metastatic disease burden, 3) a German randomized trial of RP plus hormone therapy versus hormone therapy alone in patients with limited bone metastasis. As the results of these trials become available, evaluating the quality of life effects of RP in this patient population must be carefully weighed against the survival benefit that surgery may provide.

Focal (Partial Gland) Therapy for Localized Prostate Cancer

As PCa is considered to be a multifocal disease in the majority of cases, surgical treatments aimed at part of the prostate rather than the entire gland have been met with skepticism. However, more recent advances in imaging, such as 3-Tesla multiparametric MRI and new radiotracers for PET/CT or PET/MRI, provide an opportunity for more accurate diagnosis and targeting of lesions within the prostate.[19] Multiple energy sources have been investigated for use in focal prostate ablation, including high-intensity focused ultrasound, cryotherapy, and photothermal devices. Regardless of the energy source, risks to urinary and sexual function exist, but

may be substantially lower than for RP, particularly if used on a limited portion of the prostate. More clinically meaningful for the successful uptake of focal therapy in PCa is the identification of the appropriate patient who is neither ideally suited for AS nor RP. The ideal patient would harbor enough risk of PCa-specific mortality to justify intervention but not high enough risk to require RP.[20] Despite significant improvements in imaging and image guided intervention, the state of available technology remains imperfect as a diagnostic tool, and so, focal treatments of the prostate cannot be considered a curative approach to PCa at this time.[21]

Conclusions

As the results of large randomized trials have become available and technology continues to improve, the role of surgery in the management of PCa continues to evolve. RP remains the mainstay of surgical treatment for PCa, representing a curative option for those with localized disease and a survival benefit for those with advanced disease. As the role for AS and focal therapy continue to change, the appropriate risk stratification and selection of patients for those treatment options will be critically important.

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Disclosure

None reported. **MM**

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Radiation Therapy for Prostate Cancer

by Hiram A. Gay, MD & Jeff M. Michalski, MD

Washington University in St. Louis
School of Medicine

Radiotherapy is an integral part of the modern multidisciplinary management of prostate cancer which is often underutilized or delayed.



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Abstract

Annually, there are nearly 3000 new cases and 500 deaths from prostate cancer in Missouri. When treatment is appropriate and necessary, radiotherapy offers similar cure rates to prostatectomy, with fewer long-term sexual side effects and little effect on urinary continence. Radiotherapy is delivered with external beam or implanted radioactive sources (brachytherapy). In high-risk disease, combinations of external beam and brachytherapy offers improved biochemical control. Following prostatectomy, salvage radiotherapy should be initiated as soon as possible.

Introduction

In 2017 the estimated number of new cases and deaths from prostate cancer (PCa) in the United States are 161,360 and 26,730, respectively. For the state of Missouri, the estimated new cases and deaths from PCa are 2990 and 500, respectively.[1] From birth to death, the probability of developing PCa is 1 in 8 men. There has been a sharp reduction in PCa incidence of more than 10% annually from 2010 to 2013. This drop is attributed to decreased prostate-specific antigen (PSA) testing following the US Preventive Services Task Force recommendations against the routine use of PSA testing because of growing concerns about overdiagnosis and overtreatment.[2] PCa is the third leading cause of cancer death in patients 60 to 79 years old and second in the ≥ 80 year old group.

The National Comprehensive Cancer Network (NCCN) PCa guidelines include a variety of radiation therapy modalities as part of the standard of care for the definitive treatment of PCa:

- Very low risk patients (T1c, Gleason score ≤ 6, PSA < 10 ng/mL, fewer than 3 prostate biopsy cores positive, ≤ 50% cancer in each core, PSA density <0.15 ng/mL/g) with a life expectancy ≥ 20 years, external beam radiation therapy (EBRT) or brachytherapy (BT);
- Low risk patients (T1-T2a, Gleason score ≤ 6, PSA < 10 ng/mL) with a life expectancy ≥ 10 years, EBRT or BT;
- Intermediate risk patients (T2b-T2c or Gleason score 7 or PSA 10 – 20 ng/mL), EBRT ± 4 to 6 months of androgen deprivation therapy (ADT) ± BT or BT alone;
- High-risk patients (T3a or Gleason score 8 – 10 or PSA > 20 ng/mL) EBRT + 2 to 3 years of ADT, or EBRT + BT ± 2 to 3 years of ADT.[3]

Indications for adjuvant EBRT following prostatectomy are: tumor extension through the prostate capsule

or invasion into the seminal vesicles (pT3), positive margins, Gleason score 8-10, seminal vesicle involvement, or detectable PSA. Patients who have an undetectable PSA after prostatectomy with a subsequent detectable PSA that increases on two or more occasions without detectable distant metastases should be offered salvage EBRT.[3] All PCa patients with localized PCa should have a consultation with both a surgeon and a radiation oncologist to make an informed decision regarding their care.

Which Approach Is Better: Active Surveillance, Surgery, or Radiotherapy?

The 10 year outcomes of the Prostate Testing for Cancer and Treatment (ProtecT) trial from the United Kingdom has provided valuable insights into the management of localized PCa.[4] The trial recruited 1643 men 50 to 69 years old. Of these 545 men underwent active surveillance, 553 surgery, and 545 radiotherapy. For the participants, the median follow-up was 10 years, the median age was 62 years, the median PSA was 4.6 (range, 3.0 to 19.9), 77% were Gleason 6 and 21% were Gleason 7, and 76 % were T1c and the remaining T2. There were 17 prostate-cancer–specific deaths overall: 8 in the active surveillance group, 5 in the surgery group, and 4 in the radiotherapy group. The difference was not statistically significant among groups.

Metastases developed in more men in the active-monitoring group (33 men) than in the surgery group (13 men) or the radiotherapy group (16 men) ($P=0.004$). Higher rates of disease progression were seen in the active-monitoring group (112 men) than in the surgery group (46 men) or the radiotherapy group (46 men) ($P<0.001$). In summary, at a median of 10 years, prostate-cancer–specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastases than was active monitoring, while 44% of the patients who were assigned to active monitoring did not receive radical treatment and avoided side effects.[5]

Of the three treatments, prostatectomy had the greatest negative effect on sexual function and urinary continence, and although there was some recovery, these outcomes remained worse in the prostatectomy group than in the other groups throughout the trial. By year 6, the percentage of men reporting erections firm enough for intercourse were: 17 % in the prostatectomy group, 27 % in the radiotherapy group, and 30% in the active surveillance group. By year 6, 17% of men in the prostatectomy group were using pads, as compared with 8% in the active-monitoring group, and 4% in the radiotherapy group.

Bowel function was worse in the radiotherapy group at 6 months than in the other groups but then recovered somewhat, except for the increasing frequency of bloody stools; bowel function was unchanged in the other groups. Urinary voiding and nocturia were worse in the radiotherapy group at 6 months but then mostly recovered and were similar to the other groups after 12 months. No significant differences were observed among the groups in measures of anxiety, depression, or general health-related or cancer-related quality of life.

These results are very important and relevant to our patients. From a radiation oncology perspective, we can inform low and intermediate risk PCa patients that prostatectomy, active surveillance, and radiotherapy offer a similar PCa-specific mortality. More importantly, for these low and intermediate risk PCa patients, undergoing radiotherapy can avoid long term incontinence from prostatectomy, and provide better sexual function compared to surgery.

Radiation Therapy Innovations for Prostate Cancer

Over the past decade radiation techniques have improved to allow better coverage of tumor volumes with better sparing of adjacent normal structures. In PCa, this means a lower incidence of bowel, urinary and sexual side effects.

Image-Guided Intensity Modulated Radiation Therapy (IG-IMRT)

The approach to radiation therapy has been available for more than a decade. It employs multiple radiation beams that intersect within the target volume. The dose of radiation from an individual beam is modulated to maximize energy deposition within the tumor. In addition, we have employed implanted fiducial markers that allow daily localization of the prostate using diagnostic quality x-rays. This limits the margin traditional utilized for set-up uncertainties to less than 0.5 cm. A smaller margin around the target means less radiation dose to the rectum, bladder and penile structures.

With the use of IG-IMRT, we have been able to conduct radiation dose escalation studies that have demonstrated an improved biochemical control compared to lower, conventional doses of radiation therapy. Men

Figure 1: (a) Axial CT slice showing conformality of intensity modulated radiation therapy. Radio-opaque markers are apparent in the anterior aspect of the prostate gland. (b) Axial CT slice showing conformality of proton beam radiation therapy in the same patient as panel a. More sparing of the anterior-lateral rectal wall and less dose to peripheral tissues is apparent.

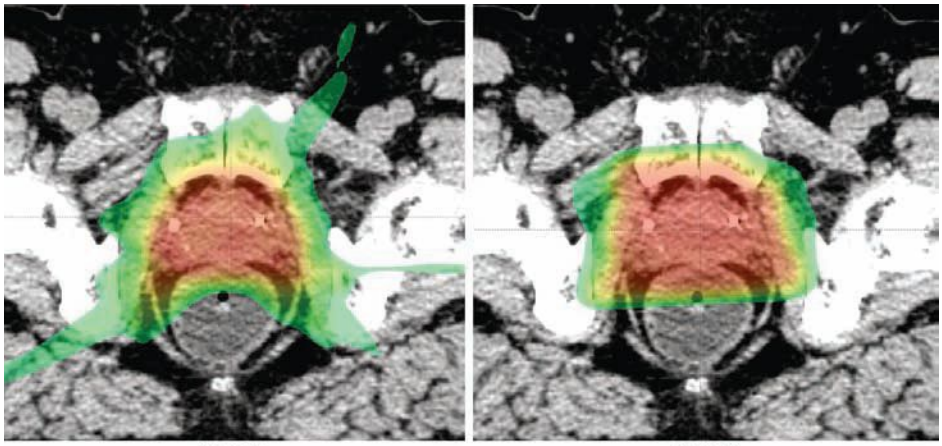
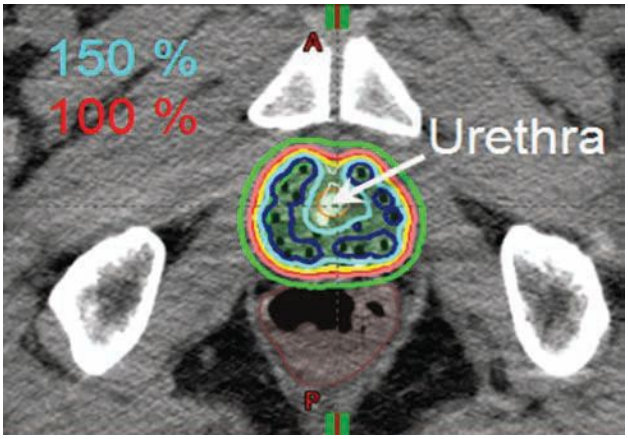


Figure 1a Figure 1b

Figure 2: HDR implant dose distribution, allow demonstrating HDR sparing the urethra.



treated with dose escalated radiation therapy have a significantly lower rate of treatment failure and subsequent salvage therapy. In addition, we have gained considerable knowledge about the radiation factors that may contribute to urinary and bowel side effects. This allows radiation oncologists to tailor the radiation plan to individual patients and optimize their expected outcomes.

Proton Beam Radiation Therapy

Proton beam radiation therapy capitalizes on a unique physical property of high energy protons generated from a cyclotron. The accelerated charged particles travel through tissue until reaching a depth determined by their energy. Once they reach that depth, the remainder of the radiation dose is deposited in a sharp Bragg peak with no dose going beyond that point. When multiple proton beams are used, a very sharp and tight radiation dose distribution is created. This modality is especially attractive when tumors are in close proximity to sensitive organs. PCa is one of the more common indications in which proton therapy is utilized.

At Washington University in St. Louis we are collaborating with investigators from Massachusetts General Hospital and the Harvard Medical School conducting a randomized clinical trial of IG-IMRT versus proton beam radiation in men with low and intermediate risk PCa. The PARTIQoL™ trial is seeking to measure and compare relative the impact of the two modalities on patient quality of life after treatment. Figure 1 provides a comparison of these two treatment modalities.

Image-Guided Brachytherapy

An alternative to external beam radiation therapy with either x-rays or protons is the use of implanted radioactive sources (brachytherapy) directly into the prostate gland. This technique was introduced in the St. Louis region by physicians at Washington University. There are two general approaches to prostate brachytherapy, low-dose rate (LDR) permanent radioactive seed implant and high-dose rate (HDR) temporary radioactive seed implant. Figure 2 demonstrates the radiation dose distribution for HDR. Both approaches utilize real time ultrasound image guidance to assure accurate placement of sources into the prostate while avoiding delivering high doses to

Figure 3: Prostate MRI (T2 sequence) before (a) and after (b) hydrogel injection. The rectum touches the prostate on the pre-injection MRI but is displaced away from the prostate by the T2 bright spacer (black arrow). This added space results in significantly less radiation dose to the adjacent rectum.

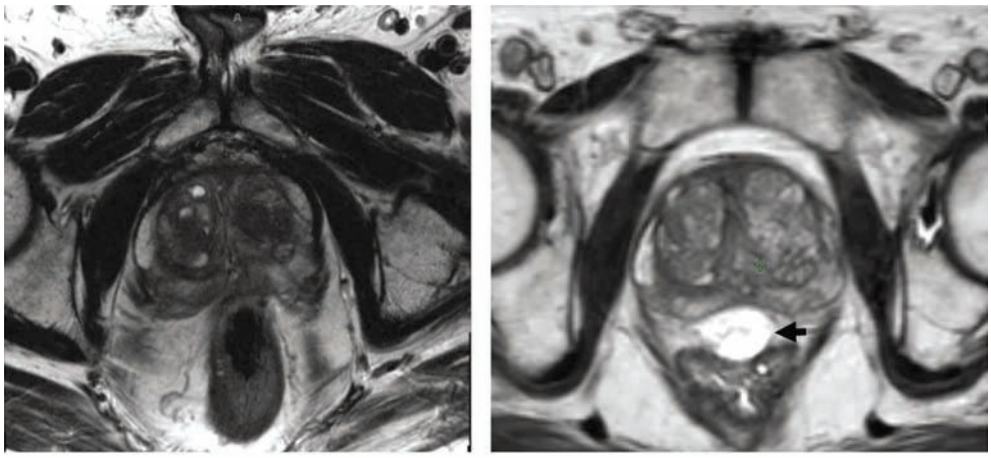


Figure 3a Figure 3b

the rectum, urethra and bladder. In addition, CT or MR imaging of the implant following the procedure. This imaging allows quality assessment of the implant and adjustment of the implant if areas of underdosing are identified.

In some cases of high risk PCa, a combination of external beam radiation therapy and brachytherapy will be recommended. A recent Canadian study, the ASCENDE-RT trial, has reported superior biochemical control compared to external beam radiation alone. Of the 398 participants, 200 were assigned to the EBRT boost and 198 to the LDR boost. Compared with the 78 Gy EBRT boost, men randomized to the LDR boost were twice as likely to be free of biochemical failure at a median follow-up of 6.5 years (P=.004). The 5-, 7-, and 9-year Kaplan-Meier biochemical progression-free survival estimates were 89%, 86%, and 83% for the LDR boost versus 84%, 75%, and 62% for the EBRT boost (P<.001). The LDR boost benefited both intermediate- and high-risk patients. From a toxicity standpoint, the LDR boost increased the risk of needing temporary catheterization and/or requiring incontinence pads. At 5 years the cumulative incidence of grade 3 genitourinary events was 18.4% for the LDR boost, versus 5.2% for the EBRT boost (P<.001). The 5-year cumulative incidence of grade 3 gastrointestinal events was 8.1% for the LDR boost, versus 3.2% for the EBRT boost (p=0.124). The 5-year prevalence of grade 3 gastrointestinal toxicity was lower than the cumulative incidence for both arms (1.0% vs 2.2%, respectively).[6]

Because of the improved biochemical progression-free survival, there is an increased interest in the radiotherapy community to boost intermediate and high risk patients with brachytherapy. Brachytherapy also has the advantage of shortening the treatment duration. At Washington University, a brachytherapy boost will reduce the EBRT treatments from 44 to 25 for the intermediate and high risk patients.

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is a highly conformal and precise method of delivering ultra-high dose radiation therapy. Also called Stereotactic Ablative Radiation Therapy (SABR), this technique will ablate malignant tissue in just five treatments delivered over 1-2 weeks.[7] This accelerated scheduling is appealing to patients due to its convenience to patients over the traditional course of radiation that takes 5 to 8 weeks of daily treatments.

Physicians at Washington University in St. Louis have participated in a phase II trial of SBRT and that has demonstrated excellent tolerance to the extremely short course of therapy. This year we will be participating in a national phase III trial comparing the standard long course of external beam radiation therapy to the short course of SBRT. Short term outcomes of this approach have been reported by several single institutional series with exceptional early results.



Injectable Hydrogel Rectal Spacer

A new product has received FDA approval to further improve the outcomes of men receiving curative radiation therapy. A biodegradable hydrogel, SpaceOAR™, is injected transperineal into the prerectal space and increases the distance between the anterior rectum and the posterior border of the prostate (Figure 3). This increased distance of 9-11 mm reduces the volume of rectum receiving a high dose of radiation and has significantly improved the quality of life (rectal domain) in men treated with dose escalated IG-IMRT. At 15 months after treatment, only 12% of men treated with the rectal spacer had a 10 point decline in bowel symptom quality of life compared to 21% treated without it. Mature results from this randomized clinical trial suggest that this hydrogel not only improves rectal toxicity outcomes, it may also improve urinary and sexual function compared to men treated without it.[8]

Conclusions

Radiotherapy is an integral part of the modern multidisciplinary management of PCa which is often underutilized or delayed. Greater efforts to educate our patients and the medical community are necessary so we can best serve our patients.

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Disclosure

None reported.

MM

Prostate Cancer Pathology: Recent Updates and Controversies

by Jennifer K. Sehn, MD

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Pathologists continue play an essential role in guiding care in prostate cancer patients.



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Abstract

Prostate cancer is common, and recent efforts in clinical management have focused on identifying patients who could be candidates from less aggressive management or who could benefit from more aggressive therapy. As prostate cancer histology, especially Gleason score, plays a critical role in predicting patient outcomes, attempts have been made to refine histologic classification and reporting in prostate cancer to facilitate patient risk stratification. This review discusses recent updates in prostate cancer grading and reporting.

Introduction

Gleason grading of acinar adenocarcinoma of the prostate represents one of the earliest and most successful applications of evidence-based medicine in routine clinical practice. For several decades, the original Gleason system was used to grade acinar adenocarcinomas based on architectural features, with excellent correlation with clinical outcomes. However, in the past ten to fifteen years, it has become apparent that further refinement of the original Gleason grades is possible, with improved correlation with patient outcomes. Indeed, much of the recent prostate pathology literature has focused on attempts to optimize pathologic grading and reporting of prostatic adenocarcinoma in support of ongoing clinical efforts to select optimal treatment for prostate cancer (PCa) patients by minimizing treatment-related morbidity while maximizing therapeutic benefit and quality of life. The most recent revision of the Gleason grading system put forth by the International Society of Urological Pathology (ISUP) and adopted in the World Health Organization (WHO) 2016 classification of prostate tumors is discussed herein, including the motivation for the revised grading and associated grade grouping, as well as controversies regarding their application and use in routine practice. (In this article, Gleason grade or Gleason pattern refers to the current ISUP consensus on Gleason grading,[1] unless otherwise specified.) Diagnosis and clinical implications of intraductal carcinoma also are covered, and general recommendations for use of immunohistochemistry in the differential diagnosis of PCa are briefly discussed. Variant histologic patterns of prostatic adenocarcinoma and rare prostate tumors such as stromal neoplasms and lymphomas are not discussed.

Prostate Adenocarcinoma Grading

In 2014, the ISUP convened a panel of expert urologic pathologists and clinicians to address issues related

to PCa grading;[1] the recommendations of the panel were adopted by the WHO in the 2016 classification of prostate tumors.[2] The primary issues addressed were histologic patterns of Gleason patterns 4 and 5 and adoption of a reporting system to group tumors according to Gleason score and associated prognosis.

Figure 1 illustrates the current state of Gleason grading in comparison with the original system proposed by Gleason himself. The main updates to Gleason grading in the 2014 ISUP consensus are related to diagnosis of Gleason pattern 4: all cribriform, glomeruloid, and fused or poorly formed glands visible at 10x magnification are considered Gleason pattern 4, though identification of only occasional poorly formed or fused glands between otherwise well-formed glands does not warrant a diagnosis of pattern 4. Additionally, the ISUP consensus specifies that mucinous adenocarcinoma, in which extravasated pools of mucin are seen in the stroma around cancer glands, should be graded based on the architecture of the glands themselves rather than uniformly be assigned Gleason pattern 4. Pools of mucin associated with otherwise well-formed tumor glands should be considered Gleason pattern 3 rather than pattern 4. The consensus points also include that any amount of comedonecrosis warrants a diagnosis of pattern 5, branched glands are permitted in Gleason pattern 3, and intraductal carcinoma (discussed later) should be reported but not graded.[1] Prostate adenocarcinomas that are exempt from grading are tumors with morphologic changes secondary to androgen deprivation, chemotherapy, or radiation. Histologic features of treatment effect include luminal collapse, poorly formed glands, nuclear pyknosis, and overall decrease in the number of glands. Metastatic tumor deposits also are not assigned a Gleason score. Alpha-reductase inhibitors (e.g. finasteride), cryotherapy, and ultrasound ablation have not been shown to have significant effect on PCa morphology, and it is appropriate to grade carcinomas in patients who have received these treatments.[3]

Figure 1. Illustrates the current state of Gleason grading in comparison with the original system proposed by Gleason himself.

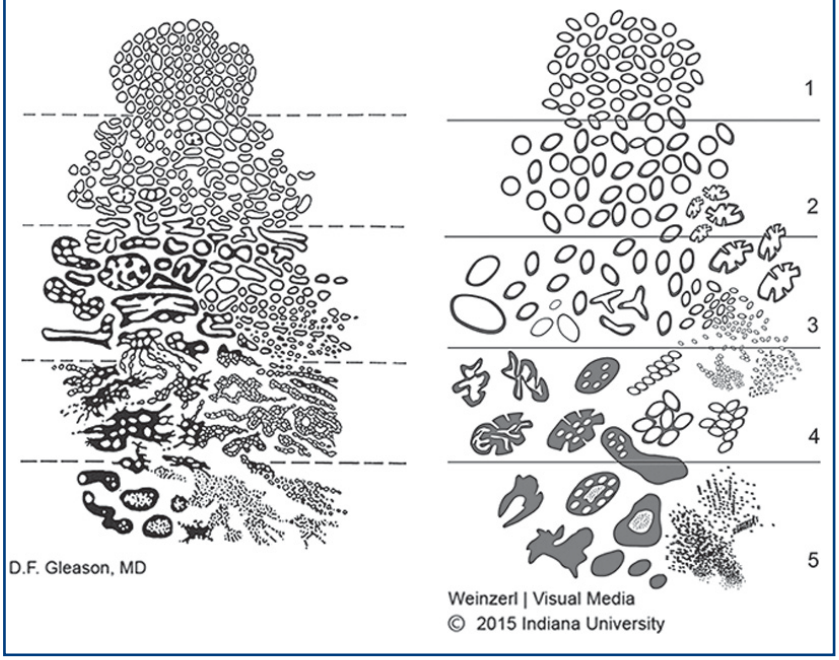


Table 1. Grade group by corresponding Gleason score.

Grade group	Gleason score
1	≤6 (usually 3+3)
2	7 (3+4)
3	7 (4+3)
4	8 (4+4, 3+5, 5+3)
5	9, 10 (4+5, 5+4, 5+5)

Prostate Adenocarcinoma Grade Grouping

In order to facilitate better communication of the pathologic diagnosis to clinicians and patients, the ISUP consensus recommends adoption of so-called grade grouping, as proposed by Epstein et al.[1,4] The grade groups (Table 1) correspond well with patient prognosis and are reasonably straightforward to adopt, since they are based on Gleason score.[4] In essence, Gleason scores

≤6 are grouped into the grade group representing the best overall prognosis (grade group 1). Notably, Gleason scores <6 have all but ceased to exist in current clinical practice. Gleason score 7 is separated into Gleason 3+4 (grade group 2) and Gleason 4+3 (grade group 3), a move that is supported by well-established evidence showing a significantly worse prognosis in Gleason 4+3 tumors compared to Gleason 3+4. Gleason score 8 tumors comprise grade group 4, and Gleason score 9 or 10 falls into the worst prognostic group (grade group 5). Translation of Gleason scores 6-10 into grade groups 1-5 is designed, at least in part, to clearly communicate to patients that Gleason score 6 is a well-differentiated tumor with an overall excellent prognosis. In contrast, a patient receiving a diagnosis of Gleason score 6 on a scale of 2-10 may be understandably confused when told that his tumor has essentially the best prognosis for PCa. The hope is that a diagnosis of "grade group 1" can prevent overtreatment of Gleason 6 tumors by more clearly communicating the indolent nature of these tumors. It is currently recommended that the Gleason score be reported in combination with the grade group in prostate biopsies and resections.[1,5]

Although the underlying motivation for changes in PCa grading and grade grouping are well intentioned, there are lingering issues related to diagnosis and reporting of high-grade adenocarcinoma (Gleason patterns 4 and 5) in particular. One critical point is that cases with a tertiary Gleason pattern were explicitly excluded in the description of the grade groups;[4] as such, grade groups cannot be applied in cases with tertiary patterns. By convention, tertiary pattern is defined as involving <5% of the tumor volume and being of higher grade than either the primary (most common) or secondary (second most common) grade in a prostatectomy specimen. Tertiary patterns are not diagnosed in prostate biopsies; the highest grade is assigned as the secondary pattern (provided that it is not the most common pattern), even if it comprises less than 5% of the tumor volume.[6]

One of the primary goals for refinement of Gleason score 7 is identification of patients with Gleason 3+4 tumors who might be candidates for active surveillance. Unfortunately, grade grouping does not address the critical question of how much Gleason pattern 4 is too much for a patient to be considered for active surveillance, as the split between grade groups 2 (3+4) and 3 (4+3) is based on an arbitrary threshold of Gleason pattern 4 comprising more than half of the tumor volume. Recent studies to evaluate the prognostic impact of Gleason pattern 4 have focused on how best to quantitate Gleason pattern 4 (e.g., 10% increments, quartiles, etc.) to correlate with patient outcomes, and on the prognostic impact of specific architectural patterns within the Gleason pattern 4 category (e.g., cribriform versus glomeruloid versus poorly formed glands).[7-9] In general, it appears as though cribriform architecture bears an overall worse prognosis compared with glomeruloid or poorly formed glands.[7,8] Importantly, diagnosis of poorly formed glands (defined in one study as "glands with no or rare lumens, elongated compress glands, and elongated nests") shows relatively poorly interobserver agreement, even among expert urologic pathologists (κ=0.34).[10] Additionally, other histologic features besides gland architecture (particularly mucinous fibroplasia/collagenous micronodules) have been shown to confer a worse prognosis than would be expected based on Gleason score alone, though there are no clear recommendations at this time as to how that information should be included in the tumor grade or in the surgical pathology report.[8] The practicing pathologist is encouraged to keep these points in mind, pending inevitable further refinement of classification and reporting.

As with Gleason pattern 4, grade grouping as currently recommended does not address complexities in the prognostic impact of varying amounts of Gleason pattern 5 in PCa. Mounting evidence shows that there are significant differences in prognosis for Gleason score 8 tumors (4+4, 3+5, 5+3), in particular related to the amount of Gleason pattern 5 that is present in the tumor.[9,11,12] In fact, even focal Gleason pattern 5 (any amount, less than 20% of the tumor) has a significant prognostic impact, with tumors showing >20% pattern 5 having an even worse prognosis.[9] Knowing that even focal (1-2%) pattern 5 confers a significantly worse prognosis than absence of pattern 5, and that the prognostic impact is similar for all percentages up to 20%, it is worrisome that there is relatively poor interobserver agreement in the diagnosis of Gleason pattern 5, even among urologic pathologists (κ=0.376).[9,13]

Quantification of High-Grade Adenocarcinoma

Although a consensus has not yet been reached on issues related to diagnosis and quantitation of Gleason patterns 4 and 5 (as discussed immediately above), the ISUP and College of American Pathologists (CAP) do currently recommend reporting the percent of tumor that is Gleason pattern 4 or 5.[1,5] One can certainly imagine that it could be helpful to know that a tumor reported as Gleason score 3+4=7 is actually 90% Gleason pattern 3 with only 10% "poorly formed glands," the diagnosis of which may be in the eye of the beholder. In contrast, one might pursue a more aggressive treatment plan in a patient with a Gleason 3+4=7 tumor if the report clearly indicated that the pattern 4 component comprised 40% of the tumor and showed predominantly cribriform architecture. The intent is to provide detailed information to treating clinicians such that patients may be optimally selected for more or less aggressive management, in keeping with long-standing efforts by urologic clinicians to tailor treatment based on predicted prognosis (e.g., through application of nomograms). Additionally, it is purported that routine reporting of the percent Gleason patterns 4 and 5 will be useful for future studies on outcomes.[6]

Intraductal Proliferations

Another primary point from the recent ISUP consensus is that intraductal carcinoma should be reported but not included in the Gleason score, qualified by a statement that intraductal carcinoma is almost invariably associated with aggressive invasive adenocarcinoma, even when the invasive component seen in a prostate biopsy is Gleason score 6.[1,14] In the 2016 WHO Bluebook, intraductal carcinoma is defined as malignant prostatic epithelial cells filling prostatic ducts and large acini, with an intact basal cell layer, and having either A) a solid or dense cribriform (more solid areas than lumen formation) architecture or B) a loose cribriform or micropapillary pattern with associated comedonecrosis or marked nuclear atypia (nuclear size at least 6x normal).[2] Some authors have highlighted limitations in the diagnosis and reporting of intraductal carcinoma.[15] As intraductal carcinoma is a relatively new diagnosis, the primary differential diagnosis is discussed briefly here.

The main differential for intraductal proliferations are high-grade prostatic intraepithelial neoplasia (HGPIN), intraductal prostatic carcinoma (IDC), and extension of urothelial carcinoma into prostatic ducts.[16] All of these lesions have a retained basal cell layer, which can be demonstrated immunohistochemically with antibodies such as p63 and/or cytokeratin 34βE12 (often used in a cocktail along with alpha-methyl acyl coenzyme A racemase, AMACR), differentiating these lesions from invasive carcinoma. HGPIN-like adenocarcinomas have been described, but these also lack basal cells.[17] Immunostaining for basal cells is primarily recommended when the differential diagnosis is IDC versus invasive carcinoma and the distinction would have an impact on Gleason scoring (e.g., cribriform IDC versus cribriform invasive carcinoma in a background of otherwise well-formed invasive tumor glands). Use of basal cell markers is probably not useful in cases that also harbor frank high-grade invasive carcinoma, as the presence of IDC is not especially important in this setting.[16]

Differentiation of HGPIN from IDC can be difficult on morphologic grounds alone, and some have proposed use of PTEN immunostaining (with or without the slightly less helpful ERG immunostaining) to differentiate these lesions: IDC frequently shows loss of PTEN and reactivity for ERG, with the opposite findings in HGPIN. However, atypical intraductal proliferations equivocal for IDC versus HGPIN by morphology are associated with invasive carcinoma in 64% of re-biopsy cases when PTEN is lost, compared with 50% when PTEN staining is retained.[18] Hence, some experts simply recommend rebiopsy in these "in-between" cases that exceed the degree of atypia typically seen in HGPIN but do not meet the criteria for IDC, without further evaluation by immunohistochemistry.[16]

Immunostaining is particularly useful in differentiation of IDC versus extension of urothelial carcinoma into prostatic ducts. A panel of prostate versus urothelial markers can be applied, including PSA, PSAP, prostein and/or NKX3.1 for prostate origin versus GATA3, 34βE12, and/or p63 for urothelial origin.

It is important to note that ductal carcinoma of the prostate (formerly referred to as endometrioid variant in reference to its columnar epithelial cell morphology) is a separate entity from what is diagnosed as intraductal carcinoma, despite having a similar name.[2]

Prostate Immunohistochemistry: Potential Pitfalls

As many laboratories utilize a prostate cocktail immunostain (usually including p63 and 34βE12 as basal cell markers and AMACR for staining of epithelial cells in HGPIN and/or carcinoma), it is worth briefly considering a few possible pitfalls in interpreting these stains. Stains useful in differentiating PCa from urothelial carcinoma are mentioned in the discussion of intraductal carcinoma above.

One consideration is the presence or absence of basal cells in focal areas of small glands. The basal cell layer may be incomplete or even only focally retained in foci of partial atrophy, adenosis, or in outpouchings of HGPIN. Careful scrutiny is required to determine whether the basal cell layer in focal small glands is truly lost or merely incomplete. All of these lesions may also show some degree of reactivity for AMACR. A diagnosis of focal glandular atypia or atypical small acinar proliferation may be warranted, if histologic and immunophenotypic features are not definitive for carcinoma. Nephrogenic adenoma, a mimicker of PCa in transurethral resection specimens, is negative for p63 and positive for AMACR; PAX8 can be used to differentiate nephrogenic adenoma (PAX8+) from PCa (PAX8-).

AMACR is not useful in diagnosis of metastatic PCa, as it is positive in a wide variety of tumor types. More specific prostate markers including PSA, PSAP, prostein and NKX3.1 are recommended instead.[19] Any collection of foamy-appearing cells in a lesional biopsy (e.g., bone lesion) from a man should be evaluated with prostate markers, as metastatic PCa often takes on a deceptively bland, foamy appearance in metastatic sites.

Conclusions

Significant changes to PCa grading and recommended reporting have occurred in the past several years, with the underlying motivation of facilitating tailored treatment based on accurately predicted prognosis. The recommended grade grouping is readily adopted, as it is based directly on Gleason grading. However, issues remain regarding diagnosis and quantification of high-grade patterns in particular. Pathologists continue to play an essential role in guiding care in PCa patients.

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Disclosure

None reported.

MM

Treatment of Advanced Prostate Cancer

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Gaps in our knowledge with respect to direct comparisons, combinations, and sequencing of these agents are currently being filled by numerous ongoing trials with the goals of improving both the quantity and quality of patients with prostate cancer.



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Abstract

Advanced prostate cancer is a heterogenous disease with multiple treatment options. Patients with advanced disease are stratified based evidence of metastasis and sensitivity to hormone therapy. Men with hormone sensitive disease are treated with androgen deprivation therapy and possibly chemotherapy. The treatment options for men with castrate resistant disease are rapidly evolving with multiple recently approved treatment options. Determining the proper sequence and combination of these therapies remains a work in progress.

Background

Patients with prostate cancer (PCa) may present with localized (80% of patients), locally advanced (10-15% or patients), or distant metastatic disease. Advanced PCa defined by the presence of disease outside of the prostate, regional lymph nodes or pelvis. Patients with advanced disease are considered incurable but highly treatable with excellent long-term survival compared to most advanced malignancies. Advanced disease may present de novo at initial presentation (approximately 4-5% of new diagnoses) or as progression following definitive therapy for localized disease.

PCa typically spreads through direct extension and hematogenously. Standard imaging consists of technetium bone scan and CT scans and should be considered in high risk patients (T1 with prostate-specific antigen [PSA] >20, T2 with PSA >10, T3-T4, Gleason >8 or symptoms). Additionally, newer imaging modalities allow for increased sensitivity in detecting metastasis.

Advanced PCa can be categorized into two main entities: biochemical recurrence (BCR) after local therapy without radiographic evidence of metastasis (M0) or with evidence of metastasis (M1). Stage M0 potentially encompasses patients with micrometastatic disease not detectable with conventional imaging techniques. Most patients will eventually develop measurable metastatic disease; this timeframe is variable but usually measured in years. Post-prostatectomy PSA should be undetectable at 6 weeks postop and PSA increases may signify incomplete resection or BCR (if initially undetectable). Post radiation therapy, BCR is typically defined by a >2.0 ng/mL rise in PSA above nadir. Several studies have pointed to improvements in metastasis-free survival with initiation of early treatment of BCR (usually defined as PSA <0.5 ng/mL). However, the superiority of adjuvant (after surgery in high risk patients) versus salvage (at time of

BCR) radiotherapy is still an open question, with several ongoing trials addressing this topic. The decision to initiate treatment is a shared decision with the patient, involving discussion of both the benefits of treatment along with the risks of side effects. Importantly, novel imaging techniques with higher sensitivities may reclassify some of these M0 patients to M1 disease status. Systemic treatment is commonly initiated for men with M1 disease. Here we briefly review current treatment modalities for men with advanced PCa.

Hormonal Therapy

Androgens are crucial for proliferation, differentiation, and spread of PCa cells.[1] Male androgens are produced predominantly in the testes (90%) with the remainder produced in the adrenal glands. The hypothalamic-pituitary axis (HPA) is the key regulator of androgen synthesis. Luteinizing hormone-releasing hormone (LHRH) is released in a pulsatile fashion from the pituitary gland and acts on the hypothalamus to release luteinizing hormone (LH). LH stimulates testosterone production in the testes with a negative feedback loop to limit testosterone production. Testosterone and the metabolite dihydrotestosterone (DHT) are required for prostate cell growth. Androgen deprivation results in an initial programmed cell death (apoptosis) in both normal and malignant prostate cells. The goal of systemic androgen deprivation therapy (ADT) for PCa is to suppress testosterone to castrate levels (<50 ng/dL). While the earliest described treatment—surgical castration—is cost effective and safe, the adverse psychologic consequences have generally limited the use of this method. LHRH analogues (i.e. antagonists or agonists) are the most frequently used method of ADT. LHRH agonists (e.g. leuprolide) hyperstimulate the pituitary gland resulting in excess LH and FSH production, with resultant pituitary desensitization over 3-4 weeks. Downstream LH and testicular androgen production then ceases. However, the initial LHRH receptor stimulation temporarily increases testosterone production that may result in tumor growth. This transient "flare" may result in worsened symptoms including urinary obstruction, increased pain, and/or cord compromise in patients with spinal metastases. Overlapping treatment with an antiandrogen will reduce this risk and should begin 7-14 days prior to a LHRH agonist administration, with continuation for typically 30 days. Continuing antiandrogen administration with an LHRH analogue (i.e. maximal or combined androgen blockade) is effective, with improved clinical outcomes and overall survival (OS) in multiple studies.

LHRH receptor antagonists (e.g. degarelix) directly compete with endogenous LHRH in the pituitary gland. This results in rapid reduction of testosterone levels without the testosterone flare risk and is equally clinically effective. Potential advantages include reduction of FSH/LH micro-surges, and decreased events in patient with cardiovascular comorbidities. All forms of ADT have similar side effects including fatigue, libido loss, cognitive effects, vasomotor symptoms, and metabolic effects.

Anti-Androgens

Anti-androgens are an additional method of hormone blockade. These therapies are used in combination with ADT and not approved for single agent use. First-generation anti-androgens include bicalutamide, flutamide and nilutamide.[2] These compete with testosterone/DHT at the androgen receptor (AR) leading to reduced signaling through the AR. Eventually PCa cells become resistant to these therapies through various mechanisms, including AR overexpression/amplification, mutations in ligand binding domains leading to constitutive signaling, and additional signaling pathways (e.g. glucocorticoid receptor, HGF/c-MET, etc.). Anti-androgen withdrawal can be an effective hormonal maneuver in which the anti-androgen is held for 4-6 weeks, although PSA responses occur in 10-15% of patients. Switching between first-generation anti-androgens may improve responses, however. Second-generation anti-androgens (e.g. enzalutamide, apalutamide/ARN-509) have been developed to combat this resistance. In addition to blockade of the AR, they additionally inhibit AR nuclear translocation, and association of AR with DNA. Enzalutamide is approved in the metastatic setting both before and after docetaxel use, while apalutamide is currently undergoing clinical trials.

Androgen Biosynthesis Inhibitors

Decreasing androgen biosynthesis is an additional tool used to block adrenal and intra-tumoral androgen synthesis. CYP17 is a key enzyme required for androgen synthesis and has been shown to be involved in the development of intra-tumoral androgen expression.[3] Ketoconazole (in combination with hydrocortisone) is a non-specific CYP17 inhibitor and has been used

extensively as a therapy in refractory PCa therapy. However, with side effects (e.g. fatal hepatoxicity, gastrointestinal symptoms), poor efficacy, and newer agents it now has a limited role in PCa treatment. Other therapies include estrogens, glucocorticoids, diethylstilbestrol (DES), all of which are rarely used due to availability of more effective therapies. Abiraterone, a selective CYP17 inhibitor, is approved in metastatic PCa in both the pre- and post-docetaxel settings. Typical side effects include electrolyte disturbances, fluid retention, adrenal insufficiency, and rarely hepatotoxicity.

Hormone Sensitive Advanced PCa After Prior Local Therapy

Patients treated with prior local therapy may have relapsed disease. The first step is to assess the disease burden. Asymptomatic patients with a rising PSA and no evidence of radiographic metastasis are said to have BCR. Asymptomatic men may initially be observed, as toxicity of systemic ADT may outweigh benefits depending on a variety of factors (e.g. comorbidities, performance status [PS], disease extent, etc.) and incorporating estimated life expectancy. Patients with oligometastatic disease recurrence may be considered for metastatectomy or radiation therapy (RT) to sites of disease.[4] This may be associated with a survival benefit and role for these therapies continues to be evaluated. Most men with radiographic evidence of disease will need ADT. Whether ADT should be indefinite or intermittent remains an open question.[5] Non-inferiority studies did not reach statistical significance but were associated with a better quality of life (QOL). However, the consensus remains that patients with high risk/high volume disease (typically defined as ≥4 bony sites or any visceral disease) are more likely to benefit from continuous ADT.

Hormone Therapy for Disseminated PCa

Metastatic PCa is currently not curative, but most patients will have significant initial responses to therapy. Upfront ADT has been the standard of care for treatment naïve PCa, based on Huggins and Hodges seminal work in 1941. Patients with symptomatic disease or metastasis at high risk sites (i.e. spinal cord, visceral disease) should be treated promptly; symptoms from metastatic PCa can rapidly resolve within days to weeks if responsive to initial ADT, and thus it is important to consider this when evaluating PS and treatment decisions. The addition of a continuous anti-androgen to an LHRH analogue has been extensively studied, and meta-analyses have shown a small but significant benefit of combined androgen blockade.[6,7] However, there is currently no recommendation for or against combined androgen blockade in this setting.[8]

Chemohormonal Therapy

More recently large clinical trials have demonstrated benefits of early initiation of chemotherapy concomitantly with ADT (chemohormonal therapy). Two major clinical trials, CHAARTED[9] and STAMPEDE[10] have evaluated the early use of docetaxel in hormone-sensitive PCa. The CHAARTED trial randomized 790 men with previously untreated metastatic PCa to ADT versus ADT with docetaxel (75 mg/m^2 every 3 weeks) for 6 cycles with a primary end point of OS. The primary endpoint was met with an OS benefit (57.6 vs. 44.0 months, HR 0.61) in the docetaxel arm. This study was stratified by disease burden (high versus low volume) with high volume disease defined by visceral metastasis and/or ≥ 4 bone metastases. The OS benefit was predominantly seen in the high-volume disease group (49.2 vs 32.2 months, HR 0.60, $p=0.0012$). The chemotherapy group was associated with a higher rate of fatigue, neutropenic fever but overall was well tolerated by most men. An OS benefit of 10 months (81 versus 71) was also seen in the STAMPEDE trial with the addition of chemotherapy to ADT. Based on this evidence, patients with high volume, newly diagnosed or recurrent hormone therapy naïve metastatic PCa with adequate PS and organ function should be considered for chemohormonal therapy; this is widely accepted as the new standard of care therapy for these patients. The role of chemohormonal therapy for patients with N0/1 and M0 disease is still being evaluated as the risk/benefit ratio in low volume disease patients is less clear.

Castrate Resistant PCa

PCa that grows despite castrate levels of testosterone (< 50 ng/dL) is classified as castrate resistant (CRPC). This progression can present as increasing PSA, new metastasis, or progression of existing metastatic disease sites. There are multiple proposed mechanisms of resistance, including overexpression or activation of AR, de novo synthesis of androgens within the tumor, or non-androgen driven

growth pathways. Several therapies have been recently Federal Drug Administration (FDA) approved that are effective at treating CRPC.

Anti-Androgens in CRPC

The addition of antiandrogens to ADT is associated with improved disease control and OS benefit in CRPC. Recent data has shown the superiority of the second-generation enzalutamide to first-generation bicalutamide. The STRIVE Trial was a double-blind, phase II study of 396 men with both metastatic and non-metastatic CRPC comparing enzalutamide versus bicalutamide in combination with ADT.[11] Enzalutamide reduced the risk of progression or death by 76% (hazard ratio 0.24, 95% CI 0.18 to 0.32, $p < .001$) with a median progression-free survival (PFS) of 19.4 versus 5.7 months, compared to the bicalutamide arm. These data, amongst others, suggest that use of enzalutamide should be favored over first-generation antiandrogens in the setting of CRPC. However, the use of enzalutamide in this setting has not yet been FDA approved, nor incorporated into the National Comprehensive Cancer Network (NCCN) guidelines as standard practice. In other studies of mCRPC, the use of enzalutamide was evaluated both before and after taxane-based chemotherapy. Enzalutamide was first demonstrated to be beneficial after taxane-based chemotherapy. The AFFIRM study included 1,199 men with metastatic CRPC (mCRPC) previously treated with 1-2 chemotherapy regimens who were then randomly assigned (2:1) to enzalutamide vs placebo.[12] Treatment with enzalutamide was associated with a 4.8 month benefit in OS (18.4 vs. 13.6 months, HR 0.63, $p<0.001$) and improved QOL (43% vs. 18%, $p<0.001$). The drug was overall well tolerated but was associated with fatigue, diarrhea, and rarely seizures. In the PREVAIL trial, chemotherapy-naïve mCRPC patients were randomized to enzalutamide vs placebo. Men receiving enzalutamide had improved radiographic PFS at 12 months (65% vs. 14%, HR 0.19, $p < 0.001$), 29% risk reduction for death (72% vs. 63%, HR 0.71, $p < 0.001$), and delayed chemotherapy by 17 months with estimated median OS at 32.4 months and 30.2 months for enzalutamide and placebo, respectively.[13] Side effects were more common in the enzalutamide group including fatigue, constipation, and arthralgia. Most recently, apalutamide was approved for use by the FDA in men with non-metastatic CRPC. In a randomized, placebo controlled Phase III trial (the SPARTAN trial), treatment with apalutamide resulted in an over 2 year delay in the development of metastatic disease. Treatment was well tolerated, and there was a trend- albeit non-significant- towards improvement in OS in the setting of still maturing data and follow up.

Androgen Biosynthesis Inhibitors in CRPC

The development of selective CYP17 inhibitors has largely replaced older agents. Abiraterone is the only FDA approved selective CYP17 inhibitor and has been evaluated and approved in both the pre- and post-chemotherapy mCRPC setting. In the COU-AA-301 trial, 1195 men with mCRPC who received prior docetaxel chemotherapy were randomized (2:1) to abiraterone 1000 mg plus prednisone (5 mg twice daily) versus placebo plus prednisone.[14] The primary end point was met with a 3.9 month OS improvement (14.8 vs. 10.9 months, HR 0.65, $p<0.001$). Improvements in PSA progression (10.2 vs. 6.6 months) and PFS (5.6 vs. 3.6 months) were also noted. Abiraterone has also been shown to be effective prior to chemotherapy. In the COU-AA-302 trial, 1088 chemotherapy-naïve mCRPC patients were randomized (1:1) to receive abiraterone or placebo, both with prednisone. Treatment with abiraterone was associated with an improvement in median OS (not reached vs 27.2 months, HR 0.42, $p<.001$) with an improvement in PFS as well.[15] A longer term follow-up study confirmed the OS improvement (34.7 vs 30.3 months, HR 0.81, $p=0.0033$).[16] The side effect profile was similar in both studies with notable adverse events occurring in the abiraterone group including fluid retention, hypertension, electrolyte and liver enzyme abnormalities.

Cytotoxic Chemotherapy for Metastatic PCa

Cytotoxic chemotherapy plays an important role in the management of metastatic PCa. There are three FDA approved chemotherapies: mitoxantrone, docetaxel, and cabazitaxel. Mitoxantrone is a synthetic anthracenedione that inhibits DNA topoisomerase II, and was the first chemotherapy approved in advanced PCa. Mitoxantrone in combination with hydrocortisone was compared to hydrocortisone alone in the CALGB 9182 trial; approval was based on improvements in QOL and bone pain.[17] However, mitoxantrone failed to demonstrate an OS advantage, with median OS 12.3 versus 12.6 months compared with hydrocortisone alone. Largely due to

newer approved agents that carry improvements in OS, mitoxantrone use in PCa has declined over the last decade.

Docetaxel is a semi-synthetic taxane, and is the most commonly used chemotherapy in PCa. The approval of docetaxel in advanced PCa was originally based on a significant survival benefit compared with mitxanterone.[18] The TAX-327 trial randomized 1006 men (1:1:1) to docetaxel 75 mg/m^2 every 3 weeks, docetaxel 30 mg/m^2 weekly (5 of 6 weeks), or mitoxantrone 12 mg/m^2 every 3 weeks. Docetaxel showed improved outcomes with median OS of 18.9 months (every 3 weeks) versus 17.4 months (weekly) versus 16.5 months in the mitoxantrone group. Docetaxel was also associated with an improvement in QOL. Side effects were similar to mitoxantrone, but docetaxel was associated with higher frequency of neutropenia and neutropenic fever.

Cabazitaxel is a second-generation taxane chemotherapy developed to overcome resistance in patients previously treated with docetaxel. In the TROPIC trial, cabazitaxel was shown to have an OS benefit (15.1 vs. 12.7 months) in comparison to mitoxantrone in mCRPC patients who progressed after docetaxel.[14] However, there were increased rates of neutropenia (82% vs 58%), neutropenic fever (8% vs 1%) and hypersensitivity reactions in the cabazitaxel arm.

Radiation Therapy in Metastatic CRPC

Approximately 90% of advanced PCa patients will develop bone metastases. Radiation therapy is an important therapeutic option for of bone disease. Patients with isolated, painful bone lesions may be treated with palliative external beam radiation. Additionally, oligometastatic disease may be treated to slow progression. Systemically administered, bone targeted radiopharmaceuticals can be used for control of bone predominant disease. Radium-223 is an alpha particle emitting agent approved for the treatment of mCRPC patients with symptomatic bone lesions, without visceral disease. Patients in the ALSYMPCA trial receiving radium-223 (vs. placebo) had an improvement in OS (14.9 vs. 11.3 months) as well as significant improvements in skeletal- and pain-related outcomes.[20] Treatment with radium-223 alone has been shown effective in comparison to placebo; however, there are several ongoing studies investigating combinations with other approved agents in mCRPC.

Immunotherapy in Metastatic CRPC

Immunotherapy aims to augment the immune response against progressing cancers. Sipuleucel-T is an FDA-approved autologous dendritic cell vaccine that acts by enhancing T-cell responses. Treatment with sipuleucel-T (n=341) produced a significant improvement in OS (median 25.8 vs. 21.7 mos, HR 0.78, p=0.032) compared with a similar leukocyte product placebo (n=171); however, there was no significant improvement in PFS, and only 2.6% of patients in the sipuleucel-T arm had PSA declines of ≥50%.[21] Prostvac is a PSA/vaccinia-based vaccine currently being evaluated, with impressive improvements in OS in phase II trials. Unfortunately, the registration Phase III trial was recently reported to be negative. However, there are several ongoing trials of Prostvac in combination with checkpoint inhibitors. . Ipilimumab (anti-CTLA-4 monoclonal antibody) has been evaluated in two recently reported Phase III studies in mCRPC patients. While there was minimal improvement in OS with borderline significance (p=0.052) in the first reported trial in post-chemotherapy patients receiving radiation,[22] a second trial in pre-chemotherapy trials was also unfortunately negative.[23] Combination studies with ipilimumab, as well as other checkpoint inhibitors (e.g. anti-PD-1, anti-PD-L1) are actively being evaluated in the mCRPC setting.

Supportive Care

A key aspect of the management of advanced PCa is adequate supportive measures. Men with PCa can develop symptoms from metastatic disease sites (pain, fractures), from prior therapies (incontinence, impotence, radiation proctitis), and from current therapies. Controlling these symptoms is paramount to ensuring good QOL in the setting of incurable disease.

Management of complications of bone metastases is important. Those with pain should be prescribed sufficient analgesic medications, to ensure relief of cancer related symptoms. Systemic therapies may help with symptoms in newly diagnosed patients. Bone strengthening agents used in metastatic PCa consist of

bisphosphonates (e.g. zoledronic acid) and osteoclast inhibitors (e.g. denosumab), and can significantly reduce the rates of skeletal related events. The use of bone strengthening agents in patients with hormone sensitive PCa, however, has not been demonstrated to reduce pain, time to first skeletal related events, or survival. In patients with osteopenia on ADT, denosumab should be considered to prevent progression of bone mineral density loss.[24,25]

Conclusions

Since the approval of docetaxel in 2004, the available therapies that improve survival and QOL for patients with advanced PCa have rapidly expanded. Novel AR-targeted therapies, chemotherapies, and immunotherapies are promising areas of research and will continue to be evaluated. Gaps in our knowledge with respect to direct comparisons, combinations, and sequencing of these agents are currently being filled by numerous ongoing trials with the goals of improving both the quantity and quality of patients with PCa.

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Disclosure

None reported. **MM**

Prevalence of Tick-Borne Pathogens in Northeast Missouri

by Deborah A. Hudman, MS & Neil J. Sargentini, PhD†

Future studies on management techniques and their influence on reducing either number of ticks or pathogen prevalence is desirable.



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Abstract

We evaluated *Amblyomma americanum* (lone star tick) and *Dermacentor variabilis* (American dog tick) in northeast Missouri for the presence of *Borrelia*, *Ehrlichia*, and *Rickettsia* bacteria and Heartland virus. We screened 436 individual adult lone star ticks (86% of all ticks collected) and infection rates were 6% for *B. lonestari*, 19% for *E. chaffeensis*, 3% for *E. ewingii*, 36% for *R. amblyommatis,* and 1% for *R. montanensis*. In the 189 individual American dog ticks, infection rates were 19% for *E. chaffeensis*, 15% for *E. ewingii*, 4% for *R. amblyommatis*, and 5% for *R. montanensis*. In addition, we screened 20 pools of adults and 30 pools of nymphs for the Heartland virus which was not detected. Understanding the presence and epidemiology of these causative (*E. chaffeensis* and *E. ewingii*) and suspected (*B. lonestari, R. amblyommatis, and R. montanensis*) agents in Missouri should increase awareness of potential tick-borne disease in the medical community.

Introduction

Ticks are vectors for a variety of microorganisms, many of which are known agents of zoonotic disease. Missouri tick species are capable of transmitting pathogens such as Rocky Mountain spotted fever (RMSF), ehrlichiosis, tularemia, southern tick associated rash illness (STARI), Heartland virus, and Bourbon virus.[1] Tick populations and associated pathogens can vary greatly across landscapes so understanding local tick population dynamics could provide valuable insight into potential threats to public health. In 2014, we surveyed four state owned conservation areas in Adair County, Missouri for ticks and evaluated 308 pools for the presence/absence of *Borrelia*, *Ehrlichia*, and *Rickettsia* bacteria.[2] In 2015, we expanded on those initial findings and attained true infection rates in adult *Amblyomma americanum* (Linnaeus, 1758), and *Dermacentor variabilis* (Say, 1821) ticks, as opposed to estimates of pooled samples, and expanded our surveillance to include the Heartland virus. We also investigated how managed vs unmanaged sites affected both the presence of ticks and their pathogens. The data collected from this study provides insight to

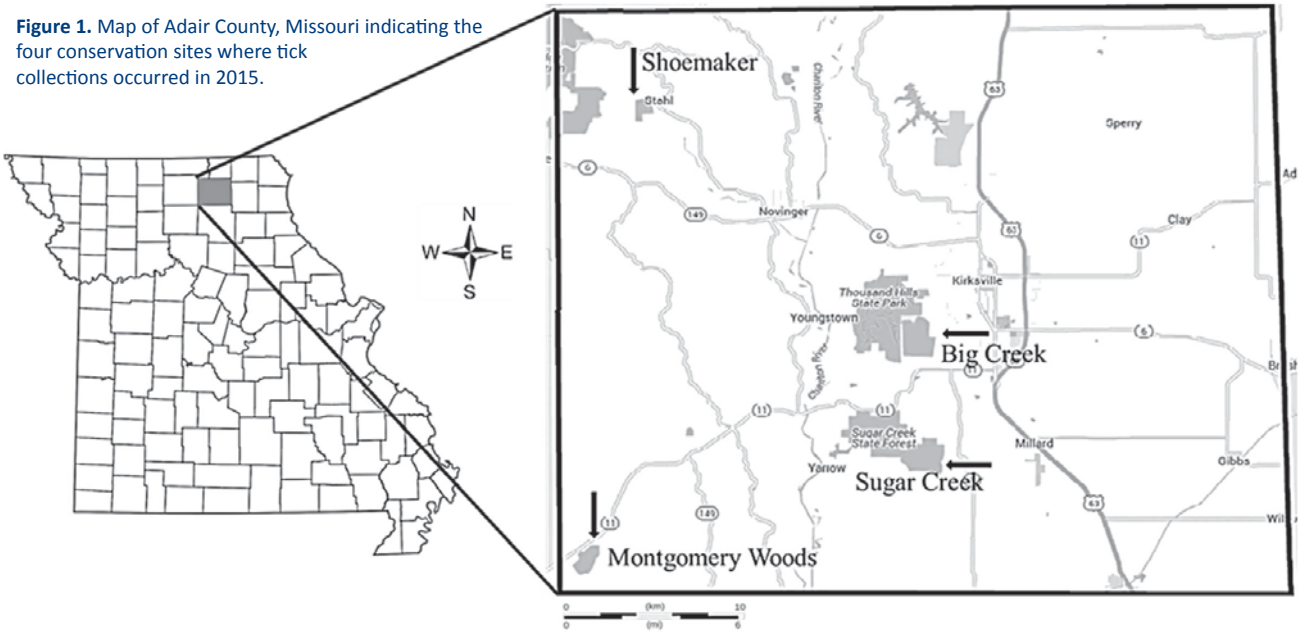


Figure 1. Map of Adair County, Missouri indicating the four conservation sites where tick collections occurred in 2015.

the potential effect of land management practices on associated tick populations and their pathogens and thus the risk of potential disease transmission.

Materials and Methods

Tick Collections

In 2015, ticks were collected from April through September at four conservation areas in Adair County, Missouri with the exception of June, due to heavy rains (Figure 1). Each collection site was sampled once per month for 5 months for a total of 20 collection days. Questing ticks were collected using a cloth drag-flag method and by removing ticks from the collector's clothing.[3] Ticks were stored in 70% ethanol until analyses. All collected ticks were identified morphologically to the species using a dissecting microscope and appropriate taxonomic keys.[4-5] Ticks were pooled according to collection site, species, developmental stage, and sex if adults. Two of these conservation areas are managed sites (Big Creek and Sugar Creek). Big Creek is managed through food plots, burning, and mowing while Sugar Creek is managed by thin and release timber prescription and mowing. The other two sites (Shoemaker and Montgomery Woods) have been unmanaged for the last ten years (Y. Amerman and B. Kelso, pers. comm.).

RNA Extraction

Twenty adult pools (5 adults/pool, n=100) and 30 nymph pools (25 nymphs/pool, n=750) had their total RNA and DNA extracted via BlackPREP tick DNA/RNA kit (Analytikjena, Jena, Germany) according to the manufacturer's instructions. All RNA lysate was stored at -80°C until analysis by quantitative real-time polymerase chain reaction (qPCR), but DNA lysate was stored at -20°C until polymerase chain reaction (PCR) analysis.

DNA Extraction. Individual adult ticks (n=625) had only their DNA extracted. An entire tick was removed from ethanol, allowed to dry, and placed in a 1.5-ml RINO screw cap tube (Next Advance, Averill Park, NY) containing 125 μl of DNAzol Genomic DNA Isolation reagent (Molecular Research Center, Inc., Cincinnati, OH) and Proteinase K (Ambion, Austin, TX) at 0.1 mg/ml. Following overnight incubation at room temperature, 150 mg of 2.0 mm zirconium oxide beads (Glenn Mills, Inc., Clifton, NJ) were placed in each RINO tube and homogenized using a Bullet Blender Storm (Next Advance, Averill Park, NY) at speed 12 for 3 minutes. The tick homogenate was then incubated at room temperature for 3 h, heated at 95°C for 10 min, and centrifuged at 10,000 x g for 10 min at room temperature as described.[6] To verify

Table 1. Numbers and Life Stages of Tick Species Collected from Four Conservation Areas in Adair County, Missouri, 2015

Location	*Amblyomma americanum* (n=1,235)			*Dermacentor variabilis* (n=206)	
	Females	Males	Nymphs	Females	Males
Big Creek	33	36	78	19	25
Montgomery Woods	93	119	152	13	30
Sugar Creek	61	70	198	9	10
Shoemaker	75	34	286	39	61
Total	262	259	714	80	126

the quantity and quality of DNA extraction, 260/280 and 260/230 nm absorbance ratios were determined using a spectrophotometer (NanoDrop®ND-2000c, ThermoScientific, Wilmington, DE) according to manufacturer's instructions.

Quantitative Real Time Polymerase Chain Reaction (qPCR)

Sequence information for HRTV primer-probe sets 1 and 4 which were used for virus detection and confirmation along with cycle conditions are as described.[7] Heartland virus strain MO4 RNA lysate (positive control) and two negative controls, one tube with no RNA and the other with no reverse transcriptase was run concurrently with the 50 pooled samples.

Polymerase Chain Reaction (PCR)

PCR-based assays were used to amplify and identify bacterial DNA within individual and pooled tick samples. PCR reactions of 25 μl contained 1.0 μM of each primer (Fisher Scientific, Pittsburgh, PA), 10 mM of each dNTP, 10 mM Tris-HCl (pH 9.0), 50 mM KCl, 1.5 mM $MgCl_2$, 1.25 U of *Taq* DNA Polymerase (Fisher Scientific, Pittsburgh, PA), and 100 ng of extracted DNA from pooled ticks. With every PCR assay, a positive and negative control was included. Negative controls consisted of water in place of DNA and positive controls consisted of known DNA samples: *Borrelia* (KPL, Gaithesburg, MD), *Ehrlichia*, and *Rickettsia* (CDC, Atlanta, GA). PCR reactants were kept on ice until transferred to a thermal cycler (T100 BioRad, Hercules, CA).

All samples of extracted DNA were tested for the presence of *Borrelia* and *Ehrlichia* species by nested PCR. The initial genus-wide PCR assays were used to amplify a segment of the *flaB* gene for *Borrelia* spp. and the 16S rRNA fragment for *Ehrlichia* spp.[8-11] The nested PCR assays used unique primers to amplify a secondary target within the initial PCR product to ensure specificity. Samples still positive for *Borrelia* spp. after the initial nested PCR were subjected to a separate nested PCR for the 16S-23S rRNA intergenic spacer region.[12] The second nested PCR was done because it is still unclear to what extent the flagellin gene is able to differentiate between closely related *Borrelia* species when sequenced. Isolated DNA was examined for the presence of *Rickettsia* spp. by amplifying a segment of the citrate synthase gene.[13] All tick DNA samples that tested positive for presence of the *gltA* gene were also tested for presence of the *rOmpA* gene.[13] *Rickettsia* DNA samples that remained positive were digested with *PstI* (Promega, Madison, WI) for restriction fragment length polymorphism analysis as described.[14-15]

DNA extractions and PCR were performed in different rooms on different days. Certified DNA/RNase-free filter barrier tips were used to prevent aerosol contamination. Also, representative positive

Table 2. The presence of *Borrelia*, *Ehrlichia* and *Rickettsia* spp. in individual adult *Amblyomma americanum* and *Dermacentor variabilis* in Northeast Missouri

Amblyomma americanum (n=436)					
Site	*B. lonestari*	*E. chaffeensis*	*E. ewingii*	*R. amblyommatis*	*R. montanensis*
Big creek (n=49)	3 (6%)	18 (37%)	0	14 (29%)	4 (8%)
Mont. woods (n=192)	16 (8%)	38 (20%)	4 (2%)	73 (38%)	0
Sugar creek (n=111)	1 (1%)	17 (15%)	2 (2%)	47 (42%)	1 (1%)
Shoemaker (n=84)	6 (7%)	11 (13%)	5 (6%)	24 (29%)	1 (1%)
Total	26 (6%)	84 (19%)	11 (3%)	158 (36%)	6 (1%)
Dermacentor variablilis (n=189)					
Site	*B. lonestari*	*E. chaffeensis*	*E. ewingii*	*R. amblyommatis*	*R. montanensis*
Big creek (n=44)	0	8 (18%)	12 (27%)	2 (5%)	1 (2%)
Mont. woods (n=43)	0	14 (33%)	5 (12%)	4 (9%)	0
Sugar creek (n=19)	0	3 (16%)	0	1 (5%)	3 (16%)
Shoemaker (n=83)	0	10 (12%)	11 (13%)	2 (2%)	3 (4%)
Total	0	35 (19%)	28 (15%)	9 (5%)	7 (4%)

PCR products were purified and bidirectionally sequenced by an outside source (Macrogen, Rockville, MD) using both the forward and reverse primers to establish and confirm identity. Nucleotide sequences were analyzed using Nucleotide Basic Local Alignment Search Tool (BLASTN) available online at the National Center for Biotechnology Information (NCBI).

Infection rates in tick pools were calculated using the Maximum Likelihood Estimation (MLE) with 95% confidence interval (CI) for unequal pool sizes and expressed as the MLE of infection rate per 100 ticks. The MLE was calculated using the PooledInfRate, ver. 4.0 add-on to Microsoft Excel.[16]

Results

Amblyomma americanum (lone star tick) comprised 86% of all collected ticks, while *Dermacentor variabilis* (American dog tick) comprised 14% (Table 1). *Ixodes scapularis*, the blacklegged tick, was present but in such low numbers that we did not analyze further. In the 436 individual adult lone star ticks screened, infection rates were 6% for *B. lonestari*, 19% for *E. chaffeensis*, 3% for *E. ewingii*, 36% for *R. amblyommatis,* and 1% for *R. montanensis* (Table 2). In the 16 adult lone star pools, infection rates were 1.3% (CI 0.1-6) for *E. chaffeensis,* 1.3% (CI 0.1-6) for *E. ewingii*, and 27% (CI 15.7-44.6) for *R. amblyommatis* (data not shown). In the 189 individual adult American dog ticks screened, infection rates were 19% for *E. chaffeensis*, 15% for *E. ewingii*, 5% for *R. amblyommatis*, and 4% for *R. montanensis* (Table 2). In the four American dog tick pools, infection rate was 5% (CI 0.3-23.5) for *E. chaffeensis* and no other bacterial species were detected (data not shown). Infection rates for the 30 nymph lone star pools were calculated as *B. lonestari* (0.3%, CI 0.1-0.9), *E. chaffeensis* (2.4%, CI 1.4-4.0), *E. ewingii* (0.3%, CI 0.1-0.9), and *R. amblyommatis* (3.5%, CI 2.2-5.6) (data not shown).

Table 3. Comparing the presence of *Borrelia*, *Ehrlichia* and *Rickettsia* spp. in managed vs unmanaged conservation areas in Northeast Missouri in individual adult ticks

Amblyomma americanum (n=436)					
Site	*B. lonestari*	*E. chaffeensis*	*E. ewingii*	*R. amblyommatis*	*R. montanensis*
Managed (n=160)	4 (3%)	35 (22%)	2 (1%)	61 (38%)	5 (3%)
Unmanaged (n=276)	22 (8%)	49 (18%)	9 (3%)	97 (35%)	1 (0.04%)
Dermacentor variablilis (n=189)					
Site	*B. lonestari*	*E. chaffeensis*	*E. ewingii*	*R. amblyommatis*	*R. montanensis*
Managed (n=63)	0	11 (17%)	12 (19%)	3 (5%)	4 (6%)
Unmanaged (n=126)	0	24 (19%)	16 (13%)	6 (5%)	3 (2%)
Total of both species (n=625)					
Site	*B. lonestari*	*E. chaffeensis*	*E. ewingii*	*R. amblyommatis*	*R. montanensis*
Managed (n=223)	4 (2%)	46 (21%)	14 (6%)	64 (29%)	9 (4%)
Unmanaged (n=402)	22 (5%)	73 (18%)	25 (6%)	103 (26%)	4 (1%)

Both species of tick were most frequently encountered in unmanaged sites vs managed sites (Table 3). Unmanaged sites had similar prevalence of pathogens in ticks collected compared to managed sites with the exception of *B. lonestari*, which was more prevalent in unmanaged sites (Table 3). All four collection sites had *B. lonestari* infections present with the highest prevalence being detected at Montgomery Woods (Table 2). *Borrelia lonestari* infections were present in both adult and nymph lone star ticks, however, none were detected in the American dog ticks. Nine samples positive for *Borrelia lonestari* were sequenced and all nine samples were 99 - 100% identical to *B. lonestari* (GenBank accession number AY363709.1).

Ehrlichia infections were present at all four collection sites and all life stages of ticks collected. *E. chaffeensis* infection in adult lone star ticks was most prevalent in Big Creek (Table 2). In American dog ticks *E. chaffeensis* was the most prevalent bacteria species detected. Six positive samples for *E. chaffeensis* were sequenced and four were 99% identical while the other two were 100% identical to *E. chaffeensis* (strain West Paces; GenBank accession number CP007480.1). *Ehrlichia ewingii* was less prevalent in tick populations when compared to *E. chaffeensis*. Three samples positive for *E. ewingii* were sequenced and all three samples were 99% identical to *E. ewingii* Panola Mtn. (GenBank accession number DQ365880.1).

All four sites had *Rickettsia amblyommatis* present (Table 2). Prevalence of *R. amblyommatis* was higher than any other bacteria species detected in the lone star tick. Three *R. amblyommatis* positive samples were 100% identical to *R. amblyommatis* (GenBank accession number CP015012.1). *Rickettsia montanensis* was not detected in Montgomery Woods and was more commonly detected in managed sites. Two positive samples for *R. montanensis* were sequenced and found 99% identical to *R. montanensis* (strain Montana; GenBank accession number U55823.1).

Discussion

Screening for potential pathogens in Adair County has provided insight into the distribution of tick species and the pathogens they may carry. Because tick populations and associated pathogens can vary, a better understanding of the pathogens carried by ticks in a given geographic area can alert health care providers of specific health risks leading to better diagnosis and treatments.

Borrelia lonestari is a putative agent of STARI and we detected a 6% infection rate in adult lone star ticks. Other studies have reported a 1 - 3% prevalence of lone star ticks containing the spirochete *B. lonestari* which is slightly lower than our findings.[9,17] It is important to note, that no *Borrelia* species in lone star ticks have been confirmed to be pathogenic to humans.[18] Lone star ticks have been shown repeatedly unable to vector *B. burgdorferi*, the etiological agent of Lyme disease, and is thus not considered a viable host to this well-known tick-borne disease.[19]

Ehrlichia chaffeensis and *E. ewingii* are causative agents for human ehrlichiosis and are the only known pathogens detected in our study. Lone star ticks are the primary vector of both these bacteria in the United States. Typical symptoms include fever, headache, fatigue, and muscle aches but this disease can be fatal. Previous reports of prevalence of *Ehrlichia* spp. in Southwest Missouri range from 3-10% infection rate.[20] Other endemic states have reported prevalences ranging from 2-18%.[17, 21-22] Our data reports on the high end of prevalence which may be a local phenomenon or an increase of infection over time. The overall rate of reported ehrlichiosis in the United States has increased 4-fold since 2000.[23] Missouri has the second highest reported incidence rate of *E. chaffeensis* following Oklahoma and tied for the highest incidence rate of *E. ewingii*.[23]

For both years, no *R. rickettsii*, the agent of Rocky Mountain Spotted Fever (RMSF), was detected. *Rickettsia amblyommatis* has been implicated as a cause of RMSF-like disease in humans and has been associated with a rash following a lone star tick bite.[24-25] Reports of RMSF disease occur in Adair County, so either we are just simply not collecting enough ticks to detect *R. rickettsii* or this data is further evidence that where lone star ticks are the predominant tick species perhaps *R. amblyommatis* can cause a RMSF-like disease.[26] *Rickettsia montanensis* is another bacteria within the spotted fever group (SFG) rickettsia that may also cause mild RMSF-like disease.[27] If *R. montanensis* can cause a rash then it is very likely that it could lead to misdiagnosis because rickettsial serologic assays are not able to distinguish between species of the SFG.[28-29] Further evidence is needed to confirm if either *R. amblyommatis* or *R. montanensis* is of any medical concern.

No Heartland virus was detected in our survey. We are not yet confident to state that the virus is not present in the area as it has been found at very low prevalence in northwestern Missouri.[7] Savage et al. report infection rates of one per 585 nymphs and 1 per 1,000 adults and we tested a total of 750 nymphs and 100 adults for the virus. More testing would need to be done to confirm absence or presence of virus.

In comparing managed sites (Big Creek and Sugar Creek) with unmanaged sites (Shoemaker and Montgomery Woods) the number of ticks was nearly double in the unmanaged sites. With the prevalence of tick-borne pathogens being more or less similar between managed vs unmanaged sites, the fact that tick numbers are nearly double in non-managed sites makes an argument that some form of management can reduce the risk of potential disease transmission. Future studies on management techniques and their influence on reducing either number of ticks or pathogen prevalence is desirable.

Acknowledgments

We thank William L. Nicholson, who provided *Ehrlichia* and *Rickettsia* DNA to use as positive controls, Brandy Russell, who provided the Heartland virus lysate as a positive control, Priscilla L. Phillips for the use of her real-time PCR machine and expertise, Matt Combes and Ryan Jones for reviewing the manuscript, the Missouri Department of Conservation for allowing us to collect on their properties, and the ATSU Warner-Fermaturo Fund/KCOM Board of Trustees Research Fund for financial support.

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Disclosure

None reported.

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Sleep Medicine Single Series

Sleep Medicine: Parasomnias

by Pradeep C. Bollu, MD, Munish K Goyal, MD, Mahesh M. Thakkar, PhD & Pradeep Sahota, MD

It is important for the sleep physician to understand the nature of the parasomnia and to differentiate it from nocturnal seizures.





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Abstract

Parasomnias are abnormal and undesirable behaviors during sleep and are thought to be due to the sleep state instability. Some of them are benign, while some of them point to a possible underlying neurodegenerative process. This article briefly discusses the clinical characteristics, demographics, and pathophysiology of major parasomnias and associated disorders. The classification outlined in this article conforms to the current version of International Classification of Sleep disorders.

Abbreviations

NREM: Non-Rapid Eye Movement; REM: Rapid Eye Movement; ICSD: International Classification of Sleep Disorders -3; SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin Nor-epinephrine Reuptake inhibitors, MAOI: Monoamine Oxidase Inhibitors; EMG: Electromyography

Introduction

The word parasomnia is derived from the Greek prefix '*Para*' (meaning alongside of) and the Latin noun '*Somnus*' (meaning sleep). In clinical terms, parasomnia refers to an abnormal or unusual behavior during sleep. Parasomnias encompass a broad spectrum of events including abnormal motor, behavioral, and sensory experiences. Excessive motor activity and abnormal motor behaviors, when present, adversely affect the patient or the bed partner resulting in sleep fragmentation, psychosocial effects, and even injuries.

In general, most parasomnias are more common in children and become less prevalent as they get older. Approximately 4% of adult population have been reported to have parasomnias.[1] Parasomnias are also more frequent in psychiatric disorders.[2] Other risk factors include sleep disorders, medical comorbidities and substance abuse.

Parasomnias are mainly categorized based on the sleep state in which they are observed. The 'Other Parasomnias' in the ICSD-third edition are sleep state independent.

Pathophysiology

The three states of human behavior are Wakefulness, NREM sleep and REM sleep, and are previously thought to be mutually exclusive. NREM sleep in turn is divided into three stages (N1, N2, and N3) Transitions from one behavioral state to another is not a quick switch but involves reorganization and transition of various neural centers before a specific state manifests unequivocally. Recent research has shown that combinations of one or more of these states can result in unstable states, and an arousal out of these unstable states can give rise to abnormal behaviors manifesting as parasomnias.[3,4] It is

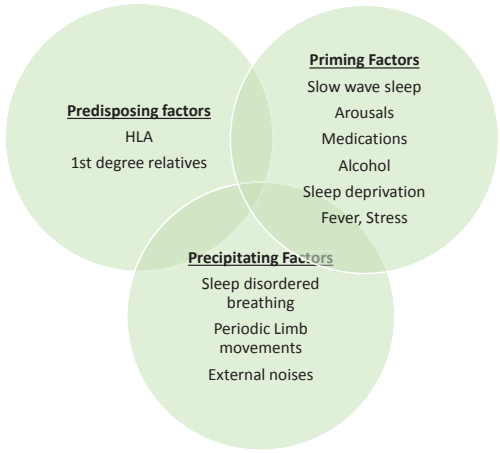


Figure 1. Model for the pathogenesis of Parasomnias.

also suggested that deafferentation of locomotor centers in the spinal and at supraspinal levels, from the generators of different sleep states may result in motor activity in the setting of arousals.[5]

Most of the NREM parasomnias arise out of N3 NREM sleep. Any condition that promotes NREM sleep fragmentation (such as pain conditions, restless legs syndrome, periodic limb movements, sleep-related breathing disorders, etc.) increase the risk of parasomnias. Also, conditions of increased sleep drive including sleep deprivation and sedative medications are risk factors for parasomnias. Certain HLA haplotypes like HLA DQ B1*05:01 and HLA DQ B1*04 are considered risk factors for the development of parasomnias. First-degree relatives of patients with parasomnias have a higher prevalence of similar parasomnias. (Figure 1)

NREM Parasomnias

The common feature of these parasomnias is recurrent episodes of incomplete awakening from NREM sleep along with amnesia for the event. Clinical phenotypes of this incomplete arousal from NREM sleep include sleepwalking, sleep terrors, confusional arousals, and sleep-related eating disorder. They usually arise out of slow wave sleep but can also arise from N2 sleep and are more frequent in the first half of the night. These parasomnias are more frequently seen in children. Factors that impair sleep consolidation and increase sleep fragmentation (eg, pain, restless legs syndrome, sleep apnea) can result in these parasomnias. Similarly, sleep deprivation and sedating medications can also increase the emergence of these abnormal behaviors by enhancing sleep inertia and by hindering normal sleep-wake transition. Consequently, these disorders manifest as arousals associated with disorientation, amnesia, and confusion.

Immaturity of sleep-wake boundary regulation may be the reason why these occur more commonly in pediatric population. Studies have shown a higher prevalence of HLA DQB1*05:01 and HLA DQB1*04 alleles in various NREM parasomnias[6]. Sleepwalking also shows an autosomal dominant trait involving chromosome 20.[7]

Sleepwalking

Ambulatory behavior is the primary manifestation of this disorder of arousal. In a systematic review analyzing 51 different studies, Stallman et al. reported a lifetime prevalence of sleepwalking of 6.9% (95% CI 4.6% to 10.3%)[8] which did not change significantly between childhood and adulthood. This number increased to 47.4% for children with one parent with history of sleepwalking and up to 61.5% for children with both parents with history of sleepwalking.[9]

The behaviors can range from aimless wandering to complex, prolonged, and inappropriate episodes that involve driving an automobile, urinating, walking naked, etc. Sleepwalkers typically do not respond to redirection during the episode. In adults, sleepwalking is frequently associated with other disorders like sleep apnea, RLS and usage of hypnotic medications. Multiple different medications like benzodiazepine receptor agonists, antidepressants (amitriptyline, paroxetine, mirtazapine, bupropion), antipsychotics(Olanzapine, quetiapine), antihypertensives(Propranolol, metoprolol), fluoroquinolones, montelukast, topiramate have been implicated as triggers for sleepwalking.[10,11]

Sleep Terrors

Sleep terrors consist of episodes of intense fear accompanied by very loud 'piercing' screams and loud crying during which the patient appears terrified. The associated autonomic activation results in increase in heartrate, breathing, pupillary dilatation, and sweating. The typical duration of sleep terrors is 3-5 minutes. The prevalence of sleep terrors varies widely in children from 14.7% to 56%[9,10]and they almost always resolve by late childhood. Sleep terrors in adults are rare, and are more likely to be associated with medications or psychopathology.

Confusional Arousals

These are partial arousals from NREM sleep that results in a state of disorientation and occasionally, automatic behavior like vocalizations and motor activity. Ambulation and significant sympathetic over-activity is typically absent. Confusional arousals are more common in pediatric population with a prevalence of up to 17%.[12] They are brief, lasting for a few minutes, but may sometimes be prolonged, particularly with sedative hypnotic usage. The individuals with confusional arousals show diminished responsiveness to external stimuli during the episode, and have a partial or complete amnesia of the episode afterward.

Sleep-Related Eating Disorder (SRED)

This parasomnia is more common in women and is characterized by recurrent episodes of binge eating after a partial arousal from NREM sleep.[13] During these episodes patients show a predilection for high carbohydrate food and other peculiar inedible items including raw meat, pet foods etc. This parasomnia is closely related to and is thought to be a variant of sleepwalking. Patients are completely amnestic of their eating behavior, and can have adverse consequences due to their nocturnal eating including weight gain, worsening of diabetes, etc. This parasomnia is different from nocturnal eating disorder/ night eating syndrome where patients are aware of their eating behavior, and is associated with anxiety in most cases. Ambien is the most common medication that induces SRED though several other psychotropic medications are known to precipitate it. Certain other factors like smoking cessation, alcohol consumption, and acute stress are also associated with SRED. Treatment should begin with elimination of precipitating factors like hypnotic medications and treating the comorbid sleep disorders. Medications that can be used to treat SRED include dopamine agonists and Topiramate.

Sexsomnia

Sexsomnia refers to sleep-related abnormal sexual behaviors. It is classified as a subtype of NREM parasomnia disorders of arousal in ICSD-3 with abnormal sexual behaviors emerging from partial arousals during slow-wave sleep. It is more common in young males. A wide range of behaviors have been reported including sexual intercourse, attempted intercourse, masturbation, assaultive sexual behavior, sexual vocalizations, etc. Like other parasomnias, other causes of sleep fragmentation should be investigated before initiating pharmacotherapy.

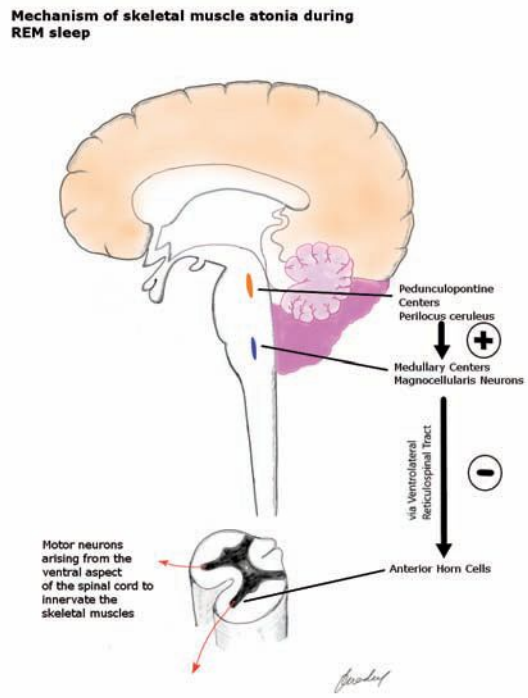


Figure 2. The Perilocus Coeruleus region of the pons exerts an excitatory influence on the medullary 'Magnocellularis' neurons via lateral tegmentoreticular tract. These neurons project on to the spinal alpha motor neurons in the ventral horn via ventrolateral reticulospinal tract and cause hyperpolarization. This results in reduced muscle tone during the REM sleep. In RBD, the brainstem mechanisms that generate REM sleep related muscle atonia are disrupted.

Nocturnal seizures, medications like SSRIs and pramipexole have been reported to be some of the other causes for sexsomnia. Treatment data is limited but Clonazepam might be helpful in bothersome cases.[14]

REM Parasomnias

REM Sleep Behavior Disorder

REM sleep is characterized by rapid eye movements and skeletal muscle atonia. Respiration is diaphragm–based during REM sleep. Dreaming during REM sleep tends to be vivid and detailed, compared to the vague dream content of non-REM sleep. Muscle atonia mediated by brainstem centers, pedunculopontine nucleus and locus coeruleus, serves as a protective mechanism preventing dream enactment during REM sleep. (Figure 2) However, conditions resulting in disruption of this protective mechanism can lead to physical enactment of dream content during REM sleep. This phenomenon is called REM Sleep Behavior Disorder (RBD)

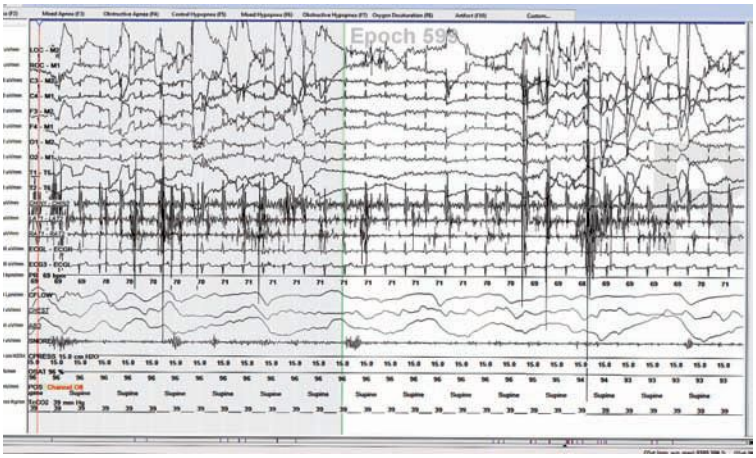


Figure 3. Increased EMG activity in the chin and the leg EMG leads suggestive of RBD in a patient with Parkinson disease.

Parkinson disease (PD) is strongly associated with RBD. (Figure 3) In fact, RBD can predate the initial motor symptoms by years, and is one of the best-known biomarkers for PD. RBD is present in 25-50% of PD patients and is even more frequent in other neurodegenerative disorders such as Multiple System Atrophy and Lewy body dementia. Forty percent of the patients with idiopathic RBD develop parkinsonian syndrome within a decade and two-thirds within two decades.

Secondary RBD can also be seen in the setting of pontine tegmental lesions, withdrawal from alcohol, medication usage (SSRIs, SNRIs, TCAs, MAO inhibitors), Type 1 narcolepsy, and other neurodegenerative disorders like fronto-temporal dementia, Alzheimer's dementia. Patients experiencing RBD may have mild, low amplitude limb movements that are often overlooked. Some patients have vocalizations. These movements can be significant and violent with apparent goal directed behaviors that can cause injury with lacerations. Curiously, the motor activity in RBD in patients with PD appears smoother, faster, and stronger than the patient's daytime motor performance. Patients experiencing RBD may report falling from their beds during the night. Their bed partners may sometimes be able to understand the dream content based on the patient's behavior. Some episodes result in arousal from sleep. Usually, RBD episodes do not cause significant sleep disruption. Nocturnal REM sleep without atonia is found to be strongly associated with pediatric narcolepsy[15].

Nightmare Disorder

This disorder is characterized by recurrent dysphoric dreams of disturbing mental experiences. These nightmares mostly occur during REM sleep and result in awakening. The theme of the nightmare is usually distressing to the individual and result in a variety of emotions including anxiety, fear, rage, embarrassment, and disgust. Nightmares are very common in children and the child that wakes up from a nightmare usually can give a good description of the dream. They are also common in patients with increased anxiety levels and in those with post-traumatic stress. Childhood nightmares usually resolve spontaneously. Diagnosis of nightmare disorder should only be given in patients that are experiencing persistent distress and impairments. (Figure 4)

Recurrent Isolated Sleep Paralysis

The core feature of sleep paralysis is complete inability to move during wakefulness. Unlike RBD where muscle tone persists during REM sleep, sleep paralysis is characterized by the extension of REM sleep-related muscle atonia into wakefulness. Most cases of sleep paralysis are isolated and sporadic with about 7% of the general population reporting at least one episode of sleep paralysis.[16] Sometimes, sleep paralysis can be associated with a sensation of difficult breathing and hallucinatory experiences. Isolated sleep paralysis is a benign condition but can contribute to significant distress when experienced for the first time. Sleep paralysis can happen either during falling asleep (hypnogogic sleep paralysis) or while when waking up (hypnopompic sleep paralysis). In some cases, triggers for sleep paralysis include sleep deprivation and comorbid sleep apnea. Though sleep paralysis is a benign problem, it can happen frequently causing a significant fear of initiating sleep at which time the more appropriate term for it would be recurrent isolated sleep paralysis (RISP).

Other Parasomnias

Sleep Enuresis

Sleep Enuresis (SE) is characterized by recurrent, involuntary voiding during sleep for at least three months. SE occurs in 15 to 20% of five-year olds, and is three times more common in boys. In primary SE, recurrent

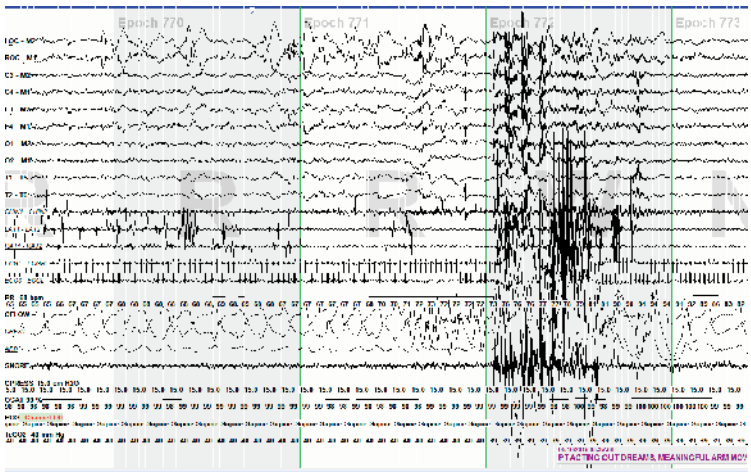


Figure 4: A two-minute window of polysomnogram showing nightmare arising out of REM sleep.

episodes of involuntary voiding happen at least twice a week during sleep after five years of age in a patient who was never consistently dry during sleep for six consecutive months. It is considered secondary SE if the patient was consistently dry for at least six months before and began wetting later. This condition is associated with difficulty waking up from sleep in response to an urge to urinate in the setting of a full urinary bladder. Though psychological problems are a rare cause of primary SE, secondary SE is more commonly seen in children who have recently experienced a significant psychosocial stress. Secondary SE is also commonly associated with chronic constipation and fecal soiling. There is often a high prevalence of enuresis among the parents, siblings and other relatives of children with primary enuresis.

Three important factors contribute to the risk of developing SE: large nocturnal urine volume production, nocturnal bladder over-activity and difficulty arousing from sleep. Multiple studies suggest that difficulty arousing from sleep is more important in primary enuresis while bladder overactivity is more important in secondary enuresis. Sleep fragmentation by disorders like sleep apnea is also highly correlated with SE and successful treatment of sleep apnea results in reduction or elimination of sleep enuresis. Typically, the spontaneous cure rate of primary SE is about 15% per year.

Sleep-Related Hallucinations

Sleep-related hallucinations are unreal experiences that occur at the onset of sleep or upon awakening from sleep. They are predominantly visual hallucinations but can also be auditory or even tactile in nature. Hallucinations occurring at sleep onset are called 'Hypnogogic hallucinations' while those occurring on awakening are called 'Hypnopompic hallucinations.' Sometimes, they can be very complex and can follow a sudden awakening without recall of a preceding dream. These 'complex nocturnal hallucinations' can result in injuries when patients jump out of bed in terror. Sleep-related hallucinations can be associated with other parasomnias including sleep talking or sleepwalking. They are also very common in narcolepsy but can also be seen in a high proportion of general population. They are more common in younger persons, and occur slightly more frequently in women. Large populations studies suggest that alcohol use, mood disorders, insomnia, and drug use increase the likelihood of sleep-related hallucinations. Complex nocturnal visual hallucinations, on the other hand, are very rare and may be seen in patients with narcolepsy, Parkinson disease, Lewy body dementia, midbrain and diencephalic pathology, and in the setting of beta-blocker medication usage.

Exploding Head Syndrome

Exploding Head Syndrome (EHS) is a condition where the affected individuals experience a sudden noise or a sense of explosion that results in abrupt arousal with a sense of fright and happens in the setting of either falling asleep or while waking up. This whole experience is not associated with significant complaints of pain. The term Exploding Head Syndrome was first coined by J.M.S Pearce[17] and despite its memorable name, relatively little is known about this condition. It is not uncommon for patients suffering from EHS to interpret their condition to be far more serious and seek medical attention. The sounds reported during EHS are varied and include violent explosions, door slamming sounds, buzzing, nearby thunder, whip lash, etc.[18] Some patients experience visual symptoms like light flashes, feelings of intense heat, epigastric sensations and an aura of electrical sensation that ascends from lower torso to the head.[19] EHS should be differentiated from headache syndromes like cluster headache, thunderclap headaches, hypnic headache and from nocturnal seizures. Patient education and reassurance are the mainstay treatments, though medications like flunarizine, nifedipine, clomipramine,

topiramate and carbamazepine have been tried with limited benefit. Stress and anxiety reduction has been found to be helpful.

Parasomnias Due to Medical Disorder

The primary feature of this diagnosis is the presence of a parasomnia that can be explained by an underlying medical or neurological disorder. Charles Bonnet syndrome (CBS) is characterized by vivid visual imagery in the setting of partial or complete visual loss. Peduncular hallucinosis is a syndrome of hallucinations that can happen in the setting of brainstem and diencephalic pathology.[20] Sleep-related hallucinations, seen in the setting of CBS and peduncular hallucinosis, are good examples of parasomnias due to medical disorder. Though REM sleep behavior disorder is technically a parasomnia that occurs in the setting of an underlying neurological disorder (α-synucleopathy), it is considered as a separate parasomnia and discussed above.

Parasomnia Due to Medication or Substance Abuse

The essential feature of this diagnosis is dependent upon the onset or worsening of a parasomnia in the setting of usage of a medication or bioactive substance. Multiple medications including selective serotonin reuptake inhibitors, venlafaxine, tricyclic antidepressants, MAO inhibitors have been associated with worsening of RBD. Beta-adrenergic blocking agents can be associated with sleep-related hallucinations. Zolpidem and Zopiclone are associated with a variety of parasomnias including sleep driving and sleep-related eating disorder.

Parasomnia in the Setting of IgLON5 Autoimmunity

Sabater, et al.[21] described a case series of patients showing a unique NREM and REM parasomnia in the setting of autoantibodies against IgLON5, a neuronal cell adhesion protein. This syndrome is characterized by breathing dysfunction, gait instability and brainstem symptoms. Despite being described as a unique parasomnia, this disease has some features of agrypnia excitata and may not be a true parasomnia.[22]

Sleep Talking

Sleep talking is highly prevalent with a lifetime prevalence up to 66%.[23,24] Due to its high prevalence and the benign nature of this parasomnia, it is typically considered a normal variant. It is characterized by varying degrees of comprehensibility, and can happen both, during REM and NREM sleep. It rarely causes problems but sometimes can be frequent and loud disrupting the sleep of bed partners or roommates.

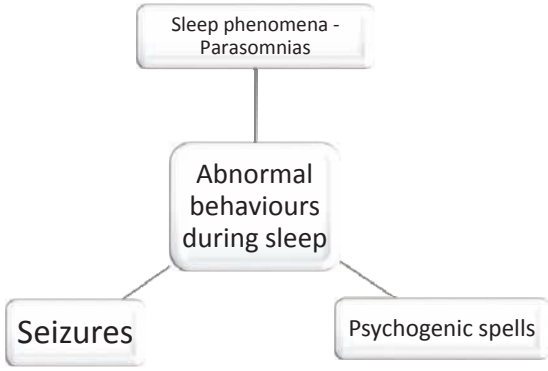


Figure 5. It should be noted that not all nocturnal abnormal behaviors are parasomnias.

Catathrenia is another sleep-related phenomenon consisting of loud groaning sounds during episodes of prolonged expiration. It was first reported in 1983 by De Roeck et al. Initially, it was classified among Parasomnias in the ICSD– 2nd edition but was later included among respiratory disorders in the ICSD-3rd edition.

Diagnostic Evaluation

The approach to a patient presenting with abnormal nocturnal behaviors should start with a good history and if possible, an account from a firsthand witness. A comprehensive video polysomnography (PSG) with expanded EEG and EMG channels should be considered if the parasomnia is presenting with an unusual phenotype or an atypical age and if it is happening frequently. The main purpose of polysomnographic evaluation is to identify triggers of parasomnias like sleep apnea, periodic limb movements and mimics of parasomnias like nocturnal seizures.

It should be noted that not all nocturnal abnormal behaviors are parasomnias. Nocturnal seizures can be sometimes confused with parasomnias. Both temporal lobe and frontal lobe seizures can present during sleep. Similarly, psychogenic/psychiatric conditions like PTSD and nocturnal panic attacks also mimic parasomnias. (Figure 5)

Treatment

As parasomnias are more common in children, their presence tends to elicit anxiety and panic in the parents. Reassurance and education is very important as most kids grow out of these behaviors without any intervention. In general, for NREM parasomnias, the diagnostic evaluation should start with an attempt to find out potential triggers.

One of the common risk factors for NREM parasomnias is sleep disruption, and so the clinician should use a combination of history and diagnostic testing to determine if there are any sleep disorders like sleep-related breathing disorder, periodic limb movements, etc. Similarly, a careful history should be able to identify any environmental stimulants like loud noise that can be contributing to sleep disruption. Patients should be educated about maintaining a good sleep hygiene. Medications (Z drugs, antidepressants, antipsychotics) that are associated with a variety of parasomnias should be evaluated for the possibility of causality.

Patients with RBD should be carefully assessed for risk of injury and safety measures should be undertaken. The first step is to make the sleeping environment safe – e.g. putting soft pads around the bed to minimize the impact of falls, using pillows, keeping distance from the bed partner, removing sharp and potentially injurious objects. Bed partner should be aware of these behaviors and try to have an alternative sleeping arrangement rather than sleeping on the same bed as the patient. Similar safety measures should be employed in cases of NREM parasomnias like sleepwalking. Bed or door alarms can help prevent patient wandering away in their sleep.

Pharmacological treatments for RBD include Clonazepam and Melatonin. Clonazepam is a benzodiazepine and acts at GABA receptors. Melatonin on the other hand is an over-the-counter dietary supplement in the United States and acts on melatonin receptors. Other medications that showed success in limited case series include pramipexole, levodopa, carbamazepine, and imipramine.

Conclusion

Much has been learned about the pathogenesis of parasomnias in the last few decades. RBD has shown to be strongly associated with an underlying neurodegenerative α-synucleopathy while many other parasomnias are benign. Despite the variety of pharmacological and non-pharmacological strategies, there are still no standard of practice guidelines. It is important for the sleep physician to understand the nature of the parasomnia and to differentiate it from nocturnal seizures. Understanding the phenomenology of parasomnias is important due to the forensic implications associated with them.

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Disclosure

None reported. **MM**

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