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Future of Treatment for Low-Risk Prostate Cancer: For All, for Some, or for None?

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See accompanying article on page 2020

INTRODUCTION

The results of the European1 and Swedish7 prostate cancer (PC) randomized screening studies have raised issues of overdetection and overtreatment for men with low-risk PC. Specifically, the additional number needed to detect to eliminate one death from PC was between 12 and 48 after 14 and 10 years of follow-up, respectively. After 7 years of follow-up, the United States (US) PC screening study3 did not observe a benefit to screening men in a population that was already heavily screened (at least 52% prostate-specific antigen [PSA] screening was estimated to occur in the control arm of the Prostate Lung Colorectal Ovarian PC study) with the possible of exception of men with no or minimal comorbidity, where the additional number needed to detect to eliminate one death from PC was only five after 10 years of follow-up.4

Concurrent with a rapid rise in the detection of low-risk PC in the US has come a surge of new technologies including stereotactic body radiation therapy (SBRT).5 What is clear, however, is that a published randomized controlled trial (RCT) comparing SBRT for PC to accepted standards of care is lacking. A single RCT (ISRCTN 45905321)6 is ongoing in Sweden comparing 78 Gy of intensity-modulated radiation therapy (IMRT) or three-dimensional conformal RT (3DCRT) in 39 2-Gy fractions to 42.7 Gy of SBRT in seven 6.1-Gy fractions, given every other day for men with T1c to T3a PC and up to 2 of the
following risk factors: T3a, Gleason score 7 or higher, and/or PSA higher than 10 but lower then 20 ng/mL. Until the report of the Swedish RCT, however, we are left with prospective single arm assessments of acute and late toxicity and early PSA outcome data retrospectively compared to historical controls, which provides a limited basis on which to make evidence-based treatment decision for current patients.

**Discussing the Evidence**

In the article that accompanies this editorial, a single-arm, prospective, phase I multi-institutional dose escalation study is reported by Boike et al, consisting of 45 men (40% low and 60% intermediate risk) who were treated with five SBRT treatments of advancing RT dose (9 to 9.5 to 10 Gy per fraction) in increments of 15 men for a total of 45 and followed for a median of 30, 18, and 12 months, respectively. As expected, given this favorable-risk subset of men and relatively short median follow-up (12 to 30 months) in addition to the use of up to 9 months of hormone therapy in 22% of the patients, which can delay the time to observing PSA failure, there have been no PSA failures observed to date. In addition, because nadir + 2 ng/mL was used to define PSA failure this will further delay the time to observing PSA failure making the maximum median follow-up of 30 months very unlikely to ascertain true PSA control rates. Specifically, the consensus panel that described this definition of PSA failure cautioned, “To avoid the artifacts resulting from short follow-up, the reported date of PSA control should be listed as 2 years short of the median follow-up.” Therefore, for this study, the results for the most mature arm could reliably report PSA control at only 6 months. The authors state that the acute toxicity compares favorably with the MD Anderson Cancer Center9 dose escalation and proton boost10 randomized dose escalation studies which used 3DCRT; however, they also state that the initial patients treated on trial experienced urinary frequency post-SBRT despite premedication with 4 mg of dexamethasone daily. Therefore, the protocol was amended to include tamsulosin (Flomax; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) use for 6 weeks from the start of treatment as is commonly done after prostate brachytherapy. However, tamsulosin use is not needed for all men undergoing IMRT or 3DCRT, particularly if prostate volume is limited to 60 cm3 as was done in this study. It is highly probable that if all men treated on the MD Anderson Cancer Center9 dose escalation and proton boost randomized studies had been pretreated with dexamethasone and tamsulosin that acute genitourinary (GU) toxicity would be even lower then reported, as it is today with the use of dose escalation using IMRT.11 Regarding late GU toxicity, the median follow-up is still short but given the 31% and 4% rate of at least grade 2 and 3 acute GU toxicity respectively despite tamsulosin and dexamethasone use and the known association between the presence of grade 2 or higher acute GU toxicity and an increased risk of late GU toxicity,12 the possibility of significant late GU toxicity exists. Moreover, the most mature data on prostate SBRT by Pham et al5 observed a crude rate of 2.5% for grade 3 or higher late GU toxicity after a median follow-up of 5 years despite the use of a lower dose per fraction; 6.7 Gy as compared 9 to 10 Gy in this study. Therefore, safety and efficacy results from the long-term follow-up of the Swedish RCT7 are needed before SBRT should be considered in the treatment of PC outside the setting of a well-formulated prospective and preferably phase III RCT.

**Impact of Health Care Reform**

Given the current climate of health care reform, stepping back and putting investigational approaches to favorable-risk PC, such as SBRT, into perspective is needed. Specifically, in the state of Massachusetts, where health insurance is mandated by law, a requirement by certain insurers will begin on January 1, 2011, which is to provide an additional category II Current Procedural Terminology code (ie, F codes) for PC risk group that provides the risk of recurrence (eg, low, intermediate, or high) when submitting requests for reimbursement for PC treatments provided to patients insured by those payers. The insurance companies have stated that the purpose of acquiring this information is not tied to payments, but rather to help researchers and policy experts understand the pattern of care being delivered to patients with PC.13 However, given the concerns raised in the US about overdetection and overtreatment of low-risk PC based on the PSA-based screening studies1-4 and the guideline by the National Cancer Center Network14 that for men with very low-risk PC, active surveillance (AS) is an acceptable treatment for men with up to a 20-year life expectancy despite having a median follow-up of only 8 years for the most mature AS study,15 it is very possible and likely that insurers are collecting this information as part of a future cost-cutting measure. While states like Massachusetts where health insurance is mandated may be the first to take such a course or action, other states and federal payers such as Medicare and Medicaid will likely follow. One must wonder if this will ultimately lead to a decrease or denial in payment for treatment of men with low-risk PC, especially if the cost of treatment is high and data from randomized studies confirming safety and efficacy as compared to current standards of care is lacking. Given what risk-assessment can and cannot ascertain for the individual patient seen in the office today, the possibility that low-risk PC categorically may not be viewed by payers as a disease worthy of treatment in the future raises ethical and medical concerns.

Specifically, low-risk PC is defined by three clinical parameters:16 a PSA level lower then 10 ng/mL, a biopsy Gleason score of 6 or lower with no grade 4 or 5 disease, and American Joint Commission on Cancer staging17 tumor category 1c or 2a. While studies18,19 of men with low-risk PC have been shown to have a lower than 1% PC-specific mortality (PCSM) rate up to 15 years after radical prostatectomy (RP) or various forms of conformal external-beam RT or prostate brachytherapy (PB), there are studies20-22 documenting substantial death rates from PC reaching 19% by 7 years after treatment in select men with low-risk PC who can be identified at diagnosis using readily available and routinely acquired information. How can this be? Simply stated, there is additional information from the prostate biopsy and PSA history that was not used in the original definition of low-risk PC, which was published in 1998.16 Specifically, some men with low-risk PC may have intermediate or high-risk PC due to undergrading based on the sampling error associated with prostate biopsy technique20 to determine the biopsy Gleason score and understaging based on the low level of accuracy for assessing actual T-category using the digital rectal examination.24

**Proportion of Positive Prostate Biopsies ≥ 50%**

Evidence from surgical series25,26 exist documenting that men who have PC found in ≥ 50% of the biopsy specimens are at increased

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**CLINICAL PARAMETERS**

**Proportion of Positive Prostate Biopsies ≥ 50%**

Evidence from surgical series25,26 exist documenting that men who have PC found in ≥ 50% of the biopsy specimens are at increased
risk for undergrading on the basis of the biopsy Gleason score, under-
staging on the basis of the digital rectal examination, metastasis, and
PCSM as compared with those with lower than 50%. Data from an RT
series specifically examined the prognostic significance of this factor
in men with low-risk PC and found that PCSM estimates were 9% as
compared with 0% by 5 years in men with at least 50% as compared
with less than 50% of the biopsy cores revealing Gleason score 6 PC.

Perineural Invasion

The presence of perineural invasion (PNI) on prostate biopsy in
an otherwise low-risk patient is associated with a significant risk
of upstaging and upgrading at RP and a resulting higher risk of pro-
gression after RT or RP. Specifically, for men with low-risk PC
conditioning using 3DCRT, PNI was significantly associated with an
increased risk of PSA recurrence ($P = .04$) and this was also found to
be true in an independent data set for men with low-risk PC undergo-
ing RP where the time to PSA recurrence was significantly shorter
($P = .04$) in men with PNI in the prostate needle biopsy. Specifically,
by 5 years after RP estimates of PSA recurrence were 18% as compared
to 5% in men with PNI versus none at biopsy. A confirmatory study
showed a 4.14-fold increase ($P = .005$) in the risk of PSA recurrence in
men with low-risk PC undergoing RT after adjusting for RT dose.

PSA Velocity Higher Than 2 ng/mL/yr

Given two men with the same PSA level, the patient experi-
encing a rise of at least 2 points in the PSA level during the year
before diagnosis has been shown to have more advanced patho-
logic stage and grade at RP and higher risk of recurrence after RP,1
PB,2 or EBRT and hormone therapy3 when compared to men
without at least a 2-point rise during the past year. In addition, a
higher risk of PCSM after RP,4 and EBRT with or without5 hormonetherapy has been observed for men with this rapid rise in
PSA compared to those without such a rapid rise. For the specific
case of men with low-risk PC managed with RP at 7 years, PCSM
estimates reached 5% versus lower than 1% for men whose PSA
level rose by at least 2 points during the year prior diagnosis as
compared to those who did not. These respective estimates were
19% and 0% for men undergoing EBRT.2

Of note, for men who do not have any of these additional factors,
with the possible exception of a PSA velocity higher than 2 ng/mL/yr,
the subgroup termed very low-risk PC has been defined (ie, PSA < 10
ng/mL, PSA density < 0.15, T1c and Gleason score 3 + 3 in at most
two cores each having ≤ 50% core involvement).14 For men in this
very low-risk subgroup, data from a surgical series35 shows that for
those who undergo immediate RP approximately 25% will have grade
4 disease and 6.6% will have evidence of extracapsular extension
(3.3%) or pelvic lymph node involvement (3.3%) at RP. Therefore, for
the 25% with unsuspected intermediate- or high-risk PC managed
with monotherapies, such as RP, RT, or PB, deemed appropriate for
men with low-risk PC, significantly higher rates of progression and
death from PC than expected can occur. In addition, when such men
with very low-risk PC are placed on AS and subsequently progress on
a surveillance biopsy defined as any Gleason pattern grade 4/5, more
than 50% cancer on any core or cancer in more than two cores and
undergo RP, 35% have extracapsular extension and 7% have seminal
vesicle invasion and/or lymph node involvement.36 While AS has been
recommended by the National Cancer Center Network for men
with very low-risk PC and a life expectancy up to 20 years, the most
mature published study of AS has a median follow-up of only 8
years, leaving one to wonder what is the basis for the 20-year life expectancy criteria. However, in September 2007, a prospective RCT
called Surveillance Therapy against Radical Treatment was initiated
comparing AS to definitive treatments with RT or RP for men with
favorable-risk PC. The trial aimed to accrue 2,100 men in Canada, the
US, and the United Kingdom but does not expect to have an answer
regarding overall survival until 2025. In addition, a request has been
made to consider adding a prerandomization stratification using a
validated measure of comorbidity to the trial so the results can be
applied appropriately to men with varying degrees of comorbidity, espe-
cially given the evidence suggesting over treatment of low-risk PC occurs
only in men with significant comorbidity. In particular, we do not know
what the death rates from PC will be for healthy men with a long life
expectancy who select AS versus a standard therapy for low-risk PC.

In closing, low-risk PC defined using PSA, Gleason score, and
American Joint Commission on Cancer staging does not ade-
quately describe the extent or aggressiveness of the disease for all men
in that category. Additional information routinely acquired at diagno-
sis including the proportion of positive prostate biopsies and the PSA velocity during the year before diagnosis can be used to identify the individual with low-risk PC whose risk of recurrence and PCSM far exceeds that of the low-risk cohort as a group. New treatments such as SBRT that treat men with
low-risk PC should be studied prospectively in the setting of a RCT comparing toxicity and cancer control outcomes to accepted standards
before being adopted. While we await the results of such studies, policy
makers have begun to collect data on low-risk PC volume for reasons yet
to be completely elucidated. Therefore, while the Swedish randomized
trial of SBRT versus does escalated 3DCRT or IMRT will eventually
provide evidence to adopt or refute SBRT as an acceptable treatment
option for men with PC, will we still be treating all men, some men or no
man with low-risk PC in the US when the results become available?

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Genetic Testing for Lung Cancer: Reflex Versus Clinical Selection

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See accompanying articles on pages 2046 and 2121

Interest in activating driver mutations in tyrosine kinase genes as therapeutic targets in non–small-cell lung cancer (NSCLC) has peaked recently as a result of the discovery that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) produce higher response rates, longer progression-free survival periods, less toxicity, improved symptom control, improved quality of life, and greater convenience compared with cytotoxic chemotherapy in the first-line treatment of patients with advanced NSCLC who harbor EGFR-activating mutations.1–4 A more recent study showed that patients with advanced NSCLC whose tumors harbor EML4-ALK fusion genes and who are treated with the ALK TKI crizotinib have high response rates and long progression-free survival times that are similar to those of patients with NSCLC who harbor EGFR mutations and are treated with erlotinib.5,6

Recent genomic studies in adenocarcinoma of the lung identified other mutations in tyrosine kinase genes including KRAS, NRAS,