THE "NEW" PROSTATE CANCER INFOLINK

Risk, prostate cancer, and being 70 to 80 years of age

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So a relatively new article in *Reviews in Urology* caught your Sitemaster's eye this morning — and worried him because it seemed to be communicating a conclusion of questionable accuracy, which we will explore below. And if we have misinterpreted the data provide in the paper, we are more than willing to be corrected.

The new paper by Shah and Ioffe (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5260947/) (available as a full text article) is based on a retrospective analysis of data from 5,100 patients of between 70 and 80 years, all of whom received radiation therapy of some type for the treatment of prostate cancer over a 10-year period from 2005 to 2015. The authors state that:

> ***Multiple studies in peer-reviewed journals document that men 70 years and older have more prevalence of prostate cancer, more high-grade disease, more metastases, and more prostate cancer-specific deaths compared with men under 70 years.***

That they have a higher prevalence of prostate cancer and more prostate cancer-specific deaths than men of < 70 years is probably undisputed, for the simple reason that they are older, incidence of prostate cancer is well understood to be age-related, and many such patients may well have at least micrometastatic disease by the time they are initially diagnosed (especially if they have never received a PSA test and/or a DRE in the prior 15 years). Whether they really have more high-grade disease at time of diagnosis, however, is not quite as clear.

So the first thing that worries us about this study is that it appears to include ***exclusively*** men who received treatment for prostate cancer. The authors state this very clearly:

> ***The study consisted of 5,100 prostate cancer patients who opted for treatment with radiation therapy — external radiation, brachytherapy (high-dose rate and/or low-dose rate), or a combination.***

So the patient cohort studied has inherent selection bias based on the fact that eligibility was confined to men of 70 to 80 years of age who had elected to have radiation therapy of some type. What happened to all the men of 70 to 80 years who may have been diagnosed with prostate cancer and who elected to do nothing about it other than watchful waiting

or active surveillance (quite apart from all those who may have had other forms of therapy)? It is quite certainly ***not*** the case that all men of 70 to 80 years of age who are diagnosed with prostate cancer elect to have radiation therapy!

Based on this cohort of 5,100 men of 70 to 80 years of age who all elected to have radiation therapy to treat their prostate cancer, the authors then report the following:

- 3,468/5,100 men (68.0 percent) were aged between 70 and 75 years.
- 1,632/5,100 men (32.0 percent) were aged between 76 and 80 years.
- All patients had a PSA value of > 2.5 ng/ml, an abnormal rectal examination, or both.
- PSA values for the 5,100 patients broke down as follows:
  - 21 percent had a PSA value of < 4 ng/ml.
  - 65 percent had a PSA value of 4 to 10 ng/ml.
  - 11 percent had a PSA value of 11 to 20 ng/ml.
  - 3 percent had a PSA value of 21 to 50 ng/ml.
- Data from rectal examinations showed that
  - 72 percent had a normal DRE
  - 28 percent had an abnormal DRE
  - Among the men aged 70 to 75 years, 27 percent had an abnormal DRE.
  - Among the men aged 75 to 80 years, 31 percent had an abnormal DRE.
- And when we look at Gleason scores, the authors state that
  - All Gleason scores of 7 to 10 were evaluated as being high grade.
  - Among the entire cohort of men aged from 70 to 80 years
    - 39 percent had a Gleason score of 6.
    - 61 percent had a Gleason score of 7 to 10.
  - Among the men aged from 70 to 75 years
    - 1,426/3,468 (41.1 percent) had a Gleason score of 6.
    - 2,042/3,468 (58.9 percent) had a Gleason score of 7 to 10.
  - Among the men aged from 76 to 80 years
    - 553/1,632 (33.9 percent) had a Gleason score of 6.
    - 1,079/1,632 (66.1 percent) had a Gleason score of 7 to 10.
- Men of &6 to 80 years of age and with an abnormal DRE had a 77 percent incidence of a Gleason score of 7 to 10.

We certainly don’t dispute any of these data. In fact we find them relatively unsurprising.

What concerns us is the authors’ conclusions from these data:

> ***In this study, septuagenarians with prostate cancer have a 61 percentfrequency of*** *[Gleason score]* ***7-10 prostate cancer and septuagenarians with prostate cancer who had an abnormal DRE result have a 74 percent frequency of*** *[Gleason score]* ***7-10 prostate cancer. As 50% of biopsy specimens underestimate the pathologic grade, we estimate that the actual frequency of*** *[Gleason score]* ***7–10 prostate cancer is approximately 80 to 85 percent with a positive DRE result.***

And they also conclude that:

> ***Based on these findings and other published studies, we strongly believe that prostate cancer screening should be made available to men 70 years and older.***

So let's look with care at what this study really did and didn't find:

- Despite their conclusion, the authors did ***not*** actually find that septuagenarians have a 61 percent frequency of Gleason 7 to 10 prostate cancer at all. What they ***actually*** found was that in their highly selected cohort of septuagenarians (all of whom had been diagnosed with prostate cancer ***and*** elected to have radiation therapy to treat their prostate cancer) there was a a 61 percent frequency of Gleason 7 to 10 prostate cancer.
- The study failed entirely to discriminate between patients with low-, intermediate-, and high-risk prostate cancer (let alone differentiating between men with favorable and unfavorable intermediate-risk prostate cancer).
- The study lumps all men with Gleason 7 prostate cancer into a "high grade" classification (despite the fact that we know that men with Gleason 3 + 4 = 7 disease fall into a very different risk category than those with Gleason 4 + 3 = 7 disease).
- The study fails to tell us anything about when the men in the study had had any prior PSA testing or biopsies. This raises the immediate question of what percentage of these men had ***never*** had a PSA test until they reached their 70s (which in and of itself is probably a risk factor for diagnosis with prostate cancer at 70 years of age or older).
- The study by its very nature is unable to tell us anything about the risk of these patients for either metastatic prostate cancer or prostate cancer-specific death, but we know there is not a lot of point in treatment for localized prostate cancer for men with a life expectancy of 10 years of less (which ***has to have been*** the case for many of these men) because they are very highly unlikely to die of prostate cancer compared to other potential causes of death. Indeed, some would argue that there is not a lot of point in treatment for localized prostate cancer with a Gleason score of < 8 among men of 70 or more years of age even if they have a life expectancy of 15 years.
- The study demonstrably indicates that many of the men involved have to have been over-treated unnecessarily for a non-life-threatening condition.

We do not dispute the fact that PSA testing may be ***entirely*** appropriate for many men aged > 70 years — but ***not*** based exclusively on their calendar age. The idea of testing such men should be based on a combination of their physical health, their life expectancy, and any known risk factors for prostate cancer. Thus one would be testing ***selected men*** of 70 years and older for their risk under this scenario, and not "screening" such men.

We would respectfully suggest that this paper by Shah and Ioffe offers an excellent example of just why so many members of the prostate cancer community (quite apart from the members of the USPSTF) are concerned about the risks for over-treatment of men with this disorder — most particularly for older men who may not be fully aware of just how low their risk is for either prostate cancer metastasis or prostate cancer specific mortality.

Alas, this paper also tell us nothing at all about the incidence of short- and long-term side effects from treatment with radiation therapy in this cohort of 5,100 men, which is another unfortunate and somewhat significant omission. There are excellent data showing the relatively high level of side effects and complications from almost any type of treatment in men of this age with localized prostate cancer

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