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TO TREAT OR NOT TO TREAT

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The decades old debate on the pros and cons of localized prostate cancer treatment was ignited again. The latest publication of 29 years follow-up results of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) in the *New England Journal of Medicine* reemphasize the challenges in measuring the benefit of curative-intent local therapy for prostate cancer. To address this issue, Scandinavian investigators conducted a prospective, randomized study in which 695 European men with localized disease according to the standard clinical practice at that time were assigned to undergo radical prostatectomy or watchful waiting and followed for an average of 23 years (maximum, 29 years). These Patients were <75 years of age and had anticipated life expectancy of more than 10 years, highly or moderately highly differentiated tumour pathology (World Health Organization classification), 79.9% of patients had a prostate-specific antigen (PSA) ≤ 20 ng/mL, clinical stage ≤ cT2, negative bone scans for osseous metastatic disease.

Since the study began 29 years ago over 80% of patients had died and 32% died from prostate cancer. With median follow-up of 23 years, the cumulative incidence of death from any cause was significantly lower in the radical prostatectomy group than in the watchful waiting group (71.9% vs. 83.8%) The corresponding relative risk based on data for the complete follow-up period was 0.74 (95% CI, 0.62 to 0.87; P<0.001), as were the cumulative incidence of death from prostate cancer (19.6% vs. 31.3%) relative risk 0.55 (95% CI,0.41 to 0.74; P<0.001), and the cumulative incidence of distant metastases (26.6% vs. 43.3%) relative risk 0.54 (95% CI, 0.42 to 0.70; P<0.001). The number needed to treat to avert 1 death was 8.4. A mean 2.9 years of life were gained with radical prostatectomy. Of interest, the benefit of radical prostatectomy was greater among men younger than 65 years of age at diagnosis than among those who were older.

Bill-Axelson and her colleagues also found that among men in the surgery group, extracapsular extension was associated with a risk of death from prostate cancer that was 5 times that of men without extracapsular extension. In addition, a high Gleason score (>7) was associated with a risk of death from prostate cancer that was 10 times higher. Unfortunately, the study did not stratify the rates of death and development of metastatic according to Gleason score or risk groups.

This remains the best randomized study of radical prostatectomy versus watchful waiting ever done. It has a long follow up, of mostly clinically diagnosed prostate cancer. The major drawback of the study is

the natural change of the way we diagnose and manage prostate cancer over the last 29 years. While most of these patients had PSA data available, prostate cancer diagnoses was not initiated based on PSA alone for most of them (which is the current practice). As the authors report this may actually help alleviating the bias of early diagnoses. In reality, the train has left the station and the practice on the ground in most developed countries is to have a PSA first. Thus, the outcomes might not translate to the PSA-detected cancers of 2019. Furthermore, the indications for cross imaging (computed tomography or magnetic resonance imaging scans) have changed over the years. Therefore, the definition of localized disease has morphed.

So, is it wrong for patients and clinicians to say that this study proves that more men should have radical prostatectomy? Is it wrong to suggest that a patient who has an aggressive prostate cancer may be better off having radical prostatectomy than observation, in terms of preventing the development of metastasis, dying of prostate cancer, and overall survival? And finally, what is the impact on quality of life? Are the side effects of localized treatment worse than the side effects of metastatic disease and its treatments? If you are the one having the pain from osseus metastasis or dealing with the debilitating impact of prolonged androgen deprivation therapy, you may not think so. But if you are the one who has to wear diapers for the rest of your life and never need to start systemic therapy, you may have a different opnion.

Fortunately, studies of PSA-detected cancers that will inform this subject with long-term follow-up include both the PIVOT trial (NEJM JW Oncol Hematol Sep 2017 and N Engl J Med 2017;377:132) and the ProtecT trial (NEJM JW Oncol Hematol Nov 2016 and N Engl J Med 2016; 375:1415). It may take us another decade to accumulate the longer needed follow up of these 2 studies. Will the train keep moving and we will be faced with the same dilemma of changing practice and applicability of their results? Thus, the question may still remain when and how to treat localized prostate cancer.