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Permalink

<https://escholarship.org/uc/item/1mg0n9wx>

Journal

Clinical Oncology, 28(8)

ISSN

0936-6555

Author

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Publication Date

2016-08-01

DOI

10.1016/j.clon.2016.04.037

Peer reviewed



Editorial

Should Treatment with Radiation and Androgen Deprivation Therapy be Considered the ‘Gold Standard’ for Men with Unfavourable Intermediate- to High-risk and Locally Advanced Prostate Cancer?



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Received 7 March 2016; accepted 29 March 2016

The ‘gold standard’ for treating prostate cancer should be based on: (i) the degree to which there is level I evidence (from prospective phase III randomised trials) supporting its efficacy; (ii) sound biological physical principles underlying the treatment; (iii) generalisability, reproducibility and applicability to most of the patients diagnosed with localised prostate cancer and (iv) there are no competing therapeutic options that are proven to be more effective. Based on the first three criteria, a very strong argument can be easily made that definitive radiotherapy [combined with androgen deprivation therapy (ADT) when appropriate] should be considered the ‘gold standard’ for managing clinically localised unfavourable intermediate- to high-risk prostate cancer [1]. For the fourth criteria there is controversy and that is the focus of this editorial. Although some studies focusing on biochemical [prostate-specific antigen (PSA)] control suggest that radiation-based treatments are as good or better than radical prostatectomy, different PSA failure definitions are used after these treatments so this area remains controversial [2–4]. Thus, I will focus my attention on overall survival and cause-specific survival (CSS) and use data from prospective phase III trials to justify appropriate care [1].

In the last 5 years there has been a substantial increase in the use of radical prostatectomy compared with radiotherapy for men with locally advanced disease, probably due to the belief by many urologists that ‘there is good evidence’ from population-based studies that radical prostatectomy offers a better survival rate than radiotherapy

[5,6]. Space does not allow me to address these studies in detail, so I encourage readers to see our critical review of this topic [7]. An example of substantial bias found in these population-based studies is readily made obvious by a recent meta-analysis conducted by Wallis and colleagues [6,8]. In their first ‘meta-analysis’, they assessed survival end points and asserted that 90% of the studies included in their meta-analysis had a ‘low risk of bias’ [6]. There seems to be a lack of relevance to what they meant by a ‘low risk of bias’ and what I mean by ‘bias’. Table 1 highlights a few examples of the shortcomings of their study, with additional criticisms previously made [9]. Some of their biases included the fact that they systematically ignored the flaws of poorly designed studies favouring radical prostatectomy while omitting higher quality studies that favoured radiotherapy. There are numerous other problems with many of these population-based studies comparing outcomes after radical prostatectomy and radiotherapy-based treatments.

For example, the Surveillance Epidemiology and End Results (SEER) data used by many of these studies is unreliable for comparing outcomes between radical prostatectomy and radiotherapy because before 2010 biopsy Gleason score was only available for radiotherapy patients, whereas pathological Gleason score was available for radical prostatectomy patients and accurate PSA data were not available [20]. In addition experts have reported that, using SEER data, major residual biases persisted, creating ‘improbable results’ and concluded ‘... the results from observational studies of treatment outcomes should be viewed with caution’ [21]. Furthermore, adjustments based on Charlson co-morbidity index also seem to be inadequate, being best applied when populations are relatively homogeneous, such as those limited to a co-morbidity index score of 0 [22]. Also of great concern, in a number of studies a death was classified ‘due to prostate cancer’ if this diagnosis was listed

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Table 1Commentary on the meta-analysis on radical prostatectomy versus radiotherapy reported by Wallis *et al.* [6; table 3]

First author	Scores by Wallis <i>et al.</i>	Comments on paper
Cooperberg [10]	Low risk of bias	75% of patients undergoing RP were <67 years of age, whereas 75% of men treated with RT were >67 years of age. As the benefits of RP compared with no initial treatment were largely limited to men <65 years of age (in a landmark phase III trial) [11] and ADT was not routinely used in patients treated with RT how can this be considered unbiased?
Merglen [12]	Low risk of bias	No ADT used in men with RT high-risk disease, no adjustment for co-morbidity or GS. Attribution miscoding errors, as previously reported in Switzerland [13]. This error was estimated to be $\geq 12\%$ for men with prostate cancer treated before 1995 and would tend to overestimate deaths among patients treated with RT because more men received RT before 1994 alone compared with RP (55% versus 27%).
Tewari [14]	Low risk of bias	Had no pre-treatment PSAs or T-stages so could not be adjusted for, ADT not used with RT high-risk disease. Death was classified as 'due to prostate cancer' if this diagnosis was listed on <i>any</i> of the top three lines of the death certificate [14]. As patients treated with RT were more likely to die of other causes, they would be at greater risk for attribution bias as they are older and had more co-morbidity, so how can there be 'low risk of bias'?
Sun [15]	Low risk of bias	SEER data used wherein the highest GS from Bx or post RP used versus Bx alone after RT, no PSAs available, ADT not used in men with RT high-risk disease, not relevant study.
Akakura [16]	Study omitted	Small phase III randomised trial, not clear why omitted?
Tward [17]	Study omitted	1% difference in cause-specific survival at 10 years, why excluded?
Tsao [18]	Study omitted	No differences in 10 year survival rates for patients with GS of 8–10 for RT versus RP $\pm$ RT, why omitted?
Lennernas [19]	Study omitted	Small phase III randomised trial, confirmed same survival rates at 10 years, why omitted?

RP, radical prostatectomy; RT, radiotherapy; ADT, androgen deprivation therapy; GS, Gleason score; PSA, prostate-specific antigen; Bx, Biopsy.

on *any* of the top three lines of the death certificate and other evidence of significant attribution errors has been noted in some studies [12–14]. As patients treated with radiotherapy were more likely to die of other causes, they would be at greater risk for attribution bias. What is clear is that using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach developed by the GRADE Working Group to assess the quality of evidence and the strength of recommendations, more than 90% of the studies included by Wallis *et al.* [6] in their meta-analysis would be considered to be 'low level of confidence' in quality, thus there cannot be 'good evidence surgery is better' [6,23]. Given these facts, we recently reported a novel approach based on level I evidence that accounts for various types of bias that may be a fairer strategy [1,7].

To ensure that two populations (radical prostatectomy versus radiotherapy) were truly comparable we postulated that overall survival should be comparable as well. Thus, in our review of radical prostatectomy vs radiotherapy series, only series including data on 10 year overall survival were eligible for inclusion in our study [10]. By contrast, to those fundamentally flawed population studies, we found that based on the most reliable studies comparing radical

prostatectomy versus radiotherapy, when men were treated in accordance with the current standard of care, the median difference in 10 year CSS was 1% (95% confidence interval –2% to 7%; $P = 0.24$). This 1% CSS difference favouring radical prostatectomy over radiotherapy is easily explained by the fact that the studies did not adjust for some factors associated with a worse outcome [10]. Another major limitation of our study was that we based our reliability score on patients treated with older radiotherapy techniques largely excluding dose escalation and brachytherapy [1,24]. It is conceivable that the results with dose-escalated radiotherapy (including brachytherapy) might be superior to those expected with radical prostatectomy for men with high-risk locally advanced prostate cancer [25]. Although treatment by both radiotherapy and radical prostatectomy have been around more than 100 years, there is only one major trial establishing the efficacy of radical prostatectomy compared with 'watchful waiting' and in this trial the benefits of radical prostatectomy seemed to be limited to men <65 years of age [11]. However, the median age of men with newly diagnosed prostate cancer is >65 years [26]. By contrast, multiple phase III trials have shown that for men who need treatment the most (locally advanced disease),

radiotherapy-based treatment is highly beneficial [1]. Not only did the median age of men on these trials exceed 70 years, but older men actually seemed to have a better cause-specific outcome, despite the fact that multiple studies have shown that older men would be expected to have more advanced disease than younger men [27–30].

In conclusion, when men with unfavourable intermediate- to high-risk locally advanced disease are managed with primary definitive radiotherapy + ADT, there is clear level I evidence based on 30+ years of large phase III randomised trials to back this treatment strategy [1]. The limited available contemporary surgical trials to date suggest that the benefits of radical prostatectomy may be limited to men less than 65 years of age. The best available data, based on current standards of care, suggest that the 10 year survival rates from cancer are essentially identical following radical prostatectomy and radiotherapy + ADT [7,19]. However, surgical outcomes are linked to surgical volumes, with the vast majority of surgeons being low volume surgeons but most surgical series published by high volume surgeons [31,32]. Furthermore, given the higher 30, 60, 90 day mortality rates, higher rates of erectile dysfunction and higher risk of incontinence associated with radical prostatectomy, clearly there should be a very high level of evidence before considering radical prostatectomy as the ‘gold standard’ [33]. The plethora of population-based retrospective studies have been poorly conducted and tainted by bias, so that they should not be used to drive treatment recommendations [6].

The assertion that radical prostatectomy is more effective than radiotherapy + ADT brings to mind the question that Abraham Lincoln asked: ‘how many legs does a dog have if you call the tail a leg? The answer, ‘four’, calling a tail a leg does not make it a leg’. Asserting that there is ‘good evidence’ that radical prostatectomy renders better survival outcomes than radiotherapy + ADT does not make it so. For more than 20 years I have worked side-by-side with some of the most outstanding urologists in the world and at no time have I doubted their sincere efforts to keep their patients’ best interests paramount. This editorial was prepared to caution the urological community in general about assuming that unresolved controversies such as radical prostatectomy versus radiotherapy are actually resolved, and assuming we know which treatment is best, when we really do not.

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