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Brief Correspondence

Changing Trends in Surgical Management of Prostate Cancer: The End of Overtreatment?

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Article info

Article history:

Accepted February 13, 2015

Keywords:

Radical prostatectomy
Overtreatment
Overdiagnosis

Abstract

The use of prostate-specific antigen (PSA) for screening or early detection of prostate cancer (PCa) results in significant stage migration toward more favorable stages and a proven decrease in PCa mortality but is accompanied by substantial rates of overdiagnosis and overtreatment. Acknowledgement of these downsides and endeavors to avoid them have led to substantial changes in treatment patterns. Many centers have reported dramatic changes, with increases in active surveillance (AS) of early cancers and local treatment of advanced disease. To estimate the impact of this development on our radical prostatectomy (RP) series, we analyzed changes in cancer and patient selection over the past 15 yr. Despite a trend toward decreased utilization of RP in Germany, the annual caseload at our institution increased due to regionalization, from 382 RPs in 2000 to 2145 in 2011, and has been stable for the past 3 yr (2106 RPs in 2014). The rate of RPs performed in patients with low-risk PCa, AS candidates, or men with a pure Gleason 6 pattern in the RP specimen dropped from 60%, 38.2%, and 56.2%, respectively, in 2004 to 27%, 14.7%, and 10%, respectively, in 2011–2013. Patients undergoing RP with solely Gleason 6 cancer were younger on average (aged 61 yr) than patients in higher risk groups (aged 65 yr). The rate of histologically insignificant PCa was low, ranging from 1% to 8.8% depending on the definition used. Patient selection is the other important tool used to avoid overtreatment. Long-term other-cause mortality (OCM) should be low in adequately selected RP candidates, and after a minimum follow-up of 15 yr, overall OCM was 14.8%. The OCM rate was 10.2% in men aged <65 yr and 24.3% in men aged ≥65 yr. The current analysis documents a clear shift in utilization of RP toward significant PCa in men with long life expectancy. Based on patient and cancer selection as described, the long-standing discussion of overtreatment with RP might become invalid.

Patient summary: Discussion of possible overtreatment has led to dramatic changes in indication for radical prostatectomy (RP). We analyzed a large European patient cohort and found that RP is rarely done in early cancers but is used more for aggressive tumors. Those who underwent RP had long life expectancy and benefit from surgery. With this change in application, overtreatment with RP is unlikely.

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After the introduction of prostate-specific antigen (PSA) and its use for early detection and screening for prostate cancer (PCa), many centers observed significant stage migration toward lower stage and grade and more curable disease [1–3]. However, substantial overdiagnosis and subsequent overtreatment have been identified as major downsides of

PSA testing and have led to intense discussion in the medical and general press [4]. Moreover, current guidelines do not recommend PSA-based mass screening [5,6].

In a recent review addressing this issue, Loeb and coworkers stated that the rate of overdiagnosis varies from 22% to 67% in screen-detected PCa, depending on the

<http://dx.doi.org/10.1016/j.eururo.2015.02.020>

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definition of overdiagnosis. The rate of possible overtreatment varies from 5% to 46%, depending on differences in the definition of histologically insignificant PCa (iPCa) and the investigated patient population and biopsy practice.

Awareness of these potential downsides reached daily practice long ago and led to a gradual change in referral patterns of counseling urologists and treatment patterns with radical prostatectomy (RP) in our institution in recent years. To document this, we described the instruments and consequences of cancer and patient selection in the largest European single-center cohort.

Cancer selection is used to avoid overtreatment. Various estimates exist to characterize PCa that might not need immediate treatment or treatment at all. When the widely used definition of low-risk disease [6] was applied to our RP cohort, the rate of low-risk cancers declined from 60% in 2004 to 27% in 2011–2013. The rate of potential active surveillance (AS) candidates, defined according to the European Association of Urology guidelines, declined from 38.2% in 2004 to 14.7% in 2013 (Fig. 1). Furthermore, the rate of men with purely Gleason 6 in RP specimens went down from 56.2% in 2004 to 10% in the past 3 yr using the same original Gleason grading system and not the revised version of 2005. Finally, the rate of organ-confined (OC) disease dropped from 80% to 62% in the same time period.

The rate of histologic iPCa in the final RP specimen is another widely used measure to define the amount of overtreatment by RP, and historical series described rates of iPCa between 16% and 32% [7,8]. For the present evaluation, three established definitions for iPCa were applied: (1) the *Epstein* criteria, consisting of OC, no Gleason 4 or 5, and cancer volume <0.2 ml [7]; (2) the *Stamey* criteria, with OC,

no Gleason 4 or 5, and cancer volume <0.5 ml [9]; and (3) the *Wolters* criteria, including OC, no Gleason 4 or 5, and tumor volume <2.5 ml [10]. We measured whole cancer volume (not just the index tumor) in a consecutive series of 913 patients with PCa operated between October 2012 and March 2013. The rate of iPCa was 1% [7], 2.8% [9], and 8.8% [10] according to the three different definitions, respectively, demonstrating a dramatic drop in the rate of iPCa in a modern RP series compared with historical series [8]. These findings are in line with other reported RP series [11,12].

The reason for such an inverse stage and grade migration can only be speculated, since a great part of tumor and patient selection is done in primary care units. Certainly, the increasing use of AS in low-risk cancers is a main factor.

In addition to suitable cancer selection, adequate patient selection based on age, comorbidities, and life expectancy is the other instrument used to avoid overtreatment. Appropriate patient selection can be estimated by a low rate of other-cause mortality (OCM) in RP series. The OCM rate in our patients (1403 with complete follow-up information, composing 88.7% of the whole cohort), with a minimum follow-up of 15 yr, was low at 14.8%. The 15-yr OCM rates in men aged <65 yr at time of RP (66% of the whole cohort) and aged ≥65 yr were 10.2% and 24.3%, respectively.

These data must be interpreted in comparison to studies questioning the beneficial effect of RP in PSA-detected PCa. The OCM rate in the Prostate Cancer Intervention Versus Observation Trial (PIVOT) at the same point in time was >50% in both the control group and the RP group [13] (Fig. 2). Investigating the role of RP in an obviously inadequately selected patient cohort might be misleading, and such findings cannot be extrapolated to current clinical

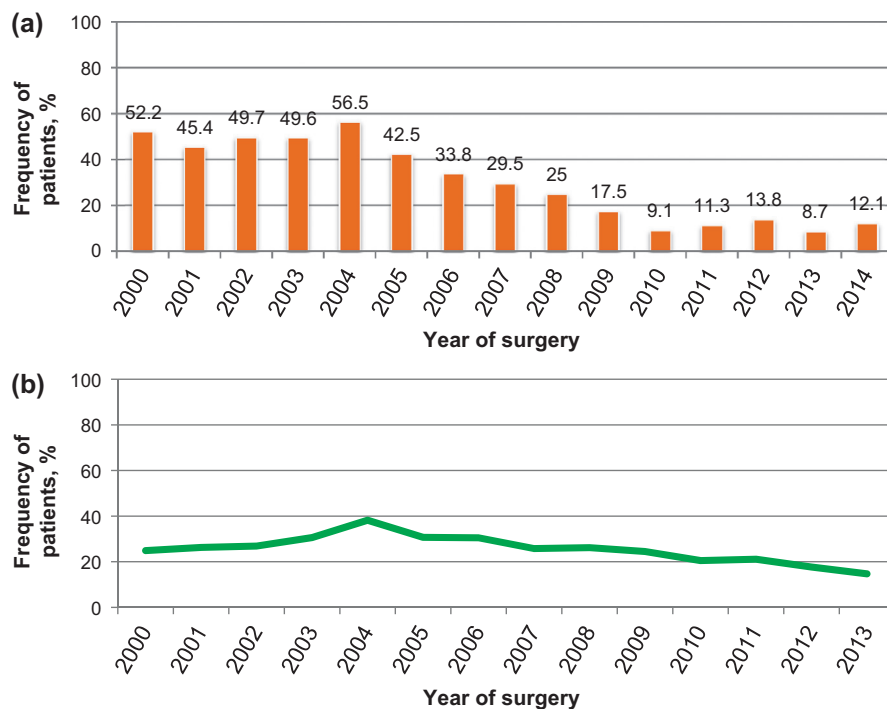


Fig. 1 – Changes in cancer selection: (a) frequency of patients with solely Gleason 6 cancer in the radical prostatectomy (RP) specimen, based on the original Gleason grading; (b) percentage of active surveillance candidates according to the European Association of Urology guidelines who underwent primary RP.

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