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The Significance of Recurrent PSA After Radical Prostatectomy: Benign Versus Malignant Sources

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The purpose of this article is to review the available means to investigate whether an elevated serum prostate-specific antigen (PSA) after radical prostatectomy may be explained by the presence of residual benign tissue. To answer this question, one may consider the following features: the kinetics of recurrent/persistent PSA, the incidence of rising PSA in the presence of capsular incisions exposing benign glands only, the level of urinary PSA and the ratio of free/total PSA in the urine, the results of anastomotic biopsy samples, and the detection of circulating prostate cells by PSA reverse transcriptase–polymerase chain reaction (RT-PCR) after surgery. Capsular incisions exposing benign tissue are not associated with a significant risk of biochemical failure. In case of an organ-confined cancer with negative surgical margins but a rising postoperative PSA, the systematic reevaluation of the initial pathological slides constantly shows capsular effraction or focal positive margins that have been overlooked at the first evaluation. Even when anastomotic biopsies document only benign tissue, the study of PSA doubling time is usually characteristic of the coexistence of residual tumoral cells. However, in a few cases, the persistent negative results of the detection of circulating prostate cells by PSA, RT-PCR in patients with organ-confined cancer and negative margins but elevated postoperative PSA might be explained by the presence of residual benign prostatic hyperplasia tissue. Most of the data in the literature are in favor of the responsibility of persistent/recurrent cancer in the recurring PSA rather than that of benign prostatic hyperplasia/normal residual tissue. Therefore, a persistent/recurrent detectable level of PSA is the serum after radical prostatectomy characterizes biochemical failure.

Key words: Prostate cancer, PSA, radical prostatectomy.

The goal of radical prostatectomy (RP) is cancer control, as witnessed by the absence of extraprostatic extension at pathology and a postoperative undetectable level of serum prostate-specific antigen (PSA). Everyone, patients and urologists, fears that tumor recurrence occurs as soon as the postoperative PSA rises over the accepted detection threshold.[1-3] However, the question arises whether an elevated PSA after surgery might be due to residual benign tissue "left behind" at surgery, particularly at the apex or at the bladder neck, and therefore does not require any adjuvant treatment.

To answer this question one may look at the following features:

1. the kinetics of recurrent/persistent PSA
2. the incidence of recurrent PSA in the presence of capsular incision exposing benign prostatic hyperplasia (BPH)
3. the level of urinary PSA and the ratio free/total PSA in the urine
4. the yield of anastomotic biopsies
5. the results of the detection of circulating prostate cells using PSA RT-PCR postoperatively.

Postoperative Rising PSA and Positive Surgical Margins in Normal Tissue

From a practical standpoint, the exponential rising PSA after a period of postoperative undetectability is more compatible with a tumor recurrence than with the persistence of normal benign prostatic tissue "left behind" at surgery, probably because of inadequate dissection of the prostatic apex, or of "over preservation" of the bladder neck.[4,5] However, if this was to be the case, one would expect postoperative PSA to be detectable at very low levels and to be stable over time. Nevertheless, even considering that a rising postoperative PSA might relate to persistent benign prostatic tissue, it is important to emphasize, as previously shown, that incisions of the capsule exposing benign tissue may occur in 37% to 90% of radical prostatectomies, according to the surgical approach, retropubic or perineal.[6] In the same study, convincing evidence showed that positive surgical margins in organ-confined tumors were associated with a significant risk of biochemical failure when exposing tumoral tissue, whereas capsular incisions exposing benign tissue were not. These findings do not support

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the hypothesis that, at least in a few cases, the secondary increase in serum PSA after radical prostatectomy may be due to residual benign prostatic tissue.

Initial Pathological Report and Pathological Understaging

In another study,[7] it was shown that a certain number of patients initially considered to have organ-confined (pT2) cancer with negative surgical margins at pathology experienced persistent/recurrent elevated postoperative PSA, possibly due to one of the following: local recurrence, micrometastases preoperatively unnoticed, or residual benign prostatic tissue. In all these cases, a systematic reevaluation of the initial pathology was done by rereviewing the slides or by performing new sections from the embedded prostate blocks, every 2 mm. In doing so, it was possible to relate the rising PSA to a microcapsular effraction or a focal positive surgical margin in every case. Again, these findings are not in favor of the responsibility of persistent normal prostatic tissue to explain a postoperative rising PSA, but are more in favor of persistent/recurrent cancer tissue.

BPH Remaining Tissue After RP and Free PSA

To determine whether a rising postoperative PSA might be due to recurrent tumoral prostatic cells or to residual benign cells, it was proposed to measure the free/total PSA ratio in the urine after massage of the urethrovesical anastomosis considering that this ratio should be higher in the presence of BPH residual tissue than in the presence of residual cancer cells.[8,9] To avoid contamination by the PSA produced by periurethral glands,[10] it was recommended to eliminate the first voided urine specimen from the analysis. The final results of this study are not yet available. However, recent data concerning the measure of the F/T PSA ratio in the serum of patients with recurrent PSA after radical prostatectomy[11] do not support its use to differentiate between cancer and BPH in this setting.

Anastomotic Biopsy

Fowler et al[12] evaluated the results of transrectal ultrasound (TRUS) guided anastomotic biopsies in the presence of PSA relapse after RP. In 10% (6 of 62) of the patients, biopsies revealed BPH tissue only. As already mentioned, theoretically, residual benign tissue may result from unintentional disruption of the prostatic capsule during surgery and may theoretically account for a detectable postoperative PSA, although several observations indicate that undetected carcinoma probably coexists with the benign tissue. In this series, when only BPH tissue was present within the biopsy specimen, the level of PSA ranged, at the time of biopsy, from 0.6 to 4.8 ng/mL. Considering that every gram of BPH tissue produces an average of 0.31 ng/mL increase in PSA,[13,14] it seems very unlikely that 1.9 to 15.5 g of BPH tissue could have been left after surgery or undergone such a fast regrowth. The PSA doubling time in these cases ranged from 7.3 to 100 months and increased in an exponential manner, whereas it is known[15] that PSA elevation in men with progressive BPH is linear and is usually around 0.09 ng/mL annually.

Circulating PSA-Positive Cells

Because PSA-positive circulating cells are detectable using a reverse transcriptase-polymerase chain reaction (RT-PCR), this method has been extensively used to discriminate, before surgery, organ-confined versus nonconfined tumors. However, the preliminary results have been conflicting. Therefore, RT-PCR was used to evaluate the presence of PSA-positive cells in the peripheral blood postoperatively. In the subgroup of pT2 patients with negative surgical margins but elevated postoperative PSA, some have negative RT-PCR results (unpublished data). To date, nobody knows whether these findings are related to residual BPH tissue or to technical problems in the RT-PCR methodology or to the intermittent nature of the shedding of cells from a cancer focus. Further follow-up of these patients is required to make conclusions.

Conclusion

Most of the data in the literature are more in favor of the responsibility of cancer relapse rather than that of residual BPH/normal tissue to explain a rising PSA after radical prostatectomy. Until the emergence of contradictory data, an elevated PSA after RP must be considered as biological recurrence even though the initial pathological report is favorable. In this setting, specimen reevaluation should be considered and will more often confirm that extracapsular extension or focal positive margins have been initially overlooked.

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