



Editorial – referring to the article published on pp. 258–265 of this issue

The Positive Surgical Margin after Radical Prostatectomy—Why do we Still not Really Know What it Means?

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Following radical prostatectomy a positive surgical margin will be found in 5–43% of the specimens [1]. Numerous factors have an impact on the incidence of positive margins: cancer volume and cancer location, surgical technique, and technique of pathologic work-up are the most important candidates. Once a positive margin is detected further questions arise: Has the positive margin status a direct influence on the subsequent treatment? Has the surgeon done a bad job? Is the prognosis independently influenced by this specific pathologic feature or is prognosis rather the result of the combined pathologic characteristics?

In the paper by Vis et al the impact of a positive surgical margin was investigated regarding biochemical and local recurrence [2]. The analysis is based on 281 patients with a median follow-up of 7 yr. The surgical margin status was considered in conjunction with other established parameters such as pathologic stage and Gleason score. Furthermore, the investigators considered percentage of high-grade cancer and total cancer volume as predictor variables, which has rarely been done in the literature because the majority of databases lack these important prognosticators.

It was found that the surgical margin remained as an independent predictor of biochemical recurrence in a multivariate setting, yet the predictive value was low. An outstanding result of this paper, however, is that the margin status was not significantly associated with clinical progression, an

end point that is usually not addressed in publications because only a few databases are mature enough to answer this question. In their analyses, the majority of men with an extensive positive margin remained free from recurrence.

What do we learn from this paper? First of all, it clearly reveals that a positive surgical margin does not necessarily mean that cancerous tissue is left behind. Second, it is not the margin status alone that drives prognosis.

The truth probably is that the impact of the margin status independently influences outcome in only a subset of patients. Ohori et al. have shown that margin status is an independent predictor in pT3a cancer, but not in organ-confined disease and not in cancers with seminal vesicle involvement [3]. The conclusion from this finding is that obviously some cancers (early organ-confined tumours) have an excellent prognosis regardless of the margin status. On the other side there are advanced cancers (ie, with seminal vesicle involvement and those with lymph node metastasis) that have a bad prognosis regardless of margin status.

If margin status is considered in a univariate fashion, the prognosis is always worse in the men with a positive margin. This is for the most part because the diagnosis of a positive margin predominantly occurs in large, locally advanced cancers with higher Gleason scores, whereas a negative margin is seen in the vast majority of organ-confined disease, which straightforwardly explains

the differences in prognosis. However, a univariate approach can not elucidate which role the margin status plays in this combination of prognosticators.

A special feature of the present paper by de Vis is that the percentage of high-grade cancer and total cancer volume was obtained in the histologic work-up. In previous papers published on the impact of margin status, the authors could not find an independent predictive ability of margin status when total and high-grade cancer volumes were included in multivariate analyses. The paper by Stamey and coworkers published in 1999 was the first that critically assessed a variety of pathologic features including total and high-grade cancer volumes and they found no independent predictive association of margin status and cancer outcome [4]. Our own group could find identical results following radical prostatectomy [5–7]. Margin status was independently associated with outcome when considered together with traditional pathologic features such as Gleason grade, capsular penetration, seminal vesicle involvement; however, as soon as total and high-grade cancer volumes were included in the analysis margin status was no longer independently associated with prostate-specific antigen relapse. This obviously means that the margin status is rather a product and the expression of a large cancer but it does not independently alter prognosis.

Does this mean that we do not have to care about margin status? Not at all! We have to realise that the results of the cited papers are based on the data of high-volume centres with high-volume surgeons who used several mechanisms to avoid surgical margins, such as careful preoperative patient selection and intraoperative frozen sections if appropriate [8]. This means that a positive margin that occurred in those series occurred despite careful surgery and represents an aggressive and advanced cancer in the majority of cases. Furthermore, numerous published papers demonstrated a significant and independent impact of margin status on long-term outcome. In a recent study based on 1389 men the impact of margin status was evaluated using different statistical methods for a subsequent adjuvant therapy [1]. In four of five statistical approaches margin status was significantly associated with outcome after adjusting for other risk factors. A similar analysis has been recently performed on an even larger multi-institutional cohort of patients ($n = 5813$), which demonstrated an independent association of margin status and prognosis [9].

If we look at this discussion we realize that beside all factors that influence positive margin incidence, it is, as well, the way of statistical method and input

variables that affect the result of whether or not the prognosis is influenced by margins status. Differences of considered prognostic factors and differences in the statistical approach can explain the controversial results in this subject.

Considering the discussion about the indication of adjuvant radiotherapy there is another lesson to learn from this paper: a positive surgical margin was not significantly associated with clinical progression. In the prospectively randomised trial recently published by Bolla and coworkers, 1005 patients after radical prostatectomy who had pN0M0 tumours were randomised to adjuvant or salvage radiotherapy [10]. Inclusion criteria were pathologic risk factors such as capsule perforation, invasion of seminal vesicles, and positive surgical margins. They found that patients with adjuvant radiotherapy have a better outcome compared to those undergoing salvage therapy. Considering the data in the present study the surgical margin alone should not necessarily indicate adjuvant therapy because we have to be aware that the majority of patients did not experience relapse and that clinical progression was not significantly associated with margin status.

Nevertheless, we should not forget about the psychological burden that a patient experiences when he is told that a positive surgical margin was found and cancer cells are potentially left in situ. Therefore, it is obvious that we should all continue to strive to reduce the rate of positive surgical margins to improve cancer control rates.

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