

Imre Romics¹, Attila Majoros¹, Péter Nyirády¹, László
Tornóci², Miklós Romics¹

EVALUATION OF THE IMPORTANCE OF THE POSITIVE SURGICAL MARGIN IN PATIENTS UNDERWENT RADICAL PROSTATECTOMY

Abstract

Introduction: Visible tumor cells on the surface of the resected tissue after radical prostatectomy signify incomplete local resection and an unsuccessful outcome of the disease and have a positive predictive value for the progression of the tumor.

Materials and methods: In our study we were trying to find correlation between the state of the surgical margin after radical prostatectomy and the rate of biochemical failure or clinical relapse and other oncological parameters in the presence of margin positivity as well.

Results: We have found significant correlation between the presence of Positive Surgical Margin (PSM) and other pathological and oncological features (just as PSA level, pre- and postoperative Gleason-score, the rate of biochemical failure, lymph node metastasis), and by that we present possible explanation for the positive predictive value of the surgical margin positivity.

Key-words: prostate cancer, radical prostatectomy, positive surgical margin

Introduction

Despite the rapid development of surgical technique the frequency of positive surgical margin on the resected specimens removed during radical prostatectomy (RP) is still fairly high, observed in one third of the cases (1). The chance of biochemical, local and systemic progression is highly increased in these patients (2). Also, the presence of the malignant cells on the surgical surface can increase the cost of

¹ Department of Urology, Semmelweis University, Budapest, Hungary

² Institute of Pathophysiology, Semmelweis University, Budapest, Hungary

treatment through the application of postoperative radio- and chemotherapy (3). The Positive Surgical Margin (PSM) can be described pathologically as „the presence of tumor cells on the surface of the specimen, where the incision has been made” (4). The malignant tissue reaching the surgical margin implies an inadequate removal of the tumor. International expertise state that the PSM is one of the predictors of tumor relapse after a radical prostatectomy. However, it is also known, that in cases where the Gleason-score is above 7 or the vesicles or the nodes have been infiltrated by malignant cells the diagnostic value of the PSM is irrelevant (5,6).

The surgical margin positivity has two types: iatrogenic and non-iatrogenic. The operation of tumors located only inside the capsule of the prostate can create a positive surgical margin if the capsule is being cut or damaged (4). This also indicates, that with a wider dissection the appearance of margin positivity can be avoided. If a tumor is already showing extraprostatic spreading, and reaches the extraprostatic tissues or the side of the the specimen being removed in the operation, we are talking about a non-iatrogenic PSM. Both types, just as the extraprostatic spreading of a tumor, can be focal (in one point only) or extensive (7). Our goals were to find the connection between the state of the surgical margin and other pathological and oncological parameters based on the results of researches in this area. Also, we have tried to find out the predictive value of PSM regarding the relapse of the tumor.

Materials and methods

417 radiacal prostatectomies have been performed in our department between January of 1998 and the late end of 2010, but in only 262 cases did we find a complete histological diagnoses we could apply in our study (table 1.). If the histological examination described cells being present in more then one point of the surgical margin of the specimen, or in only one point, but they are forming a cell line longer than two millimeters, the diagnosis was PSM.

Results

In 89 cases, out of 262, was the PSM recognizable (34%), in 173 patients (66% - forming the NSM – negative surgical margin – group) the margin was clear of malignant cells. The the mean age of the PSM group was 64 years, the group of NSM’s was 63,7.

Out of those 89 patients, whom surgical margin was infiltrated 29 had biochemical relaps (BCR) (33%), however, in only 38 NSM patients (out of 173) was found to develope the same type of condition (23%). The rate of BCR was significantly higher in the PSM group then in the NSM group ($p = 0,036$).

Local recurrence was found in 5 cases in the PSM group (5,6%), and 14 within the patients with negative surgical margin (8,1%). (The difference is not significant.)

We have also looked into the differences between the histological features of the tumors in the two groups. As it was expected, in the PSM group, the pre- and postoperative Gleason-scores, more often than not, were higher than in the NSM group. The preoperative Gleason score was an average of 6,7 and 7,4 was the average of the postoperative Gleason-scores in the group of PSM. In turn, the values in the NSM group were 5,8 and 6,3. The difference between the scores within the groups are significant, considering a p value of 0,025 in the preoperative, and 0,013 in the postoperative Gleason-score averages. Also, there was a highly visible (and significant – $p = 0,0001$) difference between the frequency of each tumor stages between the PSM and NSM groups (fig. 1.).

Furthermore we have observed a gross difference of quantity of lymph node metastases between the groups. In 14 cases (out of 89), where the malignant cells reached the surgical margin did we see infiltrated lymph nodes (12,3%). In the NSM group there was only one (0,005%) ($p = 0,0018$).

We have investigated the difference between preoperative PSA values of the two groups. The mean PSA value among the PSM patients was 17,3 ng/ml, and it was 11,2 ng/ml in the NSM group. The difference between these values is significant ($p = 0,033$).

Discussion

The incidence of margin positivity of the radical prostatectomy specimen, according to international sources, is varying widely. Papers in this topic mention rates between 5 and 43% (8,9,10) after open radical prostatectomies. This large deviation is due to the multifactorial nature of the appearance of the PSM in diverse group of patients. For example, if the average PSA level in a group of patients was low, the the rate of PSM was also lower, and vica versa. While our group of operated patients had an average PSA of 13,89 ng/ml, in many of the Western European articles it remains way below ten (11, 12). It means that our patients are in a more advanced stage at the time the operation is performed. Therefore the incidence of the PSM is expected to be higher. Thus it is perspicuous that the careful selection of the patients has a strong influence on the outcome of the state of the surgical margin, and on the possible recurrence of the tumor as well.

Also, it has to be considered, that the dimensional definition of the PSM is still not totally declared. For that reason, it is possible, that some researchers define

PSM as we did (multifocal infiltration of the surgical margin, or monofocal with at least 2 millimeters of extension), and some others designate PSM a margin with even one cell on the line.

In our investigation we have found that the two groups of our (PSM and NSM) patients showed significant difference in the rate of BCR. Therefore it is safe to state that the surgical margin positivity has a positive predictive value of Biochemical Relapse ($p = 0,036$).

The pre- and postoperative Gleason-scores were also significantly higher in the group of PSM patients. Furthermore, we have found a significant disparity in the dispersion of tumor stages in the PSM and NSM groups. Higher stages can commonly be associated with the likely appearance of the PSM. The same correlation can be found between the PSM and the commonness of lymph node infiltration: the PSM was more common in cases where malignant cells were visible in one or more nodes, then in the N0 stages ($p = 0,0018$).

We did not find a significant difference between the groups in the number of clinical relapses ($p = 0,49$). That proves that the emergence of metastases is a multifactorial incidence, and can not be explained by only the status of the surgical margin.

Comparing the preoperative PSA levels of the two groups we have also discovered a significant difference. As it is, we have confirmed the connection observed by other research groups, that the PSA level seen before RP correlates with the possible appearance of the PSM, since the patients in the PSM group had a much higher average of PSA (17,3 ng/ml) then the patients in the NSM group (11,2 ng/ml).

Conclusion

Prostate carcinoma patients with unfavorable oncological and clinical results just as higher preoperative PSA level or Gleason-score are not just more difficult to treat, but they have more chance to develop a relapse than patients with more fortunate lab results. Also, in these cases there's more chance to find a specimen with positive surgical margin that just makes it more probable to come across tumor relapses in the future. Therefore it is essential to recognize these cases and to follow them more carefully than other patients with cancer, since patients with PSM require a closer and also longer follow-up than the patients with no malignant cells on the surgical surface of the resected specimen, namely the PSM increases the chance of relapse, and may raise the need for adjuvant radio- chemo-, or combined therapy. For this reason, our goal is to decrease the PSM ratio through gaining more experience in the separative surgical technique, refining optical dissectors and other tools (loops, headlights) as well.

We do have to acknowledge that there is a certain limitation on our study, since the short follow-up time does not make it possible to draw conclusions about the correlation of the clinical relapse, long-time survival and the PSM.

Glossary:

- PSA Prostate-specific antigen
- PSM Positive surgical margin
- NSM Negative surgical margin
- BCR Biochemical recurrence
- CR Clinical recurrence
- GS Gleason-score

Parameters	Patient (sum)	PSM	NSM
n (%)	262 (100)	89 (34)	173 (66)
PSA (average) (ng/ml)	13.9	17.3 +/-12.2	11.2 +/-9
Gleason-score (preop.)	6.2	6.7 +/-1.7	5.8 +/-1.4
Gleason-score (postop.)	7.2	7.4 +/-1.6	6.3 +/-1.6
BCR	67 (25.6)	29 (33)	38 (23)
CR	19 (7.35)	5 (5.6)	14 (8.1)
Lymph node infiltration	12 (4.6)	11 (12.3)	1 (0.5)

TABLE 1.

Pathological and oncological parameters of our patients

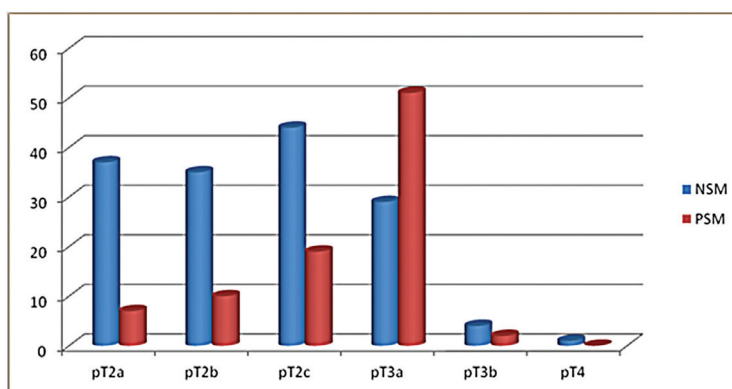


FIG. 1.

The correlation between the margin status and the tumor stages. The frequency of the margin positivity is closely correlated with the stage of the carcinoma.

REFERENCES

1. Freedland SJ, Aronson W, Presti Jr JC, et al. Should a positive surgical margin following radical prostatectomy be pathological stage T2 or T3? Results from the SEARCH database. *J Urol* 2003;169:2142–6.
2. Ofer Yossepowitch, Anders Bjartell, James A. Easthamc, Markus Graefen, Bertrand D. Guillonneau, Pierre I. Karakiewicz, Rodolfo Montironi, Franceso Montorsi; Positive Surgical Margins in Radical Prostatectomy: Outlining the Problem and Its Long-Term Consequences, *European Urology* 2009;55: 87–99
3. Hong YM, Hu JC, Paciorek AT, Knight SJ, Carroll PR. Impact of radical prostatectomy positive surgical margins on fear of cancer recurrence: results from CaPSURETM. *Urol Oncol* 2010; 28: 268–73
4. Epstein JI, Amin M, Boccon-Gibod L, et al. Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens, *Scand J Urol Nephrol Suppl* 2005; 216:34–63.
5. Matthew T. Gettman, M.D., Michael L. Blute, M.D., Radical prostatectomy: Does surgical technique influence margin control?, *Urologic Oncology: Seminars and Original Investigations* 28 (2010) 219–225
6. Stamey TA, McNeal JE, Yemoto CM, Sigal BM, Johnstone IM. Biological determinants of cancer progression in men with prostate cancer. *JAMA* 1999;281:1395–400.
7. D’Amico AV, Whittington R, Malkowicz SB, Schultz D, Schnall M, Tomaszewski JE, et al. A multivariate analysis of clinical and pathological factors that predict for prostate specific antigen failure after radical prostatectomy for prostate cancer. *J Urol* 1995;154:131–8.
8. Gettman MT, Blute ML. Critical comparison of laparoscopic, robotic, and open radical prostatectomy: Techniques, outcomes, and cost. *Curr Urol Rep* 2006;7:193–9.
9. Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, et al. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol* 2005;174:903–7.
10. Swindle PW, Kattan MW, Scardino PT. Markers and meaning of primary treatment failure. *Urol Clin North Am* 2003;30:377–401.
11. Guillonneau B, Cathelineau X, Barret E, Rozet F, Vallancien G., Laparoscopic radical prostatectomy: technical and early oncological assessment of 40 operations. *Eur Urol.* 1999;36(1):14-20
12. Jianqing Zhang, MD, Kevin R. Loughlin, The Role of Endorectal Coil MRI in the management of patients with prostate cancer and in determining radical prostatectomy surgical margin status: A report of a single surgeon’s practice, *Urology.* 2007 June; 69(6): 1134–1137.
13. Graefen M, Noldus J, Pichlmeier U, et al. Early prostatespecific antigen relapse after radical retropubic prostatectomy prediction on the basis of preoperative and postoperative tumor characteristics. *Eur Urol* 1999;36:21–30.
14. Kausik SJ, Blute ML, Sebo TJ, et al. Prognostic significance of positive surgical margins in patients with extraprostatic carcinoma after radical prostatectomy. *Cancer* 2002;95:1215–19.
15. Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, et al. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol* 2005; 174: 903-907.
16. Cheng L, Darson MF, Bergstralh EJ, et al. Correlation of margin status and extraprostatic extension with progression of prostate carcinoma. *Cancer.* 1999;86:1775-1782.
17. Fadi Brimo, Alan W. Partin, and Jonathan I. Epstein, Tumor Grade at Margins of Resection in Radical Prostatectomy Specimens Is an Independent Predictor of Prognosis, *UROLOGY* 76:1206–1211, 2010.

Anali Zavoda za znanstveni i umjetnički rad u Osijeku, sv. 30. str. 155-161, Zagreb-Osijek, 2014.
Imre Romics, Attila Majoros, Péter Nyirády, László Tornóci, Miklós Romics: Evaluation of the importance of the positive surgical margin in patients underwent radical prostatectomy

18. Blute ML, Bostwick DG, Bergstralh EJ, Slezak JM, Martin SK, Amling CL, et al. Anatomic site-specific positive margins in organ-confined prostate cancer and its impact on outcome after radical prostatectomy. *Urology* 1997;50:733–9.
19. Fesseha T, Sakr W, Grignon D, Banerjee M, Wood DP Jr., Pontes JE. Prognostic implications of a positive apical margin in radical prostatectomy specimens. *J Urol* 1997;158:2176–9.
20. van den Ouden D, Hop WC, Kranse R, Schroder FH. Tumour control according to pathological variables in patients treated by radical prostatectomy for clinically localized carcinoma of the prostate. *Br J Urol* 1997;79:203–11.
21. Koppie TM, Bianco FJ Jr., Kuroiwa K, et al. The clinical features of anterior prostate cancers. *BJU Int* 2006;98:1167–71.
22. Shekarriz B, Upadhyay J, Bianco FJ Jr, Impact of preoperative serum PSA level from 0 to 10 ng/ml on pathological findings and disease-free survival after radical prostatectomy. *Prostate*. 2001 Aug 1;48(3):136-43.