High risk prognostic factors after radical prostatectomy

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Abstract

Prostate cancer encompasses a wide spectrum of tumor phenotypes with differing prognoses and tumour recurrence is observed in a significant number of these cases. As treatment should be tailored to each individual patient depending on the features of their disease, urologists need to be able to estimate treatment outcomes. This paper presents the parameters that determine the risk of recurrence after radical prostatectomy. These parameters are based on clinical and histopathological findings, as well as on abnormal changes in PSA values after surgery. Taking these parameters into account, urologists can determine the further appropriate treatment of patients.

Introduction

Prostate cancer is considered the 3rd most common solid tumour condition in Western countries, after lung cancer and colon cancer. It is estimated that 500,000 new patients are diagnosed with prostate cancer worldwide each year and every patient is faced with two basic questions: what should be done to better manage the disease and what is his life expectancy after initial treatment? Both these questions have been difficult to answer up to now, because, despite the fact that prostate cancer shows relatively slow progression, exceptions to this rule have often been observed and many cases of aggressive forms of the disease have been described. In fact, prostate cancer is still the second most common cause of death in men.

During the last two decades, PSA mass testing has helped in the early diagnosis of prostate cancer and, subsequently, in increasing the probability of cure after local treatment. Therefore, the rate of clinically advanced prostate cancer out of all newly diagnosed prostate cancers dropped, from 41% in the 80s, to <9% in the 90s. However, despite this favourable shift in the disease stage, which has led to a significant reduction in mortality and a significant increase in disease-specific survival rates, 15% of patients present with high-risk cancer, whose characteristics are locally advanced disease or distant metastases. The majority of these patients have a worse 10-year cancer specific survival rate. However, in many cases, this rule does not apply and prognosis is better than expected. On the other hand, in 15 - 40% of patients with early-stage prostate cancer, the disease will progress, despite appropriate initial treatment. Therefore, the inaccurate assessment of the disease's risk profile may lead to improper treat-

Key words:
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ment, such as the indiscriminate use of hormonal manipulations or other adjuvants, as well as the incorrect exclusion of certain patients from potentially healing topical treatments.

This review presents the risk factors for recurrence after radical prostatectomy (RP). Radical prostatectomy (RP) is an effective method of treatment for patients with locally localised disease and has been shown to reduce the risk of death due to this. Approximately 40% of patients who choose treatment for curative purposes undergo RP. One of the key advantages of RP is the possibility of accurate staging, based on the histopathological evaluation of the removed prostate.

A disease with advanced histopathological findings is found in 38% to 52% of patients. Any form of extraprostatic extension of the disease is linked to a significantly increased risk of recurrence and progression, expressed through the early measurement of detectable PSA levels, known as biochemical failure (BCF). The natural history of prostate cancer with biochemical failure after RP may vary. However, about two-thirds of these patients will develop metastatic disease if there is no therapeutic intervention and most of them will die of the disease. The most comprehensive study of the natural history of prostate cancer and biochemical failure published was conducted in 1997, on a large series of post-RP patients. This study observed biochemical failure in 15% of cases, while the mean time between RP and BCF was 3.5 years. The five-year clinical recurrence rate was 27-60% and was found to be linked to the interval between RP and BCF, the Gleason score of the prostatectomy preparation and the PSA doubling time (PSA-DT). The mean time from BCF to clinical recurrence was 8 years.

High risk pathological factors after RP

Gleason Score of the surgical preparation

As known, the histological differentiation of the tumour usually reflects its aggressiveness. It is generally accepted that the Gleason Score (GS) is one of the most influential factors in determining the therapeutic treatment of prostate cancer. Thus, a GS of 8-10 is clearly linked to disease progression and is considered a poor prognostic factor.

In the surgical preparation, there can be more than two primary Gleason grades. The third most prevalent pattern in Gleason grading, i.e. that occupying the third largest tumour region, is called the tertiary Gleason grade. In surgical preparations where the tertiary Gleason grade is higher than the corresponding primary and secondary grades (usually grade 4 or 5), this is also recorded. There is increasing evidence that small areas with a grade 4 or 5 tertiary Gleason score are linked to aggressive abnormalities and a high risk of BCF. Recently, in a prospective study, Alenda et al. showed that the primary Gleason grade remained a statistical prognostic factor for BCF (P = 0.018) at multivariate analysis level. When the analysis was based on the pathological stage and the surgical margins, the prognostic value of the primary Gleason grade was important for pT2R0, pT3-4R0 and pT3-4R1 stage tumours, while the survival curves showed no statistical difference in tumour stage pT2R1 (P = 0.672). The authors concluded that the primary Gleason grade 4 was an independent prognostic factor for BCF.

Moreover, a high Gleason Score of the surgical preparation is a more important factor than the extracapsular extension of the disease. Epstein et al. observed that in patients with extracapsular disease extension without invasion of the seminal vesicles and lymph nodes, high-grade tumours showed a significantly greater risk of progression compared to lower grade tumours, suggesting that the extracapsular extension of the disease alone, in the absence of other pathological factors (e.g., high Gleason Score, positive surgical margins) does not imply a high risk for recurrence.

Positive surgical margins

Positive surgical margins (PSM) are defined as the presence of tumour at the inked surface of the resected RP specimen. There are two types of PSMs: iatrogenic and non-iatrogenic. In other words, PSMs can be the result of resection in patients with extraprostatic disease (stage pT3a), or of capsular incision in localised disease (stage pT2+). From an oncological viewpoint, the presence of PSMs in the RP preparation theoretically implies the inadequate removal of the malignant tumour. Retrospective studies have demonstrated the existence of PSMs as a risk factor for future BCF in all patients with clinically localised disease. Therefore, PSMs have been associated with poor prognosis in several studies, and most researchers consider them as an independent prognostic factor of prostate can-
cancer recurrence after RP. However, other researchers question the above findings, claiming that PSMs are not an independent prognostic factor of recurrence and disease progression. Furthermore, there are studies showing that, in the coexistence of abnormalities, such as a rate of Gleason grades 4/5 in the RP preparation, invasion of the seminal vesicles and lymph node invasion, the existence of PSMs plays no role in the assessment of the oncological outcome. Thus, the influence of surgical margins on disease progression in patients after RP remains controversial and it is debatable whether PSMs are the result of the unfavourable biological behaviour of the tumour, of technical errors, or both. It is understood that iatrogenic capsular incisions in low-grade localised prostate cancer have a different prognostic value than PSMs due to extraprostatic extension in high-grade tumours. In a retrospective study, Eastham et al. found that PSMs were significantly higher in patients with stage pT3 disease (35.7%) than in patients with pT2 disease (13.6%). Similar findings were reported by Vis et al. in a similar population study, in which the rates of PSMs in stage pT2 and pT3 disease were 18% and 40% respectively (p<0.01). However, in a recent retrospective study of 300 post-RP patients, Psutka et al. showed that the presence of PSMs was associated with a shorter time to BCF in patients with stage pT2, but not in patients with stage pT3 disease, whereas, in the latter, the existence of PSMs was not linked to an increased risk of BCF (HR: 0.747; 95% CI: 0.328 - 1.703). However, there are also studies showing that there are differences in the mean age and mean preoperative PSA values between cases with and without PSMs, concluding that the differences in the rates of PSMs may depend on other parameters, other than the histopathological stage of the disease, such as preoperative PSA values and the Gleason score of the prostatic biopsy. Alkhateeb et al. observed that the preoperative PSA values and the Gleason Score of preparation are linked to the rates of PSMs, and thus, when patients were categorised according to the D’Amico classification system in 3 risk categories for recurrence, those who were low-risk presented lower PSM rates than the corresponding mid- and high-risk patients. Some studies have investigated the prognostic significance of the location, number and extent of PSMs. Some of them noted a difference in the risk of recurrence between focal or solitary PSMs and extensive or multifocal PSMs, while others found no difference. Sofer et al. demonstrated that BCF was significantly more frequent in patients with multiple PSMs, compared to patients with a solitary PSM (HR: 2.19; 95% CI: 1.11 - 4.32); however, the anatomical location of the PSM did not play a role. On the other hand, Eastham et al. demonstrated that BCF was significantly affected by the specific anatomical location of the PSMs, showing that a posterolateral prostatic location has the greatest recurrence rates in the existence of PSMs. Other studies report that solitary PSMs in the area of the prostatic apex are linked to higher recurrence rates and shorter times to disease progression, while other studies show that PSMs in the prostate base area present the greatest risk for BCF. However, it remains unclear why PSMs in a specific area of the prostate can be a prognostic factor for recurrence of the disease, while in others not.

Extraprostatic extension

Extraprostatic extension (EE) of the disease is defined as the presence of neoplastic prostatic glands outside the prostate, in the periprostatic tissue. The term EE was accepted in 1996 and replaced the hitherto used terms, such as extracapsular or extraglandular invasion, penetration, or perforation. Nevertheless, disagreements about what the term Extraprostatic extension comprises still exist. This definition is, however, somewhat oversimplified as the prostate does not possess a histological capsule and it can be challenging for pathologists to identify the boundary of the gland. It therefore follows that the diagnosis of extraprostatic extension can be made with varying criteria in different regions of the prostate. In the posterior, posterolateral and lateral aspects, the diagnosis of extraprostatic extension is relatively easy, as the tumour is located in the periprostatic fat. Extraprostatic extension is a well-documented pathological prognostic factor for prostate cancer and its precise diagnosis is imperative for correct further treatment after RP. Both EE and PSMs have prognostic significance. Although several studies show the superiority of one over the other, in most of them, the separation of these two factors as to their prognostic significance proved difficult. The probability of assessing
the prognostic significance of a factor in multivariate studies depends on the type and number of other factors\textsuperscript{41}. Thus, for example, in patients with invasion of the seminal vesicles or regional lymph nodes, the PSMs or EE of the disease are probably not independent prognostic factors. Although their prognostic significance is important in the absence of other factors, it is, however, less important when other risk factors, such as invasion of the seminal vesicles and lymph nodes, coexist. The independent prognostic significance of the EE of the disease is less certain than that of PSMs. However, studies have shown that EE does have a certain prognostic value. More specifically, it has been reported that the rates of 5-year and 10-year progression-free survival in patients with EE without PSMs are 48%–76% and 46%–90%, respectively\textsuperscript{42,43,44}. In patients with EE and PSMs, these rates were 33%–55% and 20%–53% respectively\textsuperscript{24,30,44}.

The relationship between EE and PSMs remains unknown. Only a limited number of studies have evaluated the effect of these two factors on disease progression, in the absence of other risk factors. In one such study, Cheng et al.\textsuperscript{39} observed that there is a significant correlation between these two factors, as patients with EE and PSMs had higher rates of disease progression compared to those with EE or PSMs alone.

**Seminal vesicle invasion**

Seminal vesicle invasion (SVI) is defined as the invasion of the muscular wall of the seminal vesicles. SVI is linked to poor prognosis, as it usually concerns prostate cancer with a poorly differentiated large tumour, which has a high likelihood of extraprostatic extension\textsuperscript{45}. In patients with SVI, disease recurrence rates after RP are almost uniform worldwide\textsuperscript{46}. Nevertheless, few studies investigating tumours with isolated SVI have attempted to stratify the prognosis based on the parameter of SVI alone\textsuperscript{47}. Epstein et al.\textsuperscript{48} investigated the above question in a study of 45 patients with SVI as an isolated finding, who underwent long-term monitoring. They observed that the prognosis of patients with SVI was not calculated based on the malignant tumour, the extent of the SVI, or the bilateral localisation of the SVI. On the contrary, the condition of the surgical margins and the Gleason score of the RP preparation (Gleason score <7 vs ≥7) served as prognostic parameters, although without statistical significance. However, Ohori et al.\textsuperscript{49} reported that the condition of the surgical margins does not affect disease progression in cases with SVI. In a series of 137 patients with SVI as an isolated finding, Salomon et al.\textsuperscript{50} observed that only preoperative PSA values and the Gleason score of the RP preparation were independent prognostic factors for disease progression, while both capsular invasion and PSMs were not. According to the authors, the 5-year progression-free survival rate was 33.8%, but rates of 5%–60% have also been reported\textsuperscript{51}.

**Malignant tumour**

The prognostic value of malignant tumours (MT) for predicting BCF after RP has been questioned and has not yet been fully clarified. Large malignant tumours have been associated with the existence of other abnormal findings, such as a high Gleason Score, PSMs, SVI and lymph nodes\textsuperscript{52,53}. However, the role of MTs as an independent prognostic factor for BCF remains controversial. In a retrospective study, Salomon et al.\textsuperscript{54} found that, in a univariate analysis, the Gleason Score of the preparation, the pathological stage of the disease, PSMs and MTs were prognostic factors. In a multivariate analysis, however, it was found that only the Gleason Score of the preparation and the pathological stage of the disease were risk factors for disease progression, and if these parameters are known, MTs provide no significant prognostic information. Contrary to the above, Rampersaud et al.\textsuperscript{55} found that the MT rate is a significant prognostic factor for BCF and can be used as a basis for stratifying patients in relation to their pathological stage. More recently, Thompson et al.\textsuperscript{56} reported that the disagreement on the role of MTs arises because of the way in which they are measured. The authors concluded that MTs are a significant prognostic factor only if they are measured directly, by planimetry, rather than by percentile calculation. The above findings show that although a large MT can be a high-risk parameter for recurrence after RP, its precise role has not been clarified yet.

**Perineural invasion**

Perineural invasion (PI) is an abnormal finding of disputable prognostic value. It seems that PI is the route by which the disease can extend outside of the prostate. In many studies, PI is reported as simple finding, which is just monitored. For example, in a study of 17
patients with disease recurrence, PI was found in 14 (82%)\(^57\). Apart from this, no other real relationship of PI with recurrence has been found. Therefore, based on the data so far, PI is not an independent prognostic factor for recurrence of the disease\(^58\).

**Lymphovascular invasion**

Lymphovascular invasion (LVI) is an abnormal finding after RP and is defined as the presence of tumour cells in the vascular or lymphatic endothelial network. The incidence of LVI in RP preparations has been reported to be between 5% and 53%\(^59\). LVI has been associated with other abnormalities, such as a high Gleason score, a high pathological T stage, PSMs and SVI\(^60,61\). Its role as an independent prognostic factor for disease recurrence is disputed. It is reported that LVI is linked to a great extent with high rates of disease progression after RP\(^62,63\). De Taille et al.\(^63\) observed that the biochemical recurrence - free survival rate was 30% in patients with LVI and 92% in patients without LVI. Ouden et al.\(^64\) consider that LVI is a significant prognostic factor for biochemical, local clinical recurrence, distant metastases and overall survival. There are studies demonstrating an independent, significant correlation of LVI with disease progression in multivariate analyses\(^62-65\). However, other studies have found that LVI has no significance in multivariate analysis, in the coexistence of other parameters, such as preoperative PSA values, lymph node metastases, and the Gleason score\(^66\). Recently, Yee et al.\(^67\) made reference to the correlation of LVI with high preoperative PSA values and Gleason scores, and a greater likelihood for EE, PSMs, SVI and lymph node metastases in a univariate analysis (P <0.001 for all). At a median follow-up of 27 months, LVI was significantly associated with an increased risk of BCF after RP in both a univariate (P <0.001), and a multivariate analysis. (HR: 1.77; 95% CI: 1.11 - 2.82; P=0.017). Despite this, the authors concluded that LVI had a small contribution to prognosis as compared to other risk factors in a short follow-up.

**Lymph node invasion**

Lymph node invasion (LNI) is a well established independent prognostic factor in patients with prostate cancer and its existence implies a poor prognosis compared to patients without LNI\(^38,68\). Indeed, even today RP is abandoned if lymph nodes positive for metastasis are found during the resection of pelvic lymph nodes. The above management was based on a theory, supported by many authors, according to which the sur-

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### TABLE

**Characteristics and prognostic significance of abnormal findings after RP**

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<thead>
<tr>
<th>Abnormal finding</th>
<th>Prognostic significance</th>
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<tr>
<td>Gleason Score (GS)</td>
<td>• Well documented prognostic factor</td>
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<tr>
<td></td>
<td>• GS 8-10: poor prognostic factor</td>
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<tr>
<td>Positive Surgical Margins (PSMs)</td>
<td>• Independent prognostic factor for biochemical failure</td>
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<td></td>
<td>• Their prognostic value is still disputed in multivariate analyses</td>
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<tr>
<td>Extraprostatic Extension (EE)</td>
<td>• Well documented prognostic factor</td>
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<td></td>
<td>• Significant correlation between PSMs and EE</td>
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<td></td>
<td>• Its independent prognostic value is not certain</td>
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<tr>
<td>Seminal vesicle invasion (SVI)</td>
<td>• Linked to poor prognosis</td>
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<tr>
<td></td>
<td>• In the presence of SVI, other prognostic parameters such as PSMs do not play an important role in prognosis</td>
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<tr>
<td>Malignant tumour (MT)</td>
<td>• Its prognostic value is questionable and has not been fully clarified</td>
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<td></td>
<td>• Its role as an independent prognostic factor is controversial</td>
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<td></td>
<td>• In univariate analyses, it is considered as a prognostic factor for disease progression</td>
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<td></td>
<td>• In multivariate analyses, it has no prognostic value</td>
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<tr>
<td>Perineural Invasion (PI)</td>
<td>• Not considered as a robust independent prognostic factor</td>
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<tr>
<td>Lymphovascular Invasion (LVI)</td>
<td>• It is linked to the presence of other abnormal findings</td>
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<td></td>
<td>• Its role as an independent prognostic factor is controversial</td>
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<td></td>
<td>• Does not have significant prognostic value in multivariate analyses</td>
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surgical removal of the prostate in patients with positive lymph nodes does not impart any benefit in survival, due to the systemic nature of the disease. The above theory was confirmed by a large randomised EORTC trial, which investigated the difference between early and late hormone therapy in stage pN1 - 3M0 prostate cancer, without topical treatment of the primary tumour.

However, in 1999, a Mayo Clinic study in patients with high-risk prostate cancer with positive lymph node metastases showed that, compared to hormone therapy, the combination of RP and hormonal therapy significantly improved overall survival in a carefully selected number of patients with similar ages, T stages, numbers of positive lymph nodes and preoperative PSA values. The 10-year overall survival rate was 65% for patients who underwent RP and hormonal therapy, versus 30% for patients who underwent hormone therapy alone. More recently, Engel et al. published data from the Munich Cancer Registry, which supported the Mayo Clinic study and showed better survival rates in patients who underwent RP despite the presence of lymph node metastases, compared to patients in whom RP was abandoned after diagnosis.

Several studies have attempted to clarify what features of LNI have significant prognostic value. Such are considered, amongst else, the malignant tumours of lymph nodes, the number of positive lymph nodes, the density of lymph nodes, the extranodal extension of the disease, lymphovascular invasion and tumour differentiation. In the event of LNI, the small size and the small volume of the tumour are considered favourable characteristics. However, the current prostate cancer staging system has no subcategory for lymph node positive patients, which could provide a better picture for the prognosis of these patients.

Changes in PSA values after RP
Changes in PSA values after RP have been thoroughly investigated regarding their usefulness as prognostic factors for clinical progression (CP) and prostate cancer specific mortality (PCSM). The PSA doubling time (PSA-DT) after RP is directly related to CP and PCSM. Zhou et al. investigated the prognostic factors for PCSM in a series of 489 patients with biochemical failure, which included the PSA-DT, the Gleason score, and the interval between RP and BCF. The authors found that a PSA-DT of ≤ 3 months was significantly linked to PCSM, whose rate 5 years after BCF was 31% in patients with a PSA-DT of ≤ 3 months, compared to 1% in patients with a PSA-DT of ≥ 3 months. Pound et al. found that a PSA-DT of < 10 months could predict the time until metastatic disease progression. However, the PSA-DT was dependent on the Gleason score of the preparation and a Gleason score of > 7 was a more robust prognostic factor of metastatic disease progression. This study nevertheless showed that the most significant prognostic factors were the interval between RP and BCF and the advanced histopathological stage of the disease.

In general, many authors consider the PSA-DT representative for PCSM. Patel et al. report a close relationship of a PSA-DT of ≤ 3 months with clinical progression of the disease; however, 43% of patients with clinical progression in their study had a PSA-DT of ≥ 6 months. In addition, there are data supporting that the majority of patients who die from prostate cancer have a PSA-DT of ≥ 3 months, and therefore that the determination of the risk of disease progression should not be based on the PSA-DT alone.

The following table summarises the main pathological findings after RP in conjunction with their prognostic value.

Conclusion
Prostate cancer is a clinical entity that concerns a very diverse group of patients. The complex natural history of the disease and the lack of an accurate determination of risk can lead to delayed decisions on further treatment. The aim of the initial treatment is to prevent death and minimise complications. In other words, the endpoint of every therapeutic intervention is the patient’s survival. Therefore, the inaccurate determination of risk may lead to improper treatment, such as the indiscriminate use of hormonal therapy or other therapeutic options, or, on the other hand, to the exclusion of certain patients from curative treatment options. The determination of the risk of recurrence and disease progression after RP is based on specific clinical and histopathological findings. However, the assessment of these findings should be done with great care, to allow further treatment to be tailored to each individual patient.
Ο καρκίνος του προστάτη εμφανίζει ένα ευρύ φάσμα καρκινικών φαινοτύπων με διαφορετικές προγνώσεις και σε σημαντικό αριθμό περιπτώσεων παρατηρείται υποτροπή της νόσου. Καθώς η θεραπευτική αντιμετώπιση της νόσου θα πρέπει να εξατομικεύεται για κάθε ασθενή, ανάλογα με τα χαρακτηριστικά της νόσου, ο ουρολόγος θα πρέπει να είναι σε θέση να προσδιορίζει τα αποτελέσματα της θεραπείας. Στην παρούσα εργασία παρουσιάζονται οι παράμετροι που καθορίζουν τον κίνδυνο υποτροπής μετά από ριζική προστατεκτομή. Οι παράμετροι αυτές βασίζονται σε κλινικά και ιστοπαθολογικά ευρήματα, καθώς και σε παθολογικές μεταβολές των τιμών του PSA μετά το χειρουργείο. Λαμβάνοντας υπόψη τις παραμέτρους αυτές ο ουρολόγος μπορεί να καθορίσει την περαιτέρω ενδεδειγμένη θεραπευτική αντιμετώπιση των ασθενών.

**References**


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