The natural course of pT2 prostate cancer with positive surgical margin: predicting biochemical recurrence

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Abstract

Purpose To predict biochemical recurrence respecting the natural course of pT2 prostate cancer with positive surgical margin (R1) and no adjuvant/neoadjuvant therapy.

Methods A multicenter data analysis of 956 patients with pT2R1N0/Nx tumors was performed. Patients underwent radical prostatectomy between 1994 and 2009. No patients received neoadjuvant or adjuvant therapy. All prostate specimens were re-evaluated according to a well-defined protocol. The association of pathological and clinical features, in regard to BCR, was calculated using various statistical tests.

Results With a mean follow-up of 48 months, BCR was found in 25.4%. In univariate analysis, multiple parameters such as tumor volume, PSA, Gleason at positive margin were significantly associated with BCR. However, in multivariate analysis, Gleason score (GS) of the prostatectomy specimen was the only significant parameter for BCR. Median time to recurrence for GS ≤ 6 was not reached; 5-year BCR-free survival was 82%; and they...
were 127 months and 72 % for GS 3+4, 56 months and 54 % for GS 4 + 3, and 27 months and 32 % for GS 8–10. The retrospective approach is a limitation of our study. **Conclusions** Our study provides data on the BCR in pT2R1-PCa without adjuvant/neoadjuvant therapy and thus a rationale for an individual’s risk stratification. The data support patients and physicians in estimating the individual risk and timing of BCR and thus serve to personalize the management in pT2R1-PCa.

**Keywords** Biochemical recurrence · Localized prostate cancer · Natural course · No adjuvant therapy · Positive surgical margins

**Introduction**

Multiple prospective randomized trials have shown an association of positive surgical margins after radical prostatectomy with a worsened patient’s outcome in localized prostate cancer [1, 2].

As associated risks and benefits of adjuvant radiotherapy in pT2 tumors with positive surgical margin (R1) are difficult to balance, physicians face the challenge of advising an individual on the necessity of adjuvant radiotherapy. Even the most recent guidelines by the EAU and AUA do not provide stage-specific clear recommendations on adjuvant treatment [3–5].

A more precise identification of specific features within the group of pT2R1 patients would be desirable to identify those patients who benefit most likely from adjuvant treatment or even more importantly of those patients who would be rather harmed by an adjuvant approach. Even though many centers are now doing an approach of early salvage radiotherapy rather than adjuvant, there is still a lack of data on the actual risk of recurrence in this specific scenario that can be shared with the patient during planning of the individual therapeutic management.

Furthermore, the calculation of the approximate timing of the event of BCR could help in the management during follow-up in order not to miss the appropriate timing for salvage radiotherapy.

In the following study, we evaluated the natural course of pT2R1 prostate cancer and the ability of various parameters to predict BCR using data from eight urological centers. Pathohistological criteria were based on an entirely new histopathological reassessment of all prostate samples according to a strict pathologist’s protocol.

**Methods**

In eight European centers, data from 1033 patients with pT2R1N0/NX cancer between 1994 and 2013 were collected using patient charts, electronic data processing tools, personal patient contact and direct information from treating physicians after IRB approval. The deadline for all surgical procedures was set to the year 2009 for all patients to guarantee an adequate time of follow-up. Follow-up data were available from 956 patients.

Patients with neoadjuvant or adjuvant therapy were excluded. A panel of urologists, pathologists and radiation oncologists predefined clinical and pathological parameters to be included in a common database. All evaluated parameters can be found in Table 2. The actual EAU guidelines define a margin as positive if tumor cells are in touch with the ink on the surface of the specimen. Margin status is defined as negative if tumor cells are very close to the inked surface of the margin [6] or when they are at the surface of the tissue lacking any ink. It should also be mentioned here that according to these guidelines the surgical margin status is independent of the pathological stage and that a positive margin is not evidence of extraprostatic extension [7]. According to the strict centrally defined protocol, each local uropathologist re-reviewed the histopathological slides for all of the listed parameters.

As primary outcome parameter, BCR after radical prostatectomy was chosen in accordance to previous studies [1, 2]. As biochemical failure, a PSA level >0.2 ng/ml following radical prostatectomy after a postoperative PSA-“free” interval was defined according to the most recent EAU guideline [8]. Last determined PSA during follow-up had to be no older than 6 months.

**Statistics**

Survival data analysis was performed using Kaplan–Meier method, log-rank test and uni-/multivariate Cox regression models with biochemical recurrence as endpoint. Age, PSA value, tumor volume, prostate volume, percentage of tumor and maximum length of positive surgical margin were used as continuous variables in the Cox models. Gleason score was categorized into four groups (Gleason 6/3 + 4/4 + 3/8–10) using dummy variables and Gleason 6 as reference. In multivariate Cox regression analysis, a forward stepwise approach was used; the covariates are tested for entry into the model, one by one, based on the significance level of the score statistic. $p$ values < 0.05 were
considered significant. For all calculations, STATISTICA
10 (StatSoft, Tulsa, OK) and SPSS 22 (IBM, Armonk, NY)
were used.

Results

956 patients with pT2R1N0/x prostate cancer and no adju-
vant or neoadjuvant therapy were analyzed. BCR was
found in 25.4 % in T2R1 tumors after a mean of 48 months.
For patient characteristics, please see Table 1.

In univariate analysis, multiple parameters such as tumor
volume, PSA, Gleason at positive margin were significantly
associated with BCR (Table 2).

Preoperatively intended omission of pelvic lymph node
dissection had a protective effect on BCR in T2 tumors
\((p = 0.002)\), suggesting that lower malignant potential as
evidenced by R1 Nx cancers had lower preoperative PSA,
a higher proportion of T1c cancers and smaller tumor
volume.

In multivariate analysis, GS of the regular prostatectomy
specimen was the only statistically significant parameter
for pT2R1 prostate cancer (Table 3, \(p = 0.003\)). This obser-
vation remained stable even if data were analyzed respect-
ing each center separately or if larger centers were com-
pared versus smaller centers.

The following calculations are based on GS of pros-
tatectomy specimen as the only significant parameter in
multivariate analysis in pT2R1 tumors. The event of BCR
according to GS was 19 % (for GS \(\leq 6\)), 26 % (for GS
3 + 4), 44 % (for GS 4 + 3) and 59 % (for GS 8–10). The
median time to recurrence was not reached for GS \(\leq 6\), and
it was 127 months for GS 3 + 4, 56 months for GS 4 + 3,
and 27 months for GS 8–10 (see Fig. 1).

Discussion

In clinical practice, there is an imminent need for risk strat-
ification in patients with localized prostate cancer and posi-
tive surgical margins, since these are assumed to be linked
to a worsened patient’s outcome.

The latest version of the EAU guidelines on prostate
cancer (updated in April 2014) does not specifically men-
tion the issue of adjuvant radiotherapy in pT2 patients with
positive margin. However, it is stated that “In patients with
pathological tumor stage T3 N0 M0, immediate postop-
erative external irradiation after RP may improve the bio-
chemical and clinical disease-free survival, with the highest
impact in cases of positive margins.” As the previously cited
recommendation regarding T3 tumors cannot be directly
transferred to the cohort of T2 tumors, there is a high
uncertainty in the community on how to treat patients with
pT2R1 Nx/N0 tumors. Unfortunately, there is less pro-
spective data on the adjuvant treatment of pT2R1 tumors
available.

So far, there are three prospective randomized trials that
have assessed the role of immediate postoperative radio-
therapy. One is the EORTC 22911 [1] study with 1,005
included patients. Here, an immediate postoperative radio-
therapeutic approach, using 60 Gy, was compared to radio-
therapy delayed until local recurrence using 70 Gy. Patients
after retropubic RP were included who presented with pT3
pN0 tumors and different risk factors as well as pT2 tumors
with positive margins.

The study showed that for patients younger than
70 years, the immediate postoperative radiotherapy after

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**Table 1 Patient characteristics \((n = 946)\)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years] median (range)</td>
<td>64 (40–79)</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>%</td>
</tr>
<tr>
<td>&lt;4</td>
<td>13</td>
</tr>
<tr>
<td>4–9.9</td>
<td>65</td>
</tr>
<tr>
<td>10–19.9</td>
<td>18</td>
</tr>
<tr>
<td>≥20</td>
<td>4</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>52 % (500/956)</td>
</tr>
<tr>
<td>Nerve-sparing technique</td>
<td>93 % (884/947)</td>
</tr>
<tr>
<td>Surgical method: RRP</td>
<td>88</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>6</td>
</tr>
<tr>
<td>Da Vinci</td>
<td>4</td>
</tr>
<tr>
<td>Perineal</td>
<td>3</td>
</tr>
<tr>
<td>Gleason score</td>
<td>%</td>
</tr>
<tr>
<td>(\leq 6)</td>
<td>39</td>
</tr>
<tr>
<td>3 + 4</td>
<td>52</td>
</tr>
<tr>
<td>4 + 3</td>
<td>7</td>
</tr>
<tr>
<td>8–10</td>
<td>2</td>
</tr>
<tr>
<td>Bilateral tumor</td>
<td>74 % (704/956)</td>
</tr>
<tr>
<td>Prostate volume (ml) median (range)</td>
<td>42 (12–148)</td>
</tr>
<tr>
<td>Percent tumor tissue (ml) median (range)</td>
<td>9.6 (0.1–70.0)</td>
</tr>
<tr>
<td>Primary Gleason at surgical margin</td>
<td>%</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Maximum length of positive margin (mm)median (range)</td>
<td>2.0 (0.1–30.0)</td>
</tr>
<tr>
<td>Perineural infiltration</td>
<td>80 % (455/571)</td>
</tr>
<tr>
<td>Lymphovascular infiltration</td>
<td>%</td>
</tr>
<tr>
<td>L0</td>
<td>95</td>
</tr>
<tr>
<td>L1</td>
<td>5</td>
</tr>
<tr>
<td>Vascular infiltration</td>
<td>%</td>
</tr>
<tr>
<td>V0</td>
<td>99</td>
</tr>
<tr>
<td>V1</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^{a}\) Sum <>100 due to rounded percent
surgery improved significantly the 10-year BCR-free survival (60.6 vs. 41.1 %). Furthermore, a slight benefit was observed in the clinical progression rates for ART after 5 years. Nevertheless, this trend was lost after 10 years.

In pT2-3 R1 patients, the use of ART showed an improved clinical PFS after 10 years (HR = 0.69; \( p = 0.008 \)). It should be mentioned that the OS was not significantly different between the two treatment arms. The highest impact of ART on BCR (HR reduced to 0.3) was seen in patients with positive margins [2, 9].

The ARO trial 96–02 (\( n = 385 \)) showed a significant improvement for the ART group regarding BCR of 72 versus 54 %, respectively (\( p = 0.0015 \)) with a median follow-up period of 54 months. The authors conclude that ART is effective, even in the setting of an undetectable PSA after RP and additional risk factors [2].

Moreover, the SWOG 8794 trial showed that ART significantly improved the metastasis-free survival,

**Table 2** Univariate Cox regression analysis of potential prognostic parameters for biochemical recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95 % Confidence interval</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate volume*</td>
<td>1.00</td>
<td>0.99–1.00</td>
<td>0.255</td>
</tr>
<tr>
<td>Tumor percentage*</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.188</td>
</tr>
<tr>
<td>Maximum positive margin*</td>
<td>0.99</td>
<td>0.93–1.05</td>
<td>0.684</td>
</tr>
<tr>
<td>Age*</td>
<td>0.98</td>
<td>0.95–1.00</td>
<td>0.029</td>
</tr>
<tr>
<td>PSA preoperative*</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.002</td>
</tr>
<tr>
<td>Nerve-sparing surgery</td>
<td>0.99</td>
<td>0.71–1.39</td>
<td>0.964</td>
</tr>
<tr>
<td>Pelvic lymph node dissection performed</td>
<td>1.69</td>
<td>1.25–2.29</td>
<td>0.001</td>
</tr>
<tr>
<td>Pathological Gleason score</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gleason 3 + 4 = 7a versus Gleason 6</td>
<td>1.49</td>
<td>0.93–2.39</td>
<td>0.096</td>
</tr>
<tr>
<td>Gleason 4 + 3 = 7b versus Gleason 6</td>
<td>3.51</td>
<td>2.13–5.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gleason 8–10 versus Gleason 6</td>
<td>3.52</td>
<td>1.98–6.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perineural infiltration</td>
<td>1.41</td>
<td>0.72–2.79</td>
<td>0.320</td>
</tr>
<tr>
<td>L-Status</td>
<td>1.71</td>
<td>0.97–3.02</td>
<td>0.065</td>
</tr>
<tr>
<td>V-Status</td>
<td>2.19</td>
<td>0.69–6.93</td>
<td>0.183</td>
</tr>
<tr>
<td>Gleason grade at positive margin (Gl. 4/5 vs. Gl. ( \leq ) 3)</td>
<td>0.95</td>
<td>0.61–1.47</td>
<td>0.801</td>
</tr>
<tr>
<td>Bilateral versus unilateral tumor</td>
<td>4.24</td>
<td>0.60–30.28</td>
<td>0.149</td>
</tr>
</tbody>
</table>

Parameters marked with * were used as continuous variables; Gleason score was analyzed in four categories (6/7a/7b/8–10) using score 6 as reference.

**Table 3** Multivariate Cox regression analysis of potential prognostic parameters for biochemical recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95 % Confidence interval</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA preoperative*</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.110</td>
</tr>
<tr>
<td>Pelvic lymph node dissection performed</td>
<td>1.29</td>
<td>0.94–1.78</td>
<td>0.120</td>
</tr>
<tr>
<td>Pathological Gleason score</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gleason 3 + 4 = 7a versus Gleason 6</td>
<td>1.38</td>
<td>0.86–2.22</td>
<td>0.182</td>
</tr>
<tr>
<td>Gleason 4 + 3 = 7b versus Gleason 6</td>
<td>2.98</td>
<td>1.78–5.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gleason 8–10 versus Gleason 6</td>
<td>3.07</td>
<td>1.69–5.56</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Parameters with \( p < 0.01 \) in univariate analysis were included. Parameters marked with * were used as continuous variables; Gleason score was analyzed in four categories (6/7a/7b/8–10) using score 6 as reference.

**Fig. 1** Recurrence free survival over time respecting different GS
with a 10-year metastasis-free survival of 71 versus 61 % \((p = 0.016)\) and a 10-year OS of 74 versus 66 % \((p = 0.023)\) \cite{10} with a median follow-up of more than 12 years.

Respecting these and other publications, the actual EAU guidelines offer two options for patients with pT3 pN0 with a high risk of local failure after RP: either “Immediate ART to the surgical bed after recovery of urinary function” or “Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/ml.”

To better inform our patients, data on ART versus SRT are discussed in the following. Boorjian et al. compared 361 ART patients with 722 non-ART patients in a case-control analysis. Patients were selected to match by treatment period, age, pre-RP PSA, tumor stage, Gleason score and surgical margin status. No difference was seen in overall survival. However, 10-year BCR-free survival after ART was significantly improved over non-ART (63 vs. 45 %).

Moreover, Boorjian et al. \cite{11} treated 856 patients with SRT after biochemical relapse (median PSA 0.8 ng/ml) with a median follow-up of 5.9 years. In this setting, 63 % of SRT patients presented with an undetectable PSA value with a hazard ratio for local recurrence of 0.13. In the end, there was no improvement in the OS after SRT just as after ART.

Another case-control study evaluated ART versus early SRT in pT3N0 R0/R1 patients exclusively. In this study, 390 observation-plus-early-SRT patients were matched with 390 regular ART patients. Two and five years after surgery, BCR-free rates were 91 and 78 % for ART versus 93 and 82 % after SRT.

Also a subgroup analysis showed no significant differences between the two approaches. So the authors concluded that “early SRT does not impair PCa control but clearly helps to reduce overtreatment which is a major issue in ART” \cite{12}.

If we look at the current EAU guidelines the urologist will be asked “to explain to the patient before radical prostatectomy that adjuvant radiotherapy may be administered if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multi-disciplinary approach that takes into account the optimal timing of radiotherapy when it is used and provides justification when it is not, and this will help the discussion between the physician and the patient.” This recommendation leaves the treating physician somehow alone on how to proceed with this specific group of T2R1 patients. The possible side effects of adjuvant therapy need to be respected.

If we analyze data on radiation therapy, the dose and volume play an important role on the outcome, as well as on possible side effects. So far, the optimal SRT dose has not been clearly defined. According to the EAU guideline, it should be at least 66 Gy to the prostatic fossa (plus/minus the bed of the seminal vesicles) \cite{13}. Other data also claim that a higher total dose achieves higher rates of BCR-free survival at 3–5 years \cite{14}.

Further data show that the pre-SRT PSA level and SRT dose are correlated with biochemical recurrence. It is shown that the relapse-free survival decreases by 2.6 % per 0.1 ng/ml PSA and improves by 2 % per applied Gy. This observation suggests that a treatment dose above 70 Gy should be administered at the lowest possible PSA \cite{13, 15, 16}.

There are also described different attempts to define “clinical target volumes” of PCa \cite{17–19}. Yet, there has been achieved no clear consensus so far. There is a RTOG consensus available considering two PCa cases: one T2c with positive margins at both sides of the apex and one T3b with extracapsular extension at the right base and right seminal vesicle but with negative margins \cite{17}.

If we want to transfer these data and recommendations for the cohort of T2R1 patients appropriately, we need to know the actual risk of BCR (respecting local and distant failure) in this specific situation \cite{20–24}.

To differentiate between local and distant relapse, several parameters have been established. According to Roach et al. as well as Pound et al. \cite{25}, a PSA increase within the first 2 years after radical prostatectomy is more often associated with distant recurrences.

So far no larger study provides a separate analysis of BCR in pT2R1 patients, or a separate analysis of BCR risk broken down by pathological factors other than pT or R status in their control arm.

In the presented study, all of the specimens were meticulously reviewed by experienced uropathologists at each single site to secure that all predefined parameters were assessed across all specimen. When doing so, we were able to show a distinct pattern of recurrence also within the group of pT2R1 prostate cancers. Astounding was a likelihood of 59 % BCR in men with pT2R1 and Gleason grade \(\geq 4+4\). This means that 59 % of patients in the highest Gleason group had BCR and 41 % did not. So there would be “overtreatment” using primary adjuvant radiotherapy in a relevant number of cases. Conversely, only about one-fifth of those with Gleason 6 had BCR in this cohort.

In the light of our findings, it is now possible to inform our patients on the likelihood of BCR on an individual basis. These data provide us with new information for the discussion of the risk of BCR or the need for future SRT. Also the need and timing for follow-up examinations in this specific patient cohort can be stressed better than ever before. Maybe PSA should be checked more intensively over a certain time frame respecting the individual risk of a pT2R1 patient.

A final, but also important result of the presented study is the observation of an impaired relevance of other
published prognostic factors on multivariate analysis (such as length of positive margin and Gleason of positive margin) in comparison with pathological Gleason score in pT2R1 cancers. However, it has to be respected that the presented data have been gained retrospectively and can be only partly compared to other smaller prospective trials on BCR predictive parameters.

Our study is not devoid of limitations. One drawback is the fact that there was no central pathology to avoid inter-observer variability. Nevertheless, all predefined parameters were respected and analyzed by each specifically instructed uropathologist at each site. Also the processing of the prostate sample was not performed uniformly over the participating centers due to the retrospective setting. Another point of debate could be the fact that we analyzed only the endpoint BCR and not survival or metastasis-free survival and had no control arm in the form of pT2R0 cases. Also at the time of BCR, there was not enough information available to rule out systematic or local disease. Likewise, we had no comparison to an intervention arm pT2aR1 plus adjuvant radiation therapy. This precludes us to make solid assumptions on the efficacy of adjuvant radiation therapy in these patients, has it been administered to the patients. However, as recent studies could show that positive surgical margins are not associated with a significantly increased risk of cancer-specific mortality [26, 27], the main focus of our analysis was to inform patients on their risk of biochemical recurrence and their possible need for secondary therapy (adjuvant/salvage, etc.). As BCR may be a source of considerable patient anxiety, our data could help to put this information into perspective.

A point of debate could be the fact that no patients with adjuvant therapy were respected in the final analysis. However, the aim of the presented study was to follow the natural course of patients with pT2R1 patients who were exclusively treated with radical prostatectomy. Only these patients were included into the study protocol, and only these underwent meticulous histopathological work up again that we wanted to base our analysis on.

The strength of our data can be found in the large number of cases without adjuvant therapy, enabling us to shed an undisturbed light on the patterns of BCR in a well-defined group of separately analyzed pT2R1 patients. Moreover, the large number of cases and the fact that all 956 R1 cases underwent a pathological re-evaluation, analyzing virtually all clinical and pathological variables discussed in the current literature, eliminate biases due to different pathological evaluation and add to the robustness of the data. Finally, the results are quite straightforward: Only one basic pathological feature, GS in pT2R1 was sufficient to identify the distinct subgroups. As these are standard to be reported, the risk determination of BCR for pT2R1 can be easily implemented in clinical practice.

Conclusions

In pT2 prostate cancers with positive surgical margin, only the parameter “Gleason score of the specimen” allows for an estimate of the risk of BCR and the approximate timing of the event of BCR. Based on the data, a new and easy way to apply risk stratification allows for a personalized patients management and information.

Conflict of interest All authors declare that they have no conflict of interest.

Ethical standard Manuscripts submitted for publication has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

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