Prostate Cancer

Pretreatment Tables Predicting Pathologic Stage of Locally Advanced Prostate Cancer

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Abstract

Background: Pretreatment tables for the prediction of pathologic stage have been published and validated for localized prostate cancer (PCa). No such tables are available for locally advanced (cT3a) PCa.

Objective: To construct tables predicting pathologic outcome after radical prostatectomy (RP) for patients with cT3a PCa with the aim to help guide treatment decisions in clinical practice.

Design, setting, and participants: This was a multicenter retrospective cohort study including 759 consecutive patients with cT3a PCa treated with RP between 1987 and 2010.

Intervention: Retropubic RP and pelvic lymphadenectomy.

Outcome measurements and statistical analysis: Patients were divided into pretreatment prostate-specific antigen (PSA) and biopsy Gleason score (GS) subgroups. These parameters were used to construct tables predicting pathologic outcome and the presence of positive lymph nodes (LNs) after RP for cT3a PCa using ordinal logistic regression.

Results and limitations: In the model predicting pathologic outcome, the main effects of biopsy GS and pretreatment PSA were significant. A higher GS and/or higher PSA level was associated with a more unfavorable pathologic outcome. The validation procedure, using a repeated split-sample method, showed good predictive ability. Regression analysis also showed an increasing probability of positive LNs with increasing PSA levels and/or higher GS. Limitations of the study are the retrospective design and the long study period.

Conclusions: These novel tables predict pathologic stage after RP for patients with cT3a PCa based on pretreatment PSA level and biopsy GS. They can be used to guide decision making in men with locally advanced PCa.

Patient summary: Our study might provide physicians with a useful tool to predict pathologic stage in locally advanced prostate cancer that might help select patients who may need multimodal treatment.

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1. Introduction

The best management of locally advanced prostate cancer (PCa) is a challenging problem. In the absence of randomized trials comparing different treatment modalities (ie, surgery, radiation therapy [RT], androgen-deprivation therapy, or a combination), it is very difficult to counsel patients properly on the optimal treatment strategy. For patients with localized PCa, radical prostatectomy (RP) is considered an ideal therapy [1]. However, several studies have shown that RP as the initial treatment may also show acceptable long-term outcomes in patients with locally advanced PCa [2–10]. This may be partly due to the fact that a significant portion (13–27%) of cT3a tumors are overstaged and are actually T2 at RP [5,6,8,11]. In contrast, a number of cT3a tumors are understaged and invade the seminal vesicles (pT3b) or neighboring organs (pT4). As expected, the outcome of RP for pT2 and pT3a tumors is significantly better than for pT3b and pT4 tumors [5,8,12,13]. International guidelines support the addition of an extended pelvic lymph node dissection (ePLND) to RP in locally advanced PCa because the risk of finding positive lymph nodes (LNs) at surgery is considerable [1,14].

Although a number of patients with cT3a need adjuvant or salvage RT or hormonal therapy, a non-negligible proportion may be treated with surgery alone and will not need any further therapy, thereby sparing them from associated morbidity. The problem remains how to best select those patients suitable for RP. The Partin tables, using combinations of preoperative serum prostate-specific antigen (PSA) level, biopsy Gleason score (GS), and clinical stage, are widely used to predict final pathologic stage after RP for men with clinically localized PCa (T1c–T2c) [15,16]. However, despite the fact that such tables would also be of high value for men with locally advanced PCa, regrettably only one published paper provides a single-center non-validated pretreatment prediction table [11].

In the present study, we constructed and validated a pretreatment table for predicting the final histopathology and the presence of positive LNs after RP for locally advanced PCa (cT3a), based on a retrospective analysis of a large multicenter European database. This could aid physicians in making treatment decisions for patients with cT3a PCa in daily clinical practice.

2. Patients and methods

2.1. Patient population

This retrospective cohort study included patients with cT3a PCa as assessed by digital rectal examination (DRE) diagnosed between July 1987 and May 2010 at seven high-volume European tertiary referral centers (Brussels and Leuven, Belgium; Hamburg and Wurzburg, Germany; Milan, Novara, and Turin, Italy). DRE was performed by the attending surgeon before prostate biopsies. All men underwent a bone scan and a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the pelvis. Patients were excluded if they were found to have radiographic evidence of a pelvic node or distant metastatic disease. All patients underwent RP with bilateral PLND. Patients receiving neoadjuvant therapy before RP were excluded from the analysis. Following the noted exclusions, a total of 759 men remained in the study.

2.2. Biopsy and pathologic examination

Prostate biopsies were performed under transrectal ultrasound (TRUS) guidance, and pretreatment PSA was measured before DRE or TRUS. All biopsy material underwent review by a pathologist with expertise in genitourinary pathology at each institution. The RP specimens including prostate, seminal vesicles, and bilateral pelvic LNs were examined microscopically after routine preparation. The pathologic stages were recorded according to the 2002 TNM classification.

2.3. Statistical analysis

We used ordinal logistic regression in the analysis. The methodology used was described previously in detail by Hosmer and Lemeshow [17]. The PSA level was divided into three strata (≤10 ng/ml, 10.1–20 ng/ml, and ≥20 ng/ml). The GS was categorized into three levels (≤6, 7, and 8–10). These variables and their interactions were included in all regression models. Pathologic outcome at RP was considered an ordinal outcome with four levels (organ confined, extracapsular extension [ECE], seminal vesicle invasion [SVI], and adjacent organ invasion). The same analyses were repeated to predict positive surgical margins (PSMs) and lymph node invasion (LNI). The repeated split-sample approach was used to validate the model. Patients were randomly split into two groups, A and B, with group A twice as large as group B. The regression analysis was carried out on group A, and the resultant model was then used to predict the outcomes for each individual patient in group B. The state estimated to be most likely for each patient was compared with the observed state for that patient. The model was deemed to have made a correct prediction if the two states were the same. The percentage of correct predictions in both subsamples and the difference between them was calculated. The difference was defined as percentage correct in group A minus the percentage correct in group B. This process was repeated 1000 times to examine the robustness of the predictions. The same analyses were performed to predict LNI in a subcohort of patients undergoing ePLND (defined as the removal of ≥15 lymph nodes). We repeated our analyses in patients diagnosed after 2002.

All statistical tests were performed using the R statistical package (v 3.0.2). All tests were two sided with a significance level set at p < 0.05.

3. Results

3.1. Study population

Table 1 presents the preclinical and pathologic characteristics of patients included in the study. A total of 194 patients (25.8%) had positive LNs.

3.2. Prediction of pathologic outcome after radical prostatectomy

In the logistic regression models predicting pathologic outcomes after RP, the interactions between GS and PSA strata were nonsignificant (p = 0.71), based on the likelihood ratio. The main effects of GS and PSA were significant. Table 2 presents the predicted probabilities of pathologic outcomes after RP according to preoperative PSA level and biopsy GS. Patients with higher GS and/or higher PSA levels were more likely to have a worse pathologic outcome after RP than patients with low values on these variables (Table 2). For
example, a man with cT3a, a preoperative serum PSA level of 9 ng/ml, and a biopsy GS of 6 has a 30% chance of having organ-confined PCa. A man with cT3a, a preoperative PSA level of 25 ng/ml, and a biopsy GS of 8 only has a 4% chance of having organ-confined PCa. These results were confirmed when evaluating only patients diagnosed in more recent years (between 2002 and 2010; data not shown).

3.3. Prediction of positive lymph nodes

In the logistic regression model predicting positive LNs, the main effects of GS and PSA strata were significant; the interaction was not. Interactions between GS and PSA strata remained nonsignificant in all models; the main effects of these variables were significant.

Table 2 shows the predicted probability of positive LNs after RP according to preoperative PSA level and biopsy GS for patients with cT3a PCa. Men with higher GS and/or higher PSA levels were more likely to have positive LNs than patients with low values on these variables. For example, 5% patients with a GS ≤ 6 and a PSA ≤ 10 would be expected to have positive LNs. This would increase to 9% for patients with the highest GS and the same PSA value. These results held true when evaluating the predicted probability of positive LNs in patients undergoing ePLND (n = 166; Table 3).

Table 2 – Predicted probabilities of final pathologic outcome after radical prostatectomy

<table>
<thead>
<tr>
<th>PSA level</th>
<th>Pathologic outcome</th>
<th>GS ≤ 6, % (95% CI)</th>
<th>GS 7, % (95% CI)</th>
<th>GS ≥ 8, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 ng/ml</td>
<td>Organ confined, pT2</td>
<td>30 (24–35)</td>
<td>22 (22–33)</td>
<td>23 (13–31)</td>
</tr>
<tr>
<td></td>
<td>ECE, pT3a</td>
<td>60 (53–66)</td>
<td>50 (44–57)</td>
<td>41 (31–50)</td>
</tr>
<tr>
<td></td>
<td>SVI, pT3b</td>
<td>8 (4–12)</td>
<td>20 (14–24)</td>
<td>26 (17–35)</td>
</tr>
<tr>
<td></td>
<td>Adjacent organ invasion, pT4</td>
<td>2 (1–4)</td>
<td>2 (1–3)</td>
<td>10 (4–16)</td>
</tr>
<tr>
<td></td>
<td>Positive lymph nodes</td>
<td>5 (1–7)</td>
<td>14 (9–18)</td>
<td>25 (16–33)</td>
</tr>
<tr>
<td></td>
<td>Positive surgical margins</td>
<td>25 (19–30)</td>
<td>28 (22–33)</td>
<td>45 (35–55)</td>
</tr>
<tr>
<td>10–20 ng/ml</td>
<td>Organ confined, pT2</td>
<td>20 (14–26)</td>
<td>20 (14–26)</td>
<td>22 (13–30)</td>
</tr>
<tr>
<td></td>
<td>ECE, pT3a</td>
<td>54 (45–62)</td>
<td>42 (34–49)</td>
<td>30 (20–39)</td>
</tr>
<tr>
<td></td>
<td>SVI, pT3b</td>
<td>20 (14–27)</td>
<td>35 (28–42)</td>
<td>38 (28–47)</td>
</tr>
<tr>
<td></td>
<td>Adjacent organ invasion, pT4</td>
<td>6 (2–9)</td>
<td>3 (1–5)</td>
<td>10 (3–16)</td>
</tr>
<tr>
<td></td>
<td>Positive lymph nodes</td>
<td>18 (12–24)</td>
<td>18 (11–24)</td>
<td>38 (28–47)</td>
</tr>
<tr>
<td></td>
<td>Positive surgical margins</td>
<td>28 (21–35)</td>
<td>43 (35–51)</td>
<td>47 (38–57)</td>
</tr>
<tr>
<td>&gt; 20 ng/ml</td>
<td>Organ confined, pT2</td>
<td>17 (11–22)</td>
<td>8 (4–11)</td>
<td>4 (1–6)</td>
</tr>
<tr>
<td></td>
<td>ECE, pT3a</td>
<td>37 (30–44)</td>
<td>21 (15–27)</td>
<td>14 (9–20)</td>
</tr>
<tr>
<td></td>
<td>SVI, pT3b</td>
<td>33 (26–40)</td>
<td>54 (47–61)</td>
<td>56 (48–63)</td>
</tr>
<tr>
<td></td>
<td>Adjacent organ invasion, pT4</td>
<td>13 (8–17)</td>
<td>17 (11–21)</td>
<td>26 (18–32)</td>
</tr>
<tr>
<td></td>
<td>Positive lymph nodes</td>
<td>28 (21–35)</td>
<td>39 (32–45)</td>
<td>59 (51–65)</td>
</tr>
<tr>
<td></td>
<td>Positive surgical margins</td>
<td>50 (43–57)</td>
<td>54 (47–61)</td>
<td>78 (71–84)</td>
</tr>
</tbody>
</table>

CI = confidence interval; ECE = extracapsular extension; GS = Gleason score; PSA = prostate-specific antigen; SVI = seminal vesicle invasion.

* By preoperative PSA level and biopsy GS in men with cT3a prostate cancer.

Table 3 – Predicted probabilities of lymph node invasion

<table>
<thead>
<tr>
<th>PSA level</th>
<th>Pathologic outcome</th>
<th>GS ≤ 6, % (95% CI)</th>
<th>GS 7, % (95% CI)</th>
<th>GS ≥ 8, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 ng/ml</td>
<td>Positive lymph nodes</td>
<td>5 (2–12)</td>
<td>19 (9–29)</td>
<td>25 (5–45)</td>
</tr>
<tr>
<td>≥ 20 ng/ml</td>
<td>Positive lymph nodes</td>
<td>45 (32–67)</td>
<td>51 (38–63)</td>
<td>82 (68–96)</td>
</tr>
</tbody>
</table>

CI = confidence interval; GS = Gleason score; PSA = prostate-specific antigen.

* By preoperative PSA level and biopsy GS in men with cT3a prostate cancer in patients undergoing radical prostatectomy and extended pelvic lymph node dissection (defined as the removal of ≥ 15 lymph nodes).
3.4. Validation

The percentage of correct predictions in the training sample and validation sample and the difference between these was calculated. For the pathologic outcome model, the mean difference ranged between 3.7% and 6.2%. This indicates that the model has good predictive ability. Figure 1 depicts calibration plots for the prediction of organ-confined disease, ECE, SVI, adjacent organ invasion, PSMs, and positive LNs.

4. Discussion

Patients with clinical stage T3a disease constitute a high-risk PCa group, recognized by clinical guidelines [1,14]. Despite an extensive practice of PSA screening and early detection of PCa, a fair proportion of patients still present with locally advanced disease. In the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC), published in 2012, 8.6% and 1.2% of the patients had clinical stage T3 and T4 tumors, respectively; those numbers were 15.9% and 3.6% in the control arm [18]. Moreover, 76.8% of the “escapes,” that is, men who developed metastasis and/or died from PCa despite screening, in the Rotterdam arm of the ERSPC were patients with high-risk PCa (defined as clinical stage ≥T3, or PSA >20 ng/mL, or GS ≥8). More specifically, 51.2% of the escapes had clinical stage T3 or T4 disease [19].

The optimal management of patients with locally advanced PCa continues to be debated. Although surgical treatment has traditionally been discouraged secondary to an increased risk of PSM, SVI, and LN metastases, studies indicate that surgery may have a place in the management of T3a PCa [2–8,12]. Currently, RP, combined with ePLND, is a valid strategy accepted by international guidelines [1,14]. The 5- and 10-yr overall survival rates after RP for cT3a PCa have been reported to range from 75% to 97.6% and 60% to 94.8%, respectively. In addition, 5- and 10-yr PCa-specific survival rates ranged from 85% to 100% and from 57% to 92%, respectively [2–5,11].

Pathologic stage has been reported to be an important factor influencing outcomes after RP. In the update of the SPCG-4 study on radical prostatectomy versus watchful waiting, extracapsular tumor growth was associated with a sevenfold increase in the risk of death from PCa when compared with those without extracapsular growth (relative risk: 6.92; 95% confidence interval, 2.6–18.4) [20]. Likewise, in retrospective analyses of patients who underwent surgery for clinical stage T3 PCa, the outcome after RP in patients with pT2 PCa was also shown to be better than those with pT3 PCa [5,8,12]. About 13–27% of cT3 PCa patients are actually overstaged and have pathologically organ-confined disease at RP [2–8]. However, patients with SVI or extensive ECE might less likely benefit from RP alone [13]. A total of 6–68% of cT3a patients are understaged and in reality have pathologically confirmed SVI or adjacent organ invasion [11].

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From these observations, it appears that an important heterogeneity exists in the outcomes of patients presenting with locally advanced PCA. The need for improved prediction of surgical pathology in these patients is key because studies in high-volume referral centers have shown an “inverse” stage migration toward more aggressive PCA [21,22]. Thus the ability to predict the final pathologic stage of a patient with cT3a PCA may substantially influence treatment decisions in daily clinical practice. For example, patients with pT2 disease at final pathology might be cured by surgery alone. However, patients with ECE, SVI, and PSMs might benefit from a multimodal approach. In this context, randomized controlled trials reported that the administration of adjuvant RT improved the 10-yr biochemical-free survival rates [23]. However, because additional treatments are not devoid of short- and long-term side effects, the identification of patients who might benefit from multimodal therapy can be useful during preoperative patient counseling about possible treatment options and expectations.

Not only the primary tumor pathologic stage, but also the presence of positive LNs has an important effect on the outcome of RP [2,5,8]. For this reason, a high possibility of positive LNs will have an impact on the extent of surgery that should be performed, whether a PLND is indicated and to what extent [1,14]. Amples evidence is available to recommend an ePLND in men presenting with cT3 disease. A few publications have proposed pretreatment nomograms for accurate prediction of the presence of positive LNs after ePLND [24,25]. Unfortunately, the population of patients with locally advanced disease was largely underrepresented in those studies, thus questioning the applicability of the nomograms in this particular patient group. In these studies including mostly patients with cT1–2 PCA, the percentage of patients with positive LNs was in the range of 8%; the incidence of positive LNs in men with cT3a PCA has been reported to range from 8% to 49% [2–8,11,12]. In the present study, this was 25.8%. A better prediction of risk of positive LNs in patients with locally advanced PCA would thus provide additional information to guide surgical practice as well as radiation fields for those men opting for this treatment. In our analyses, the predicted probability of positive LNs after surgery was 45% in patients with a GS ≤6 and high PSA levels receiving an ePLND. Although these findings might suggest a potential aggressiveness for low-grade diseases, they should be interpreted with caution. We should underline that recent series report that upgraging was experienced in up to 45% of patients presenting with biopsy GS 6 at diagnosis [26].

We present tables predicting primary tumor pathologic outcomes and presence of positive LNs after RP for patients with cT3a PCA based on pretreatment PSA levels and biopsy GS. We opted to construct these as “look-up” tables instead of a nomogram because for many, tables are more user friendly and perhaps easier to apply in clinical practice and would provide a welcome addition to the existing Partin tables for localized disease. The main effects of biopsy GS and pretreatment PSA were significant in the model, and the validation procedure showed that the model has good predictive ability. This table can be considered in the prediction of pathologic outcomes at RP for patients with cT3a PCA, which can help urologists counsel RP patients preoperatively and can also benefit radiation oncology in regard to treatment field planning. The risk of positive LNs also increases with preoperative PSA levels and biopsy GS. Validation using the split-sample approach also showed excellent predictive power of the model.

Our study is limited by the fact that the patients were included from several centers over a relatively long period (1987–2010). Over time, improvements have been achieved in both diagnostic and surgical techniques potentially leading to different outcomes in particular subgroups of patients. Interpretative changes to the Gleason grading system might have potentially changed the pattern of grade distribution over time [27]. However, the results of our analyses were also confirmed when evaluating only patients diagnosed in most recent years. Clinical stage was determined by DRE alone, and this assessment may vary from one physician to another. However, all the patients included in our analyses were carefully evaluated by board-certified urologists at referral tertiary centers. Also, the lack of data on preoperative imaging in our multi-institutional database prevented us from addressing the impact of imaging techniques such as CT and MRI on the assessment of clinical stage. Although the number of biopsy cores taken, the percentage of positive cores, and tumor volume per core might be associated with the risk of adverse features at final pathology [28–30], our preoperative model did not include these covariates. A potential selection bias may have been introduced in our study, selecting the “more favorable” among cT3 cancers because our patient population consisted of patients treated initially with RP. Therefore, these tables might be applicable only to patients who are candidates for surgery. Only the PSA prior to RP was analyzed, limiting our ability to assess PSA kinetics and its potential prediction application to this patient group. No standardized PLND template was applied, and the mean of 11.5 nodes removed per patient lies below the LN count threshold for optimal pelvic LN staging. Abdullah et al. demonstrated that to achieve a correct LN staging in 90% of cases, an ePLND should contain at least 20 LNs [31]. However, according to the same authors, a mean of 11.5 LNs still achieves 75% correct staging. Thus underestimation of our table is thought to be limited. We tried to circumvent this limitation by performing a separated analysis only in patients undergoing ePLND. Central pathology review was not available, potentially limiting the generalizability of the results. Nevertheless, dedicated uropathologists from tertiary referral centers assessed all biopsies and resection specimens, thus limiting bias. Finally, the tables were constructed with European patients, and these results might not be applicable to other patient populations. For all the reasons just cited, the tables still need to be externally validated, even though an internal split-sample validation was applied.

Notwithstanding the limitations, our study has important strengths. First, a high number of patients were included compared with previous studies, leading to robust
statistical outcomes. Second, in contrast to previous studies, our study reports for the first time an analysis strictly focusing on patients with cT3a PCa. In those patients, the need for stratification is high due to the substantial heterogeneity in outcomes published. Former pretreatment tables or nomograms included only a small minority of cT3a patients, severely limiting the reliability of predictions for this specific population [15,32]. One other pretreatment table had already focused on cT3a PCa. However, the table was based on a single-center series of only 200 patients, and no predictions on the risk of LN invasion were provided [11].

Clearly, a fair proportion of patients with cT3a will have favorable pathologic outcomes, especially in the presence of more favorable PSA and biopsy GS. Those patients may be ideal candidates for surgery as a monotherapy. On this note, a former analysis from the European Multicenter High-Risk Prostate Cancer Clinical and Translational Research Group has shown patients with specimen-confined PCa (ie, pT2–3a, node negative, margin negative) to have exceptionally good outcomes following RP only [33]. The benefits of these tables extend beyond urologists’ exclusive use. As noted previously, this information may prove to be equally useful for radiation oncologists in treatment planning.

5. Conclusions

The presented tables allow for a better prediction of final histopathologic stage after RP in locally advanced PCa and may help differentiate between patients with cT3a PCa at low and at high risk for an unfavorable outcome. This can help guide decision making in men with locally advanced PCa. Nonetheless, the decision regarding the best management of these patients should be individualized after considering other factors such as age and comorbidities.

Author contributions: Steven Joniau had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Joniau, Spahn, Briganti, Gontero, van Poppel, Tombal.

Acquisition of data: Joniau, Spahn, Briganti, Gontero, Tombal, Marchioro, Walz, Bader, Kneitz, Hsu.

Analysis and interpretation of data: Joniau, Spahn, Briganti, Gontero, Tombal, Gandaglia, Tosco.

Drafting of the manuscript: Joniau, Gontero, Spahn, Tombal, Gandaglia, Tosco.

Critical revision of the manuscript for important intellectual content: van Poppel, Gontero, Spahn, Briganti, Tombal, Karnes, Montorsi.

Statistical analysis: Joniau, Gandaglia.

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