Oncological outcomes of surgery in very high risk pT3b prostate cancer

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Background. The aim of the study was to present the oncologic outcomes and to determine the prognostic factors of overall (OS) and cancer-specific survival (CSS) as well as disease-progression-free survival (DPFS) after surgery for pT3b prostate cancer.

Materials and methods. In 2002–2007, a pT3b stage after radical prostatectomy was detected in 56 patients. Patients were divided into groups according to the prostate-specific antigen (PSA) level (<10 vs. 10–20 vs. >20 ng/ml), lymph nodes status (N0 vs. Nx vs. N1) and the Gleason score (6–7 vs. 8–10). The Kaplan–Meier analysis was used to calculate OS, CSS and DPFS. The Cox regression was used to identify the predictive factors of survival.

Results. Five-year OS, CSS and DPFS rates were 75.1%, 79.6% and 79.3%, respectively. The survival was significantly different when comparing the Gleason 6–7 and 8–10 groups. The 5-year OS, CSS and DPFS were 91.2% vs. 48.6%, 97.1% vs. 51.1% and 93.8% vs. 51.1%, respectively. There was no difference in survival among the groups with a different PSA level. The OS and CSS but not DPFS were significantly different when comparing the N0 and N1 groups. The 5-year OS and CSS was 84.4% vs. 37.5% and 87.3% vs. 47.6%, respectively. The specimen Gleason score was a significant predictor of OS and CSS. The risk of death increased up to 4-fold when a Gleason score 8–10 was present at the final pathology.

Conclusions. Radical prostatectomy may offer acceptable CSS, DPFS and OS rates in pT3b PCa. However, outcomes in patients with N1 and specimen Gleason ≥8 were significantly worse, suggesting the need of multimodality treatment in such cases.

Key words: prostate cancer, locally advanced, surgery, outcome

INTRODUCTION

During the last decade, the definition of the optimal treatment in high risk prostate cancer (PCa) is among the topics that are of most interest to the urological community, but no consensus in this field is still reached. Up until a decade ago, most T3 PCa patients underwent radiotherapy (RT) or androgen deprivation therapy (ADT) or a combination of both, while only about 36% were initially treated by surgery (1). Recent publications have revealed that in selected cases of locally advanced and high-grade tumours, surgery as monotherapy or as part of a multimodality treatment may be used instead of RT (2). The high-risk PCa population, usually described as having a prostate-specific antigen (PSA) >20 ng/ml, biopsy Gleason score ≥8 or an advanced clinical stage (T3a–b) (3) is, however, not homogeneous. Recent studies have shown that treatment outcomes can vary widely, depending on whether patients present with only one or a combination of those high-risk factors, the latter patients having the worst
outcomes (4–7). It is still unclear which patients, according to the accepted predictors of aggressive disease behaviour, are the best candidates for surgery, mostly due to the lack of data on long-term oncologic outcomes and randomized clinical trials. According to the European Association of Urology guidelines, surgery is optional in patients presenting with cT3a, Gleason score ≥10 or PSA >20 ng/ml, and life expectancy of more than 10 years (8). Even in highly selected patients with cT3b or cN1 PCa, surgery may be offered as part of a multimodality approach (8). We believe that radical prostatectomy is indeed an appropriate treatment for very aggressive PCa, but the confirming data are still insufficient.

The purpose of this study was to present the oncologic outcomes of patients having pT3b PCa after surgery, including overall survival (OS), cancer-specific survival (CSS) and disease-progression free-survival (DPFS). Furthermore, we aimed to analyze their survival-predictive parameters.

MATERIALS AND METHODS

During the period 2002–2007, 840 radical retropubic prostatectomies (RRP) were performed in our tertiary referral institution; of them, 59 had the pathological stage T3b (7%). Three patients were lost for additional follow-up. Final analysis was carried out using data on 56 patients with a complete follow-up. No patients received neoadjuvant treatment. The last PSA before biopsy was used for the analysis.

The biopsy Gleason score ≥7, or PSA >10 ng/ml, or the clinical stage T3 were indications for lymph node removal; 43 of 56 (76.8%) patients of our study population had such criteria. For other 13 (23.2%) patients, no lymphadenectomy was performed.

The pathological examination of radical prostatectomy specimens and bilateral pelvic lymph nodes were performed by one dedicated uropathologist.

Serum PSA and physical examination were performed every 3 months in the first year after surgery, every 6 months in the second and third years, and annually thereafter. The PSA data were taken from outpatient clinic files. Data about patients’ death and cause of death were received from the National Cancer Registry.

OS was defined as the time from surgery to death from any cause. CSS was defined as the time from surgery to death caused by PCa or complications of this disease. Biochemical progression was defined as the time from surgery to the PSA level ≥0.2 ng/ml confirmed by a repeated test. Disease progression was defined as the development of either local disease recurrence or distant metastases. Adjuvant treatment was defined as either ADT or RT given within 3 months after surgery. Salvage treatment was defined as any kind of therapy (RT or ADT) given later than 3 months after surgery.

The Kaplan–Meier survival analysis was used to calculate the OS, CSS and DPFS. The differences were tested by the log-rank test. The Cox regression analysis was used to determine the prognostic factors for survival.

RESULTS

An overview of the patients’ preoperative and postoperative parameters is shown in Table 1. The median follow-up was 50.5 months (range, 6–94). The 5-year rates for OS, CSS and DPFS in our study cohort were 75.1%, 79.6% and 79.3%, respectively (Fig. 1 A–C). The Cox regression analysis revealed that of all the parameters (age, biopsy and surgery Gleason score, surgical margin and lymph node status, preoperative PSA level), only postoperative Gleason score (p = 0.004, HR 2.88, 95% CI 1.403–5.923) had an impact on overall mortality (Table 2). The Gleason score also had the strongest impact on cancer-specific survival (p = 0.001, HR 4.068, 95% CI 1.798–9.207). According to the Cox regression analysis, there were no parameters influencing disease progression.

Lymph node status. A mean of 6.48 (range, 1–15) lymph nodes were removed, and the overall positive node detection rate was 23.3%. During the study period, the overall mortality rate in pN1 patients was 60% and the cancer-specific mortality rate 40%. Patients with pN0 or pNx had a significantly lower overall (18.2% and 7.7%, respectively) and cancer specific mortality rate (15.2% and 7.7%, respectively). The disease progression rate was 40% in N1, 18.2% in N0 and 7.7% in the Nx patients’ group.

The Kaplan–Meier analysis showed that the 5-year OS (84.4%, 83.6% and 37.5%, Fig. 2A), CSS (87.3%, 83.6% and 17.9% and 71.7%, respectively). The disease progression rate was 40% in N1, 18.2% in N0 and 7.7% in the Nx patients’ group.

The Kaplan–Meier analysis showed that the 5-year OS (84.4%, 83.6% and 37.5%, Fig. 2A), CSS (87.3%, 83.6% and 17.9% and 71.7%, respectively). The disease progression rate was 40% in N1, 18.2% in N0 and 7.7% in the Nx patients’ group.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yr), (range)</td>
<td>65 (48–76)</td>
</tr>
<tr>
<td>Median PSA (ng/ml), (range)</td>
<td>11.6 (3.1–98.4)</td>
</tr>
<tr>
<td>Mean biopsy Gleason, (range)</td>
<td>6.8 (5–10)</td>
</tr>
<tr>
<td>Gleason ≤6</td>
<td>41.1%</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>41.1%</td>
</tr>
<tr>
<td>Gleason ≥8</td>
<td>17.9%</td>
</tr>
<tr>
<td>Mean surgery Gleason (range)</td>
<td>7.5 (6–9)</td>
</tr>
<tr>
<td>Gleason ≤6</td>
<td>3.6%</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>58.2%</td>
</tr>
<tr>
<td>Gleason ≥8</td>
<td>38.2%</td>
</tr>
<tr>
<td>R (%)</td>
<td>71.7%</td>
</tr>
<tr>
<td>N+ (rate)</td>
<td>23.3% (10 / 43)</td>
</tr>
<tr>
<td>PSA relapse</td>
<td>75.0%</td>
</tr>
<tr>
<td>Deaths (rate)</td>
<td>23.2% (13 / 56)</td>
</tr>
<tr>
<td>Deaths from cancer (rate)</td>
<td>17.9% (10 / 56)</td>
</tr>
<tr>
<td>mts</td>
<td>17.9%</td>
</tr>
<tr>
<td>Median follow-up (mo) (range)</td>
<td>50.5 (6–94)</td>
</tr>
</tbody>
</table>
Surgery in high risk prostate cancer

rates were significantly different comparing pN0, Nx and pN1, respectively. However, no significant difference in DPFS was detected according to lymph node status (Fig. 2C). There was no difference between Nx and pN0 in any survival analysis.

**Gleason score.** The Gleason score upgrading was detected in 55.4% of cases and downgrading in 7.1% of cases. An increased Gleason score was correlated with an increased positive lymph node rate: 38.9% at Gleason ≥8 vs. 12.5% at Gleason ≤7 (p = 0.047). During the study, a close correlation between survival and cancer differentiation was established. The Kaplan–Meier analysis demonstrated significant differences between Gleason ≤7 and ≥8 for OS (Fig. 3A), CSS (Fig. 3B) and DPFS (Fig. 3C) in the total study population. The estimated 5-year OS, CSS and DPFS rates in patients with the Gleason score ≥8 were 48.6%, 51.1% and 51.1%, respectively, while in the Gleason score ≤7, 5-year OS, CSS and DPFS were 91.2%, 97.1 and 93.8%, respectively.

**Preoperative PSA.** Preoperative PSA <10 ng/ml was found in 41.1%, PSA 10–20 ng/ml in 33.9%, and >20 ng/ml in 25% of the study patients. There was no significant difference in survival among these groups. The 5-year OS, CSS and DPFS rates were the same (81.8%) at PSA <10 ng/ml. In the group with PSA 10–20 ng/ml, the 5-year OS, CSS and DPFS rates were 71.1%, 75.2% and 76.1%, respectively. Patients with highest >20 ng/ml PSA levels had 71.4% 5-year OS, 83.9% CSS and 85.1% DPFS rates.

**Post-operative treatment.** Patients with pT3b PCa are generally considered at risk for disease progression. Therefore, adjuvant or salvage treatment (RT or ADT) are often

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**Table 2. Cox multivariate regression analysis of preoperative and histopathologic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall survival</th>
<th>Cancer-specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR, 95% CI</td>
<td>p value</td>
</tr>
<tr>
<td>Age</td>
<td>1.041, 0.945–1.148</td>
<td>0.415</td>
</tr>
<tr>
<td>Lymph node</td>
<td>1.258, 0.593–2.669</td>
<td>0.549</td>
</tr>
<tr>
<td>Preoperative PSA</td>
<td>1.012, 0.979–1.046</td>
<td>0.498</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>0.858, 0.168–4.334</td>
<td>0.855</td>
</tr>
<tr>
<td>Biopsy Gleason score</td>
<td>0.838, 0.571–1.995</td>
<td>0.838</td>
</tr>
<tr>
<td>Surgery Gleason score</td>
<td>2.883, 1.403–5.923</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Kaplan–Meier analysis of overall survival (A), cancer-specific survival (B) and disease-progression-free survival (C) in all study patients.
Fig. 2. Kaplan–Meier analysis with log-rank test for overall survival (A), cancer-specific survival (B) and disease-progression-free survival (C) stratified for lymph node status (Nx, N0 and N1).

Fig. 3. Kaplan–Meier analysis with log-rank test for overall survival (A), cancer-specific survival (B) and disease-progression-free survival (C) stratified for the Gleason score (≤7 vs. ≥8).
applied. In our study population, additional treatment was
given in 57.1% of cases. ADT received 33.9%, RT 8.9%,
and RT with ADT was applied to 14.3% of patients. All
ten patients with N1 received adjuvant treatment: one of
them – RT with ADT and the other nine ADT alone. At the
final follow-up visit, PSA <0.2 ng/ml was detected in 36.4%
of all the study cohort.

DISCUSSION

During the last decade, the discussion about the role of
surgery in locally advanced PCAs became increasingly
active. Before that time, treatment of locally advanced PCAs
has mostly been in hands of radiation oncologists [1]. Such
discussion became possible for several reasons: a successful
approach using RT and ADT [13]. The outcomes of another
long-term study comparing RT vs. RT with concomitant
ADT were reported by Bolla et al. (14). In the EORTC-trial,
412 patients with locally advanced PCAs were treated with
RT alone or in combination with ADT. The five-year OS and
CSS rates were respectively 62 and 79% in the group of ra-
diation alone. A better survival was reported in the com-
bination group: 78% and 94%, respectively. Our study data
showed a comparable 75.1% 5-year OS, similar to RT and
ADT combination therapy.

The group of pT3b PCa is heterogeneous with the dif-
ferent lymph-node status, PSA level and Gleason score.
Nevertheless, the incidence of nodal metastases in patients
submitted to RP has dramatically decreased in the PSA era
(3), positive lymph nodes being still diagnosed in up to 40% of
cases submitted to extended PLND (15). In our study, the
positive node rate was 23.3%. The impact of lymph node sta-
tus on survival is very important. In cases of N1, the 5-year
OS and CSS was significantly lower as compared with N0
(37.5% and 47.6% vs. 84.4% and 87.3%, respectively), despite
the received adjuvant treatment. Historically, because of the
high disease progression and mortality rate, patients with
nodal metastases were not considered surgical candidates.
However, recent studies have demonstrated excellent can-
cer-specific outcomes in patients with histologically proven
nodal metastases, with or without adjuvant ADT (16–20).
Moreover, patients with N1 are not at an equal risk of cancer
recurrence and death. Indeed, patients with a low volume
of nodal disease have significantly higher survival rates as
compared with patients with a higher volume of N1, regard-
less of adjuvant treatment (16–20). More importantly, N1
patients with complete RP showed an improved survival as
compared with patients with abandoned RP (21). This study
results suggest that RP may offer a survival benefit, and RP
abandonment in node-positive cases is not justified.

PSA are usually described as a potentially significant
factor for the survival in high-risk prostate cancer. However,
classifying such patients only on the basis of a PSA level is
questionable because it does not consider the total number
of recognised risk factors. Nevertheless, some authors have
recently demonstrated that the 10-year prostate cancer
specific mortality (PCSM) rate was 9% in cases with PSA
>20 ng/ml versus 3% in those with PSA ≤20 ng/ml (4). Sim-
ilarly, Stephenson et al. found that the 15-year PCSM was
22% in patients with PSA 20.1–50.0 ng/ml and up to 11% in
those with PSA <20 ng/ml (22). Another recent study pub-
lished by Spahn et al. presents data of a large multi-institu-
tional European study in patients with PSA >20 ng/ml be-
fore surgery. The authors have concluded that patients with
>20 ng/ml have varying risk levels of disease progression
or PCSM, and elevated PSA in isolation are not sufficient to
define a patient as high-risk (5). Our study shows that even
in the pT3b stage, the PSA level alone does not significantly
correlate with the survival. In cases with PSA <10 ng/ml,
the 5-year OS, CSS and DPFS was 82%. Patients with PSA
>20 ng/ml had similar 71.4% OS, 83.9% CSS and 85.1%
DPFS. A possible explanation for this observation could be
the variable application of adjuvant therapies. However, we
agree that PSA alone does not allow predicting oncologic
outcomes in very high risk PCAs.

Gleason score has long been recognized as an impor-
tant risk indicator of a worse outcome. In locally advanced
PCAs, biopsy Gleason sum has a tendency to be upgraded,
and in our series the upgrading was indeed frequent (up
to 55%). In fact, in our study, the specimen Gleason score
was identified as the most important outcome predictor.
Our data showed a significant difference between survival
curves comparing the Gleason score 6–7 vs. 8–10. More im-
portantly, patients with the postoperative Gleason ≥8 are
associated with a 2.9-fold higher risk of death. If cancer
differentiation after surgery is ≥8, the risk of death from
cancer increases more than 4-fold.

The gleason score 8–10 is also associated with a higher	node-positive rate as compared with the Gleason score
deed determines a worse biochemical or disease-free survival (23–25) both in locally advanced and organ-confined diseases (26). However, it does not eliminate patients with a high-grade PCa from surgical treatment. Our study shows that the 5-year OS, CSS, and DPFS rates in the Gleason score 8–10 PCa were 48.6%, 51.1% and 51.5% as compared with 91.2%, 97.1% and 93.8% the Gleason score was 6–7. However, the significant difference in survival between high and moderate grade PCa does not mean that a more advanced tumour grade is a contraindication for surgery. Tewari et al. have noted that long-term results in high-grade PCa after surgery are better in surgically treated patients that in those who underwent RT or conservative treatment (27). In 453 patients with biopsy and the Gleason score 8–10, the median OS after surgery was 9.7 years, while after radiation it was 6.7 years and after conservative treatment 5.2 years. The risk of cancer-related death after surgery was by 68% lower than after conservative treatment and by 48% lower than after RT.

The pT3b stage is associated with the poorest pathological findings after surgery. In our study, the rate of positive margins was 71.7%, 23.8% had the PN disease, and 38.2% had the specimen Gleason score 8–10. These adverse pathological findings are directly related to the oncological outcomes: the biochemical failure-free survival was 25%, the 5-year CSS was 79.6%, the OS 75.1% and DPFS 79.3%. There were no possibilities to compare the results of surgery and RT in such a small cohort of patients. If compared with the outcomes (5-yr OS rates >75% and CSS >85%) of radical prostatectomy at an advanced stage and a high-grade PCa in a large review presented by van Poppel (2), our pT3b survival data are similar. This suggests that not all patients with cancer extending into the seminal vesicles are destined to have poor outcomes. The lymph node status and the Gleason score seem to play the most important role in pT3b PCa outcomes.

As regards 5-year OS, CSS, and DPFS of 75.1%, 79.6% and 79.3%, our study shows that radical prostatectomy with adjuvant or salvage therapy may provide comparable outcomes with those of RT plus ADT in locally advanced very high risk pT3b PCa. However, this finding should be confirmed in prospective randomized studies.

CONCLUSIONS

Radical prostatectomy may offer acceptable CSS, DPFS and OS rates in pT3b PCa. However, outcomes in patients with N1 and specimen Gleason ≥8 were significantly worse, suggesting the need of a multimodality treatment in such cases.

References

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Milonas Daimantas, Smailytė Giedrė, Trumbeckas Darius, Jievtals Mindaugas

LABAI AGRESYVAUS pT3b STADIJOS PROSTATOS VĖŽIO CHIRURGINIO GYDYMO REZULTATAI

Santrauka

Įvadas. Šio tyrimo tikslas yra pateikti labai agresyvaus prostatos vėžio chirurginio gydymo rezultatus ir nustatyti bendrą įtaką įvairioms duomenų grupėms: patikimumui (BI), specifiniam patikimumui (SI) bei išgyvenamumui (IBL). Nustatytais šiuos veiksnius galima taikyti pagerinti pacientų atvejus, kai galime pasiekti geresnį gydymą.

Metodai. Nuo 2002 iki 2007 metų po chirurginio prostatos vėžio gydymo pT3b šios ligos stadija nustatyta 56 pacientams. Pacientai buvo suskirstytai į grūdus pagal PSA koncentraciją (< 10 vs. 10–20 vs. > 20 ng/ml), limfmazgių būklę (N0 vs. Nx vs. N1), taip pat pagal vėžio įvairias modalitęs (Gleason) suma ir skirtingą prostatos vėžio šalinimą, taip pat pagal patikimus (BI, SI, IBL).

Rezultatai. Tiek BI, tiek SI, tiek IBL atitinkamai sudarė 75,1, 79,6 ir 79,3 %. Išgyvenamumas reikšmingai skyrėsi esant skirtingų duomenų grupėms: < 10, 10–20 ir > 20 ng/ml, taip pat esant skirtingų limfmazgių būklėms (N0, Nx, N1) bei patikimų (BI, SI, IBL) grupėms. Išgyvenamumas šio atvejo produkto skirtingų duomenų grupių skirtingose duomenų grupėse įvertinamas Kaplan–Meier analizė bei Cox regresijos analize.

Išvados. Taikant chirurginį gydymą galima tikėtis pakankamai efektyvios rezultatų pacientams su visiškai sąlygamais duomenų sąlygomis. Tačiau esant skirtingoms duomenų grupėms (biuletė, patikimai ir limfmazgių būklė) galime pasiekti geresnį gydymą.