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1 **Pathological findings and PSA outcomes after laparoscopic radical**
2 **prostatectomy for high risk prostate cancer**

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22 recurrence

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ABSTRACT

Objective: The aim of our study was to review the biochemical recurrence-free survival (RFS) rates of laparoscopic radical prostatectomy (RP) in patients with high risk of disease progression as defined by preoperative d'Amico criteria.

Patients and Methods: Between October 2000 and May 2008, 110 patients underwent extraperitoneal laparoscopic radical prostatectomy and bilateral pelvic lymph node sampling for high risk prostate cancer in our department. High-risk prostate cancer was defined as follows: a PSA level greater than 20ng/ml, and/or a biopsy Gleason score 8 or above, and/or a clinical AJCC T2c to T4 stage. Median follow-up was 37.6 months. Risk factors for time to biochemical recurrence were tested using log rank survivorship analysis and Cox proportional hazards regression.

Results: Prostate cancer was organ-confined in 35.5% of cases. Overall RFS was 79.4% and 69.8% at 1 and 3 years, respectively. The 3-year RFS rates for organ-confined cancer versus extracapsular extension were 100% and 54.3%, respectively ($p<0.001$). The 3-year RFS rates for tumor-free seminal vesicle versus seminal vesicle invasion were 81.8% and 33.6%, respectively ($p<0.001$). The 3-year RFS rates for negative surgical margins versus positive were 85.2% and 47.3%, respectively ($p=0.001$). Compared with men with any single pathological risk factor or any 2 risk factors, men with all 3 risk factors had significantly shorter time to PSA failure after RP (log-rank test: $p<0.001$).

52 *Conclusion:* Among patients at increased risk of disease progression as defined by
53 preoperative d'Amico criteria, a third of men with organ-confined disease have
54 favorable prognosis. Men at high risk for early PSA failure could be better identified
55 by pathological assessment on prostatectomy specimens, and selected for phase III
56 randomized trials investigating adjuvant systemic treatment.

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58 INTRODUCTION

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60 Prostate cancer is the most common solid malignancy in men in EU, with 186,320
61 new cases diagnosed each year and the second cause of death attributable to cancer
62 with 28,660 deaths per year [1]. Despite the widespread use of prostate-specific
63 antigen (PSA) screening some patients are diagnosed with a locally advanced prostate
64 cancer. In these cases, treatment options remains unclear with no clear consensus.
65 D'Amico et al proposed a useful classification using clinical and pathological
66 parameters to classify relapse risk before treatment [2]. Patients with a PSA >20 ng/
67 mL, Gleason 8-10, T2c to T4 disease are considered to be at high risk, with recurrence
68 rates ranged from 50 to 100 percent after a local therapy alone especially if they are
69 young, healthy and with a long life expectancy. A nomogram from the Memorial
70 Sloan-Kettering Center has also been validated to predict biochemical recurrence-free
71 survival (RFS) after radical prostatectomy (RP) [3]. For patients with organ-confined
72 and high risk of disease progression prostate cancer, external beam radiation therapy
73 and RP are two recommended treatment options. One important advantage for RP is
74 that cancer aggressiveness is correctly evaluated on RP specimen. Thus, postoperative
75 nomograms can be used to better characterize high risk patients and predict the
76 probability of prostate cancer recurrence for each patient [4]. Pathological risk factors
77 for disease recurrence and disease specific survival after radical prostatectomy (RP)
78 include extracapsular extension, high Gleason score, positive surgical margins,
79 seminal vesicle invasion and positive lymph nodes [5]. Despite treatment, a significant
80 proportion of these patients will experience PSA-defined failure and cancer-specific
81 death indicating a need for more aggressive initial therapy. However, no adjuvant
82 standard treatment after surgery is clearly recommended for high risk and locally

83 advanced tumors. Immediate adjuvant radiotherapy decreased the risk of PSA
84 recurrence but at the cost of increased toxicity and with no metastasis-free or overall
85 survival benefit [6,7]. Adjuvant hormone therapy significantly improves survival in
86 patients with positive lymph nodes with benefit for immediate therapy [8,9]. In case of
87 negative lymph nodes, this survival advantage is not demonstrated. Recently,
88 neoadjuvant or adjuvant therapy for patients with high risk prostate cancer was studied
89 and demonstrated feasible with acceptable toxicity [10,11,12]. Therefore, stratifying
90 patients according to the prognosis is important for postoperative counseling and the
91 consideration of adjuvant therapy.

92 The purpose of the current study was to estimate the biochemical outcome after
93 laparoscopic RP for high risk of disease progression prostate cancer and to investigate
94 whether the number of pathological risk factor on prostatectomy specimens is
95 significantly associated with the time to PSA failure.

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MATERIALS AND METHODS

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Study population.

Between October 2000 and May 2008, 110 patients underwent extraperitoneal laparoscopic radical prostatectomy and bilateral pelvic lymph node sampling for high risk prostate cancer in our department. High risk cancers were defined as follows: a PSA level greater than 20 ng/mL, and/or a Gleason score of $\geq 8-10$, and/or clinical T2c to T4 disease regarding d'Amico criteria [2]. The patients have negative bone scan and negative computed tomography (CT) scan. Baseline and follow-up information were collected prospectively in our database including preoperative clinical and biological characteristics, patient demographics, surgical data and postoperative parameters. The clinical stage was determined from the digital rectal examination findings according to the AJCC staging system. A standard pelvic lymph node dissection (external iliac artery area) was performed in all patients. A mean of 7.4 lymph nodes were sampled. Nerve-sparing surgery was performed in 34 patients (30.9%). Pathological Gleason score, surgical margin (SM) status, presence of extracapsular extension (ECE), seminal vesicle invasion (SVI) and pelvic lymph node positivity were recorded. All prostatectomy specimens were assessed by a referee genitourinary pathologist. Biochemical recurrence was defined as any detectable serum PSA (greater than 0.2 ng/ml). Patients who had pelvic lymph nodes metastases received immediate androgen deprivation therapy. Others patients who received adjuvant or neoadjuvant hormonal and/or radiation therapy before PSA failure which was the primary end point in this study, were excluded from analyses. Men who experienced PSA failure were managed according to standard practice. Table 1 lists the preoperative characteristics of the 110 patients. Patients were classified at higher

122 risk of disease progression on PSA level alone in 61 patients (55.5%), on high
123 Gleason score alone in 31 patients (28.2%), on combination of these two parameters
124 in 9 patients (8.2%) and on clinical AJCC stage alone in 9 patients (8.2%). The mean
125 and median follow-up for all patients was 38.1 and 37.6 months, respectively (range:
126 1.1-92.2). The frequency of follow-up visits was standardized for all patients.

127 128 Statistical analysis.

129 Preoperative clinico-biological parameters were studied according to time-to-PSA
130 failure. We used dichotomized values of preoperative PSA (20 or less versus greater
131 than 20ng/ml), prostate weight (30 or less versus greater than 30ml) and age (<60
132 versus >60 years old). A Cox proportional hazards regression was used.

133 For purpose of illustration, estimates of PSA outcomes were calculated using the
134 Kaplan-Meier actuarial method and graphically displayed. PSA failure was defined by
135 a PSA level > 0.2 mg/ml. The time to PSA failure was considered to be the time that
136 the first detectable value was measured. The day of surgery was reported as the
137 starting point of analysis. The analysis endpoint was biochemical recurrence-free
138 survival (RFS). Postoperative significant risk factors for time to biochemical
139 recurrence were examined using log rank survivorship analysis. All data were
140 analyzed using SPSS 13.0 software (Chicago, Illinois). The limit of statistical
141 significance was defined as $p < 0.05$.

145 RESULTS

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148 *Pathological parameters on prostatectomy specimens (see Table2)*

149 Of the 110 patients undergoing RP, the pathological findings were extracapsular
150 extension (ECE) in 71 (64.5%), seminal vesicle involvement (SVI) in 27 (24.5%),
151 positive surgical margin (R+) in 43 (39.1%) and pelvic lymph node metastases (N+)
152 in 4 (3.6%). Surgical margins were positive in 21.0%, 27.3%, 61.1% and 71.4% of
153 pT2, pT3a, pT3b and pT4 cancers, respectively.

154 Concordance between biopsy and postprostatectomy Gleason scores was 49.1%.

155 Biopsy upgraded pathological Gleason score in 16 patients (14.5%) and downgraded it
156 in 40 patients (36.4%). The rate of favourable disease (defined as pT2 cancer and a
157 Gleason score ≤ 7) on RP specimens was 26.4%. Only 7 patients (6.4%) fulfilled all
158 favourable criteria, i.e. a PSA < 20 mg/ml, a pT2 cancer and a Gleason score ≤ 7 on RP
159 specimen.

160

161 *Time to PSA failure analyses*

162 During a mean follow-up of 38.1 months, PSA failure occurred in 23 patients (20.9%)
163 of which 20 received salvage therapy (radiotherapy or hormonal therapy). Fourteen
164 patients were treated by radiotherapy and 6 men received androgen deprivation
165 therapy. Mean time to progression was 7.2 months. No patient died as a result of
166 prostate cancer before PSA failure.

167 Multivariate time-to-failure analysis on preoperative parameters showed PSA level
168 higher than 20 ng/mL (p=0.003; HR=7.14 [95% CI 1.93-26.3]) and high biopsy
169 Gleason score (p=0.023; HR=3.14 [95% CI 1.17-8.43]) to be independent predictors

170 of biochemical recurrence. Age ($p=0.658$; HR=0.82 [95% CI 0.34-1.95]), clinical
171 stage ($p=0.362$; HR=1.49 [95% CI 0.63-3.48]) and prostate weight ($p=0.530$;
172 HR=0.62 [95% CI 0.14-2.75]) were not significantly associated with biochemical
173 relapse.

174 Overall RFS was 79.4% at 1 year (95% confidence interval [CI]: 75.1-83.7%) and
175 69.8% at 3 years (95% CI 63.9-75.7%) (Figure 1).

176

177 *PSA failure stratified by pathological data (Figure 2)*

178 The 3-year RFS rates for organ-confined cancer versus extracapsular extension were
179 100% and 54.3% (95% CI 46.3-62.3%), respectively ($p<0.001$). The 3-year RFS rates
180 for tumor-free seminal vesicle versus seminal vesicle invasion were 81.8% (95% CI
181 76.1-87.5%) and 33.6% (95% CI 20.4-46.8%), respectively ($p<0.001$). The 3-year
182 RFS rates for negative surgical margins versus R+ were 85.2% (95% CI 79.4-91.0%)
183 and 47.3% (95% CI 36.9-57.7%), respectively ($p=0.001$).

184 The estimated rates of RFS stratified by the number of pathological risk factors
185 present are illustrated in Figure 3. When these 3 pathological factors were associated
186 (SVI, R+, ECE), the 1-year and 3-year RFS rates were 42.2% (95% CI 29.5-54.9%)
187 and 15.8% (95% CI 2.8-28.8%). Statistically significant difference appeared
188 according to the number of these factors present (log-rank test: $p<0.001$).

189 None of the 9 patients with pT2 cancer and positive margin developed PSA
190 recurrence. Comparatively, the 1-year and 3-year RFS rates were 84% and 74.7% in
191 patients with pT3 cancer and negative margin. Difference did not reach significance
192 (log-rank test: $p=0.185$).

193 DISCUSSION

194
195 An accurate prediction of probability of disease recurrence is essential for proper
196 patient selection. Preoperatively, the identification of high risk prostate cancer can be
197 based on, at least, three well-defined predictors of the disease extent and outcome
198 after treatment: AJCC clinical T stage, serum PSA level, and Gleason score. Patients
199 with AJCC clinical stage T2c-T4 disease and/or a PSA level of more than 20ng/mL
200 and/or a biopsy Gleason score of 8 or more have a risk higher than 50% at 5 years of
201 post-treatment PSA failure. This risk group was established from a review of literature
202 and well defined by d'Amico et al. studying PSA failure and prostate cancer-specific
203 mortality [2,13]. In addition, PSA velocity greater than >2 ng/mL/year and more than
204 50% of positive biopsies can be considered [14,15]. D'Amico et al reported in a study
205 including 1,095 patients who underwent RP and who did not receive adjuvant therapy
206 that on multivariable analysis, preoperative PSA velocity >2 ng/mL/year was
207 associated with an increased risk of cancer specific mortality and with an increased
208 risk of overall mortality [16]. Others preoperative nomograms or scores have been
209 developed and validated in internal and external studies, documenting a high level of
210 consistency [3,17]. However, despite a good predictive accuracy among different risk
211 groups, certain inconsistencies have been reported regarding high risk cases. In the
212 present series we studied PSA-defined follow-up and results of local therapy for
213 patients at high risk of cancer progression regarding preoperative d'Amico criteria [2].
214 Survival analyses were driven in order to identify different risk subgroups of PSA
215 failure according to final pathological assessment among patients suspicious for high
216 risk of biochemical failure.

218 In multivariate time-to-failure analysis, high biopsy Gleason score and serum PSA
219 were significantly associated with biochemical relapse in our cohort. Preoperative
220 PSA greater than 20ng/ml and a Gleason score 8 or above carried a 7.14 and 3.14-time
221 increased risk of recurrence, respectively. No other preoperative variables were
222 significantly associated with time to PSA failure. However, we did not study PSA
223 velocity in this series [16]. Interestingly, clinical AJCC stage did not appear as
224 significant predictor of biochemical recurrence in this subgroup of high-risk prostate
225 cancer, on the contrary of published data concerning low-risk and intermediate-risk
226 group [2,13]. Kupelian et al have already shown that clinical stage was not
227 independent predictor of PSA-defined failure in a population of patients with biopsy
228 Gleason score 8 or above [18]. Our data confirmed these results.

229
230 Biochemical control rates were encouraging for these high risk patients. A third of
231 these patients have prolonged disease-free survival. Among the 110 patients, prostate
232 cancer was organ-confined in 35.5% of cases on final pathological assessment.

233 Biochemical RFS was excellent for this subgroup with no cases of recurrence after a
234 mean follow-up of 37.1 months (± 23.2). No early PSA failure appeared in case of
235 organ-confined disease. Moreover, no patient with pT2 cancer and positive surgical
236 margin had PSA failure. Thus, the biology of organ-confined disease appeared
237 different compared with the behavior of pT3 cancers. In this series of high-risk PCa,
238 patients with pT3 cancers and negative surgical margins had poorer survival than
239 those with pT2 cancer and positive margin (74.7% versus 100% at 3 years after the
240 surgery). However, difference failed to show significance.

241 In case of biochemical recurrence, patients with positive surgical margins were
242 preferentially treated by salvage radiotherapy, whereas patients with non organ-

243 confined disease or early PSA failure received preferentially androgen deprivation
244 therapy.

245 As expected, seminal vesicle invasion and positive surgical margins were statistically
246 strong predictors of early biochemical recurrence [19]. The 3-year RFS rates for
247 tumor-free seminal vesicle versus seminal vesicle invasion were 81.8% and 33.6%,
248 respectively ($p < 0.001$). The 3-year RFS rates for negative surgical margins versus R+
249 were 85.2% (95% CI 79.4-91.0%) and 47.3% (95% CI 36.9-57.7%), respectively
250 ($p = 0.001$). The biochemical recurrence in patients with 3 combined pathological
251 adverse factors was extremely frequent and early with a 3-year RFS of 15.8%.

252 Therefore, men at high risk for early PSA failure could be identified on the basis this
253 pathological assessment. Not all patients with ECE, positive surgical margins or VSI
254 will fail biochemically postoperatively, but combination of these 3 parameters was
255 reported to be a strong predictor of early PSA failure. Compared with men with any
256 single pathological risk factor or any 2 risk factors, men with all 3 risk factors had
257 significantly shorter time to PSA failure after RP (log-rank test: $p < 0.001$). However,
258 the overall risk of relapse may be underestimated in spite of the relative short follow-
259 up of our cohort. The PCa progresses slowly and a median follow-up of 3 years may
260 be considered as insufficient.

261
262 Despite the independent statistical significance of two preoperative clinico-biological
263 parameters (PSA level and high Gleason score) to predict time to postoperative PSA
264 failure, most of the variation in PSA follow-up was not accounted for on the basis of
265 the d'Amico criteria. For patients with organ-confined disease, the outcomes were
266 remarkably good with RP. Pathological criteria explained a significant amount of the
267 variation in the postoperative PSA data. Longer follow-up including more patients in

268 the higher risk categories would provide stronger conclusions. One reason of the good
269 cure rates might be that PSA failure was defined by a PSA level over 0.2 mg/ml
270 whereas in other series a “0.2 or greater” or a “0.1” cut-off was used [20]. The use of
271 such a cut-off might be too high when a 3-year RFS is studied and might have limited
272 detection. We’d also like to emphasize that the biochemical recurrence but not the
273 prostate cancer specific mortality has been chosen as criteria of disease progression.
274 The ideal end point on which to make treatment decisions is survival and PSA-defined
275 failure may not accurately reflect the likelihood of prostate cancer-specific death.
276 However, early PSA failure is established to be associated with an increased risk of
277 progression to metastatic disease and prostate cancer-specific death [21].
278 If longer follow-up and rates of specific mortality confirm these results, adjuvant
279 therapy might not be mandatory for achieving adequate cure rates for the subgroup of
280 patients with organ-confined disease. On the contrary, men with two or three
281 pathological risk factors should be considered for phase III randomized trials
282 investigating adjuvant systemic treatment. Integrate taxane-based chemotherapy with
283 local treatment could be relevant to address microscopic hormone-refractory prostate
284 cancer cells that may be present at initial assessment in men with high-risk disease
285 [10,11,12].
286 One limitation of our study is the bias due to the selection of men candidates for RP.
287 During the study period, 97 others patients have been diagnosed with localized PCa at
288 high risk of recurrence according to the d’Amico criteria. These patients have been
289 treated by radiotherapy in 40 cases and by androgen deprivation therapy in 57 elderly
290 patients. We excluded 47 patients who have been included into a prospective trial
291 investigating the role of adjuvant paclitaxel after RP. Adjuvant radiotherapy is not

292 performed for high risk PCa before PSA failure at our department and no patient has
293 received neoadjuvant therapy during the study period.

294 Our findings supported evidence that organ-confined disease, even in preoperatively
295 high risk patients can lead to excellent RFS outcomes after RP without adjuvant
296 therapy. Local therapy such as RP has to remain a standard of care for these high risk
297 patients. Pathological evaluation on prostatectomy specimens provides better
298 predictive assessment of high risk compared with only preoperative criteria. Despite
299 high accuracy and mandatory use for selecting men for clinical trials, high risk group
300 established according to the d'Amico criteria remains heterogeneous, including a third
301 of patients with excellent prognosis. Radical prostatectomy can help to distinguish
302 patients who would benefit from adjuvant therapy and close surveillance, from those
303 who could be watched in a more spaced out way.

304 Finally, this series confirms that laparoscopic approach is a validated treatment of
305 clinically localized but high-risk disease. Oncological results and positive surgical
306 margins rates were in line with values published in open surgery series [22,23].

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CONCLUSIONS

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Three years after laparoscopic radical prostatectomy for high risk prostate cancer, biochemical recurrence-free survival is 69.8%. Our findings support evidence that organ-confined disease, even in preoperatively high risk patients can lead to excellent RFS outcomes after RP without adjuvant therapy. Among these patients with high risk disease defined by preoperative data, a third of men with organ-confined disease have favorable prognosis. Thus, men at high risk for early PSA failure could be better identified by pathological assessment on prostatectomy specimens, and selected for phase III randomized trials investigating adjuvant systemic treatment.

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LEGENDS

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Table 1. Baseline characteristics of the 110 patient study cohort.

Table 2. Pathological postprostatectomy parameters.

Figure 1. Biochemical recurrence-free survival after RP for high risk prostate cancer.

Figure 2. Biochemical RFS after RP stratified by the type of pathological risk factor present.

Figure 3. Biochemical RFS after RP stratified by the number of pathological risk factors (ECE, VSI, R+).