Prediction of pathological stage is inaccurate in men with PSA values above 20 ng/mL

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Introduction: We hypothesized that either very low (0-2.5 ng/mL) or very high (>20 ng/mL) PSA values may limit the accuracy of pathological stage predictions. To test this hypothesis, we examined 5193 consecutive patients subjected to radical prostatectomy (RP) for localized prostate cancer (PCa).

Material and Methods: Patients were divided into three cohorts according to their pre-treatment PSA value: \(<2.5 \text{ (n=331)}, 2.51-20 \text{ (n=4545)} \text{ and } >20 \text{ ng/mL (n=317). Subsequently in each cohort, the ability of PSA, clinical stage and biopsy Gleason sum was tested in multivariable logistic regression models predicting three separate endpoints: extracapsular extension (ECE), seminal vesicle invasion (SVI) and lymph node invasion (LNI). Predictive accuracy represented the performance benchmark. All models were adjusted for year of surgery and subjected to 200 bootstrap resamples to reduce overfit bias.

Results: For PSA \(<=2.5 \text{ ng/mL, predictive accuracy was 76.7%, 72.3% and 82.8% for respectively ECE, SVI and LNI. For PSA 2.51-20 \text{ ng/mL, the predictive accuracy for the same endpoints was 67.8%, 77.4% and 81.6%. Finally, for PSA > 20 \text{ ng/mL, predictive accuracy was 63.6%, 63.7% and 70.6%. Conclusions: The ability to predict pathological stage in patients with PSA values in excess of 20 ng/mL significantly decreased, compared to patients with lower PSA values. Therefore, accurate staging of these patients may require alternative markers or staging schemes.

Editorial Comment

The authors of this multi-institutional survey investigate whether the current prognosticators and tables (e.g. Partin) are useful in very low and very high PSA levels. They analyzed the radical prostatectomy results of 5193 patients. Altogether, the predictive accuracy was rather satisfactory even in the very low and the very high PSA ranges. In the latter, predictive accuracy declined.
It may be allowed to shed a critical view on the figures in detail, which may decrease the enthusiasm for prognosticators somewhat. Overall, extracapsular extension (ECE) was found in 20.4% and seminal vesicle invasion (SVI) in 10.6%. In the PSA range > 20 ng/mL, ECE was found in 30.6% and SVI in 33.4%. Otherwise, still of patients 13% had ECE and 10% had SVI in the PSA range below 2.5.

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Intravesical instillation of bacille Calmette-Guérin for superficial bladder cancer: cost-effectiveness analysis
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Objectives: Frequent recurrence of superficial bladder cancer is a major problem that impairs patients’ quality of life. We studied the current treatment of superficial bladder cancer, including the economic aspects of intravesical instillation.

Methods: A total of 138 superficial bladder cancers were assessed. The tumor characteristics and treatments were investigated during a mean observation period of 86 months by univariate and multivariate analyses. The costs associated with intravesical instillation of bacille Calmette-Guérin (BCG) and its side effects were subjected to cost-effectiveness analysis.

Results: Tumor histologic examination revealed grade 1 in 21 lesions, grade 2 in 60 lesions, grade 3 in 40 lesions, and unclassified in 17 lesions. The pathologic stage was Stage Ta in 85 lesions, T1 in 47 lesions, and Tis in 6 lesions. Univariate and multivariate analyses showed that intravesical instillation of BCG was the most significant factor preventing recurrence, and intravesical chemotherapy had no impact on recurrence. The 5-year recurrence-free survival rate was 78% and 28% for tumors with and without BCG instillation, respectively. The cost-effectiveness ratio of BCG instillation was approximately 3900 dollars/5-yr recurrence-free period.

Conclusions: Our results have indicated that BCG is an effective adjuvant therapy after transurethral resection of superficial bladder cancer in the current medical environment.

Editorial Comment
The discussion on whether to give intravesical chemotherapy or immunotherapy is viable since many years. As these authors state “When prophylaxis with intravesical therapy is performed, it is necessary to strike a balance between more benefit with severe side effects versus less benefit with mild side effects.” The authors shed another perspective onto this discussion in analyzing and comparing the overall costs (including costs of e.g. antibiotics) of intravesical chemotherapy and BCG immunotherapy against superficial bladder cancer in 138 consecutive patients.

The figures are based on the Japanese health care system. Still, they are meaningful for the treatment of superficial bladder cancer in toto.
The treatment of BCG related complications are 11% of the total BCG treatment costs. As BCG treated patients had significantly lower recurrence rates, the cost-effectiveness ratio was clearly in favor of BCG immunotherapy with 525 US$ per year.

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A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C

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Objective: The primary aim was to search for lower doses of Bacillus Calmette-Guerin (BCG) that are effective and have lower toxicity.

Methods: A low dose of BCG 27 mg was compared with BCG 13.5mg, using mitomycin C (MMC) 30 mg as the third arm of comparison. A total of 430 patients with intermediate-risk superficial bladder cancer were randomised into three groups. Instillations were repeated once a week for 6 wk followed by another six instillations given once every 2 wk during 12 wk.

Results: There was a significantly longer disease-free interval for BCG 27 mg versus MMC 30 mg (p=0.006). There were no statistically significant differences between BCG 27 mg and BCG 13.5mg (p=0.165) or between BCG 13.5mg and MMC 30 mg (p=0.183). Cox proportional hazards regression showed that disease-free interval in the multivariate analysis was significantly better for primary disease and treatment with BCG 27 mg. There were no significant differences among the three groups with regards to time to progression and cancer-specific survival time. Local and systemic toxicity were higher in both BCG treatment groups.

Conclusions: One third of the standard dose, BCG 27 mg, seems to be the minimum effective dose as adjuvant treatment for intermediate-risk superficial bladder cancer, being more effective than MMC 30 mg. One sixth of the standard dose, BCG 13.5mg, has the same efficacy as MMC 30 mg but it is more toxic.

Editorial Comment
This trial is based upon precious trials from the CUETO group on low dose BCG in superficial bladder cancer. Within these non-blinded trials low dose BCG had shown a reduction in side effects together with equal efficacy against tumor recurrences. As with most trials, data on progression suffer from the relatively low numbers of patients in each arm. Furthermore, the maintenance schedule with BCG was very different from other trials as a “slow-dose long-term schedule” was applied with 2-weekly instillations for 6 weeks following the typical 6 weeks induction course.
Still, there are meaningful results to be drawn from this trial, which are generally important for BCG immunotherapy. BCG immunotherapy is dose-dependent. One-third (27 mg) of the full dose (81 mg) may be equally effective, but one-sixth certainly was inferior to one-third. The Kaplan-Meyer curves still showed superior efficacy of all doses of BCG over MMC.

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Serial markers of bone turnover in men with metastatic prostate cancer treated with zoledronic Acid for detection of bone metastases progression
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Objectives: This study assessed the usefulness of serial measurements of bone turnover markers in men with metastatic prostate cancer treated with zoledronic acid to detect disease progression.

Methods: Serum measurements of total alkaline phosphatase (tALP), bone-specific alkaline phosphatase (bALP), cross-linked N-terminal (NTx) and cross-linked C-terminal (CTx) telopeptides of type I collagen, amino-terminal procollagen propeptides of type I collagen (PINP), C-terminal telopeptides of type I collagen (ICTP), and prostate-specific antigen (PSA) were performed in 77 prostate cancer patients suffering from bone metastases and treated with zoledronic acid up to 15 mo. Fifty patients were with and 27 patients without objective evidence of metastatic bone progression during the administration of zoledronic acid.

Results: The baseline bone marker concentrations were not significantly different between the groups. After administration of zoledronic acid all bone markers except of ICTP decreased compared with baseline. CTx showed the greatest decrease. In patients with metastatic bone progression PINP, tALP, bALP, and ICTP were significantly higher at weeks 24, 36, 48, and 60 after starting treatment with zoledronic acid compared with patients without progression. In addition to the information of prostate-specific antigen as a monitoring parameter, the bone formation marker showed a better distinction between patients with and without disease progression.

Conclusions: Selected bone turnover markers provide valuable information regarding progression of bone metastasis in men with metastatic prostate cancer under bisphosphonate therapy. The clinical impact should be confirmed in prospective randomised studies.

Editorial Comment
Many patients with prostate cancer ultimately suffer from bone metastases. In this trial, bone turnover markers were analyzed with regard to their predictive value upon progression in patients with bone metastases.

Basically, PSA was the most important marker to predict progression. All patients received zoledronic acid resulting in an initial reduction of bone turnover markers. Interestingly, if these initial levels were taken as baseline, a subsequent increase was a significant predictor of bone progression.
Thus, bone turnover markers could become an important tool in the monitoring of patients with advanced prostate cancer.

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