ОНКОУРОЛОГИЯ 4'2015 ТОМ 11 | CANCER UROLOGY 4'2015 VOL. 11

Devising and external validation of a prognostic classification of metastatic involvement risk to pelvic lymph nodes in patients with newly diagnosed prostate cancer

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Objective: *assessing the predictive significance of clinical, histologic and biochemical factors for prediction of metastases in pelvic lymph nodes (MPLN), devising and validating of prognostic classification.*

Material and methods: *the study enrolled 1140 patients subjected to radical prostatectomy (RPE) with standard pelvic lymphadenectomy for prostate adenocarcinoma: 865 of them at the classification devising stage and 275 in the course of validation.*

Results: *according to the findings of multivariate logistic regression analysis, PSA level, the tumor cT stage and Gleason score are independent predictors of MPLN detection after RPE ($p < 0.05$). The prognostic factors were stratified by score for assessing the detection of regional metastases after RPE, depending on the combination of predictors. In the group of patients with a score estimate of prognostic factors < 10, the MPLN detection rate was significantly lower than in the group of patients with a score estimate > 15, accounting for 3.5 % and 23.7 % respectively ($p < 0.0001$). In the course of validating the obtained findings in clinic, metastatic involvement of pelvic lymph nodes found in the result of RPE was diagnosed in 40.0 % of the patients with a score estimate > 15 and only in 1.3 % of those with a total estimate of prognostic factors < 10 ($p < 0.0001$).*

Key words: *prostate cancer, prognostic classification, metastases, pelvic lymph nodes*

DOI: 10.17650/1726-9776-2015-11-4-59-64

Introduction

Radiotherapy (RT) is one of the principal treatment modalities for localized and locally advanced prostate cancer (PC), its efficacy not being inferior to radical prostatectomy (RPE). However, the effect of radiation treatment is strongly related to accuracy in evaluation of the extent of malignancy spread, which directly determines the choice of the radiation-exposed area, single and total radiation doses. In particular, the need for inclusion of regional lymph nodes in the radiation area improves, according to some reports, long-term results of treatment for PC patients with high risk of progression [1, 2]. An appreciable limitation for this approach is a higher probability of developing toxicity of the gastrointestinal and urogenital systems with an extended radiation area, associated with increased volumes of rectum and urinary bladder exposed to ionizing radiation [3].

However, the complexity of addressing this clinical issue consists in the fact that tomographic modalities (computed tomography and magnetic resonance imaging) are insufficiently sensitive in detecting metastases in pelvic lymph nodes (MPLN) as they rely only on the criteria of a lymph node size as a predictor of its metastatic involvement [4, 5]. Moreover, sensitivity of the above modalities differs insignificantly and is 42 % for CT and 39 % for MRI, specificity is 82 % for both of them [6]. Neither is regional node biopsy advisable because of technical complications with surgical access to some pelvic lymph nodes [7, 8].

The described limitations of the instrumental modalities for MPLN detection have led to emergence and wide use of calculation formulas for predicting the risk of pelvic lymph node metastatic involvement. Until now, Roach formula [9] remains to be the most common prognostic tool employed by radiation oncologists, which was derived on the basis of early versions of Partin tables [10], using for calculation the findings of prostate-specific antigen (PSA) level and Gleason score in prostate tissue samples. However, current literature frequently voices the opinion that the shift of newly diagnosed PC cases to more localized forms after the wide-scale introduction of PSA level screening into clinical practice resulted in a decline in the prognostic value of this formula [11].

Subsequently, some more methods were proposed for calculation of MPLN probability, among them Nguyen [10] and Yu [12] formulas. The main limitation of Nguyen formula is its being a modification of Roach formula and hence not taking into account the extent of local tumor spread, although updated Partin tables indicate the relation of these factors [13]. Yu formula allows for this criterion but it is applied for calculation only with localized tumors (T1c–T2c) and is inapplicable with locally advanced disease.

The objective of the study is assessing the diagnostic significance of clinical, histologic and biochemical factors for prediction of MPLN in patients with newly diagnosed PC with subsequent devising and validating of a prognostic classification.

Materials and methods

The study enrolled 1140 patients with histologically verified diagnosis of PC. To devise the prognostic classification, we used the data on 865 males who had RPE with standard pelvic lymphadenectomy (PLAE) in 2005–2013. The procedure of standard PLAE consisted in excision of interior and exterior iliac LN, as well as LN of the obturative fossa from the obturative orifice to the common iliac artery bifurcation. The devised prognostic classification was validated on 275 patients subjected to RPE with standard PLAE for prostate adenocarcinoma at N.N. Alexandrov National Cancer Centre of Belarus in 2014.

Patient eligibility criteria at the both stages were as follows: available data on the preoperative PSA level, the disease clinical stage and Gleason score. The data on patients receiving preoperative hormonal therapy over a long period of time were excluded from the analysis. Patient characterization is presented in table 1.

To assess the predictive value of clinical (disease stage), histologic (Gleason score) and biochemical (PSA level) factors, mono- and multivariate logistic regression analyses were performed, with PSA level categorized as < 10 ng/ml, 10–20 ng/ml and > 20 ng/ml, the extent of local spread as T1c – T2c, cT3a and cT3b, Gleason score as 7 and less, 8 and more. The odds ratio (OR), confidence intervals (CI), Wald test and statistical power were also calculated for the above rates.

The model accuracy was estimated by the concordance index (c-index) determined in the case of logistic regression by area under the curve of characteristic (area under the curve, AUC). AUC value of 1 is consistent with absolute prognosis, the value of 0.5 is equivalent to random choice.

The relative rates in the groups were compared using Pearson's χ^2-test. The differences were considered significant at the significance level $p < 0.05$. The results of the study were analysed with Statistica 7 and SPSS 16.0 software packages.

Results

Devising the prognostic classification

In the learning sample following the postoperative histologic examination, MPLN were detected in 66 (7.6 %) patients. According to the findings of monovariate logistic regression analysis, preoperative PSA level, the extent of local tumor spread and Gleason score were predictors of MPLN detection ($p < 0.05$) (table 2).

Table 1. *Characterization of patients enrolled in the study*

Variable	Variable	Examination sample
Patients, *n*	865	275
Median age (range), y	65 (42–79)	62 (46–75)
Median PSA level (range), ng/ml	10,8 (1,0–165,1)	8,7 (0,7–170,0)
Clinical stage, *n*: cT1c – T2c cT3a cT3b	 656 138 71	 157 84 34
Gleason score, *n* (%): ≤ 6 7 8–10	 680 (78,6) 93 (10,8) 92 (10,6)	 181 (65,8) 73 (26,6) 21 (7,6)

Table 2. *Monovariate analysis*

Variable	OR	95 % CI	*p*
Pretreatment PSA level, ng/ml: < 10 10–20 > 20	 1 7,2 19,8	 – 2,7–19,3 7,7–15,2	< 0,0001
Direct extent of the tumor: cT1c-2c cT3a cT3b	 1 3,5 7,3	 – 1,9–6,4 3,8–14,1	< 0,0001
Gleason score: ≥ 8 vs. ≤ 7	3,8	1,8–7,8	0,0003

Then the prognostic factors considered were included in multivariate analysis which also proved them to be independent predictors of MPLN detection after RPE ($p < 0.05$). For further analysis, the prognostic factors were stratified by score presented by OR values rounded off to the integer (table 3).

MPLN detection rate was considerably lower in the group of patients with a score estimate of prognostic factors <10 versus the patients with a score estimate >15 (table 4).

To assess diagnostic information capacity of the devised predictive method, ROC analysis (Fig. 1) was carried out, which defined the accuracy of the proposed classification in MPLN prediction as 0.796 (95 % CI 0.746–0.846); this value is regarded as good according to the expert scale for AUC values (AUC > 0.7 or 70 %) [15].

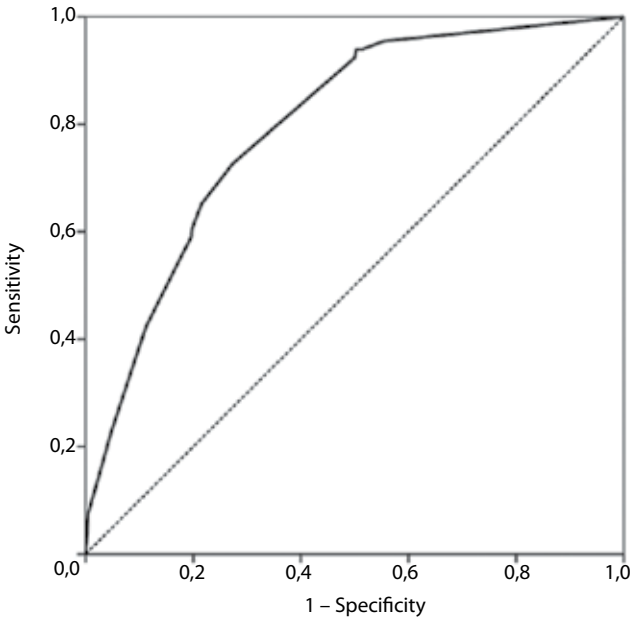

Fig. 1. *ROC curve for devising the prognostic classification*

Validation of the prognostic classification for metastatic involvement of pelvic lymph nodes

The rate of MPLN detection following RPE with PLAE in the examination group accounted for 5.82 %.

The analysis of the relation between pelvic LN metastatic involvement detection rate and the combination of prognostic factors employed in the classification devised found their statistically significant correlation (table 5). The highest MPLN rate was established with PSA level > 20 ng/ml (33 %; 95 % CI 17.3–49.4), the extent of local spread cT3b (17.7 %; 95 % CI 4.8–30.5) and Gleason score 8 and more (28.6 %; 95 % CI 9.3–47.9).

Table 3. *Multivariate analysis*

Variable	B*	OR	95 % CI	*p*	Score
Pretreatment PSA level, ng/ml: < 10 10–20 > 20	 – 1,856 2,542	 1 6,4 12,7	 – 2,4–17,2 4,7–34,4	< 0,001	 1 6 13
Direct extent of the tumor: cT1c – T2c cT3a cT3b	 – 0,519 1,036	 1 1,7 2,8	 – 0,9–3,2 1,4–5,8	0,018	 1 2 3
Gleason score: ≤ 7 ≥ 8	 – 0,810	 1 2,2	 – 1,0–4,9	0,043	 1 2

* *Regression coefficient.*

Table 4. *The rate of MPLN detection based on the findings of RPE with standard PLAE depending on the combination of independent predictors (score estimate)*

Score estimate of the combination of independent predictors	MPLN detection rate		*p*
	Patients with N1/ total number of patients	% (95 % CI)	
< 10	23/650	3,5 (2,3–5,3)	< 0,0001
10–15	15/97	15,5 (9,5–24,1)	
> 15	28/118	23,7 (16,9–32,2)	

Table 5. *The rate of MPLN detection based on the findings of RPE depending on the prognostic factors*

Variable	The rate of MPLN (n) based on the findings of RPE		*p*
	n/total number of patients	% (95 % CI)	
Pretreatment PSA level, ng/ml: < 10 10–20 > 20	 3/157 2/85 11/33	 1,9 (4,0–5,7) 2,4 (1,4–8,7) 33,3 (19,7–50,5)	< 0,001
Direct extent of the tumor: cT1c – T2c cT3a cT3b	 5/157 5/84 6/34	 3,2 (1,2–7,4) 6,0 (2,2–13,5) 17,7 (8,0–33,9)	0,005
Gleason score: ≤ 7 ≥ 8	 10/254 6/21	 3,9 (2,1–7,2) 28,6 (13,6–50,2)	< 0,001
Total	*16/275*	*5,8 (3,6–9,3)*	–

Table 6. *MPLN detection rate depending on the total score according to the classification devised*

Score estimate of the combination of independent predictors	MPLN detection rate		*p*
	Patients with N1/ total number of patients	% (95 % CI)	
< 10	3/230	1,3 (0,3–3,9)	< 0,0001
10–15	3/20	15,0 (4,4–36,9)	
> 15	10/25	40,0 (23,4–59,3)	

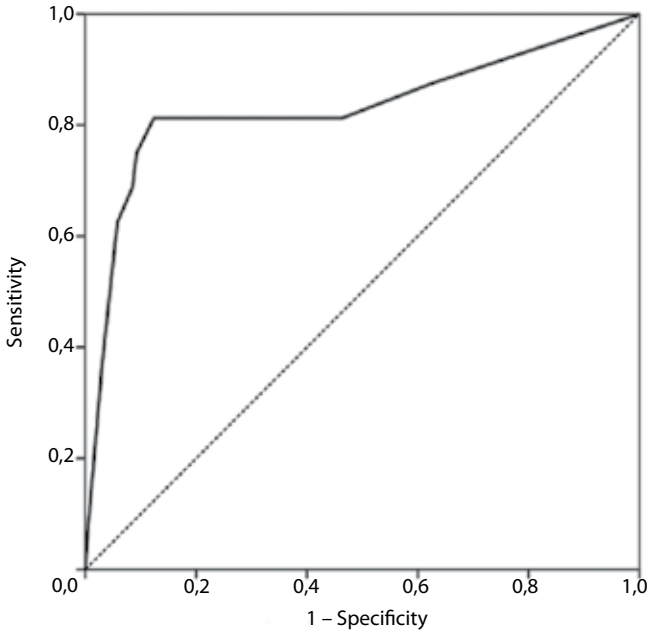

Fig. 2. *ROC curve for validation of the prognostic classification*

Subsequently, the predictors of MPLN presence were stratified by score according to the devised method, and the rate of MPLN detection was calculated using the findings of histologic examination following RPE in each of the groups (table 6).

Table 6 demonstrates that the validation results prove a statistically significant direct relation between the total score and MPLN detection rate: MPLN were found in 1.3 % of patients in the group with a score estimate of prognostic factors <10, while with a score estimate >15 they were detected in 40.0 %.

Diagnostic information capacity of the proposed prognostic classification at the validation stage was also assessed with ROC analysis (fig. 2). AUC accounted for 0.831 (95 % CI 0.694–0.968) which is an indication of the devised model reproducibility in the examining sample.

Discussion

Historically, Roach formula has been the basic method of MPLN presence prediction in PC patients for making a decision about the target volume. However, the most recent studies proving a decline in the prognostic value of this formula, taking into consideration current PC pathomorphism [10, 11], have led to emergence of new calculation methods.

Modern tools for prediction of MPLN probability also have considerable limitations: Nguyen formula [10] does

not take into account the extent of local tumor spread, and Yu formula [12] is used for calculation only with localized tumors.

With the aforesaid in mind, we have devised a prognostic classification basing the calculation of regional lymph node metastatic involvement probability on the following indices: Gleason score, PSA level and cT tumor category (including locally advanced forms).

In the proposed prognostic classification for MPLN risk, the above basic prognostic factors were assessed using mono- and multivariate regression analysis to reveal correlation between them and to take into account the obtained results for calculation. In the multivariate analysis, all the assessed variables appeared to be independent predictors of detecting metastases in regional lymph nodes after RPE and were used to compose the prognostic classification.

In the group of patients with a score estimate of prognostic factors < 10, MPLN detection rate was statistically significantly lower ($p < 0.001$) than in the group with a score estimate > 15, accounting for 3.5 % and 23.7 % respectively.

The efficacy of the devised prognostic classification was confirmed by the results of its validation in clinical practice. The analysis of clinical findings and histologic reports of 275 patients who underwent RPE with standard PLAE has established that MPLN are detected in 1.3 % of patients with a total score estimate of prognostic factors <10, in 15.0 % with a score of 10–15 and in 40.0 % with a score estimate > 15.

We emphasize that the probability of pelvic lymph node metastatic involvement is high enough (15 %) even with a score estimate of 10–15. This fact makes it possible to recommend RT on the whole pelvic area in the case of a total score estimate of prognostic factors 10 or more.

The method of ROC analysis also confirmed the diagnostic efficacy of the proposed classification: AUC accounted for 0.796 (95 % CI 0.746–0.846) at the stage of devising the technique and 0.831 (95 % CI 0.694–0.968) at its validation.

Thus, the devised prognostic classification of MPLN risk in patients with newly diagnosed PC is easily reproducible and can be used for selecting the target volume in RT without a significant risk of overtreatment in patients with uninvolved pelvic lymph nodes.

Conclusions

1. The level of PSA prior to RPE, cT tumor category and Gleason score are independent predictors of MPLN detection.

2. At the stage of devising the prognostic classification, MPLN detection rate in the group of patients with a score estimate > 15 was 23.7 %, which is statistically significantly higher ($p < 0.001$) than with a score estimate < 10 (3.5 %).

3. At the validation of the obtained results in clinic, metastatic involvement of pelvic lymph nodes according to RPE findings was diagnosed in 40.0 % of patients with a score estimate >15 and only in 1.3 % of men with a total score estimate of prognostic factors < 10 ($p < 0.0001$).

4. The efficacy of the proposed classification was corroborated by the method of ROC analysis: in the course of devising the prediction technique, AUC accounted for 0.796 (95 % CI 0.746–0.846), and 0.831 (95 % CI 0.694–0.968) at its validation.

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