Tumor free distance is the best predictive marker in patients with early-stage cervical cancer treated by primary surgery

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Background:
Main limitation of the majority of previous studies on prognostic markers lied in an insufficient standardisation of both clinical management and the method of assessment of individual parameters.

Methods:
All consecutive patients with early-stage cervical cancer treated by primary surgery in a single centre between 01/2007 and 12/2016 were eligible if they were assessed by standardized protocols for preoperative imaging and pathology. Fifteen prognostic parameters were evaluated, including age, 11 tumour-related (stage; largest tumour size; tumour size binarized; depth of stromal invasion; minimal tumour free distance (TFD); TFD binarized; lymphovascular space invasion (LVSI); tumour type; grade; parametrial invasion) and 3 lymph node (LN) status related ones (number of positive LNs; LN involvement; type of metastasis in LN).

Results:
Data from 379 consecutive patients were analysed. Table 1 shows characteristics of the whole group (Cohort A) and LN negative patients (Cohort B). All parameters were associated with a risk of recurrence (RR), except for age and grade, in Cohort A, but only 4 remained significant in Cohort B (tumor type, grade, minimal TFD, TFD binarized). The best predictive model for Cohort A entailed a combination of TFD≤3.5 mm and LN positivity, which discriminated a subgroup of 42 patients with RR 36% versus 6.5% in the rest of the cohort (Figure1). In Cohort B a combination of TFD≤3.5 mm and adenosquamous tumour type discriminated a small group of 9 patients with RR 33% versus 6% (Figure 2).

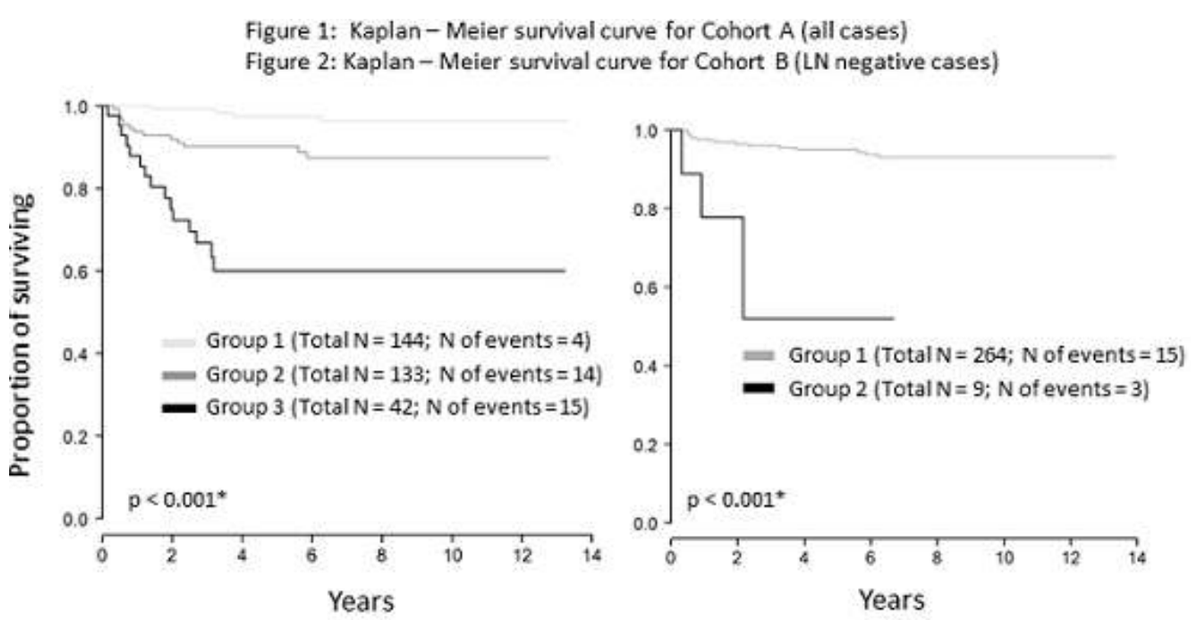
Conclusions:
Tumor free distance (TFD) surpassed all other traditional tumor-related markers in the assessment of the recurrence risk in both cohorts. Predictive models combining TFD with LN status (whole cohort) or histological type (LN negative cases) can easily be used in daily practice and can identify the smallest possible group of patients with the highest risk of recurrence.

Table 1: Summary of demographic and clinical parameters according to cohort.

		All patients N=379 (Cohort A)	LN- negative patients (without MAC, MIC, ITC) N=320 (Cohort B)
Age (years)		41.9 (27.8; 70.3)	41.8 (27.7; 70.7)
BMI		24.4 (18.4; 36.6)	24.7 (18.7; 36.1)
Stage (pT)	1a1	66 (17.4%)	66 (20.6%)
	1a2	9 (2.4%)	9 (2.8%)
	1b1	203 (53.6%)	182 (56.9%)
	1b2	46 (12.1%)	27 (8.4%)
	2a	11 (2.9%)	7 (2.2%)
	2b	44 (11.6%)	29 (9.1%)
Tumour type	Adenocarcinoma	76 (20.1%)	63 (19.7%)
	Adenosquamous	11 (2.9%)	6 (1.9%)
	Squamous	292 (77.0%)	251 (78.4%)
Grade	1	44 (11.6%)	44 (13.7%)
	2	171 (45.1%)	150 (46.9%)
	3	164 (43.3%)	126 (39.4%)
LVSI		144 (38.0%)	97 (30.3%)
Fertility-sparing treatment		65 (17.2%)	62 (19.4%)
Type of parametrectomy	SH or C*	51 (13.5%)	51 (16.0%)
	B	33 (8.6%)	29 (9.0%)
	C1	133 (35.1%)	119 (37.3%)
	C2	162(42.8%)	121 (37.7%)
SLN biopsy		234 (61.7%)	194 (60.6%)
Pelvic lymphadenectomy		301 (79.4%)	244 (76.3%)
No. of removed LN per patient		31.0 (0.0; 58.0)	30.5 (0.0; 58.0)
Type of LN metastases	MAC	32 (8.4%)	-
	MIC	18 (4.7%)	-
	ITC	9 (2.4%)	-
	Negative	320 (84.4%)	320 (100.0%)
Preoperative assessment by imaging:			
Largest tumour size (mm)		22.0 (0.8; 54.0)	19.0 (0.0; 52.0)
Minimal TFD (mm)		3.0 (0.0; 14.0)	4.0 (0.0; 14.0)
Pathological assessment:			
Largest tumour size (mm)		24.0 (2.5; 65.0)	20.0 (2.2; 57.0)
Depth of stromal invasion (mm)		15.0 (5.0; 25.6)	14.0 (5.0; 25.0)
Tumor volume (mm³)		3 811.8 (7.3; 44 588.8)	2 358.8 (4.2; 39 964.5)
Adjuvant treatment		76 (20.1%)	33 (10.3%)
Follow-up length (months)		78.1 (9.2; 152.8)	78.4 (9.3; 152.8)
Recurrence rate		43 (11.3%)	23 (7.2%)

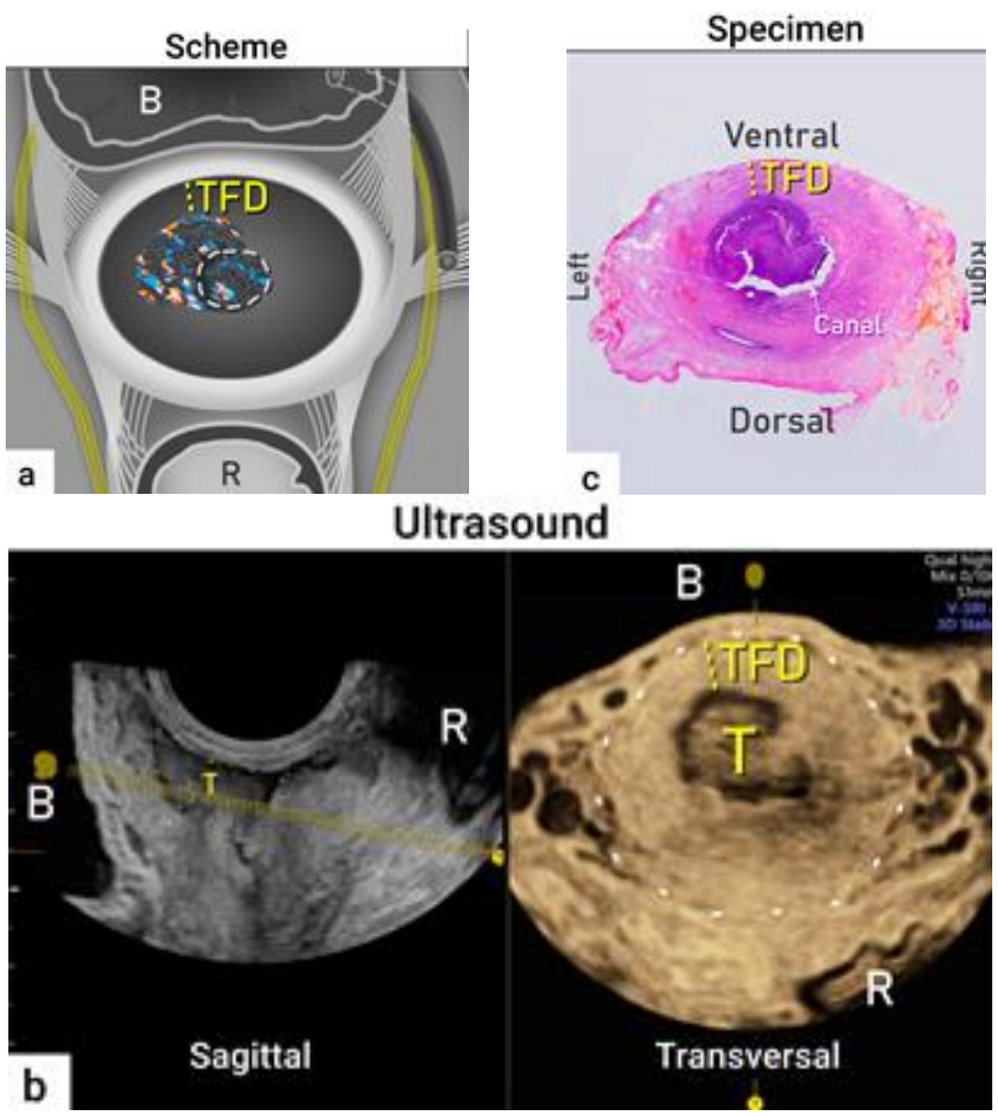
[1] absolute and relative frequencies for categorical variables; median supplemented with 5th–95th percentile range for continuous variables; **simple hysterectomy or conisation

Figure 1: Kaplan – Meier survival curve for Cohort A (all cases)
Figure 2: Kaplan – Meier survival curve for Cohort B (LN negative cases)



Group description: ***Group 1:*** **TFD > 3.5**; N0** ***Group 2: TFD*** **≤ 3.5**; N0**** ***Group 3: TFD*** **≤ 3.5**; N1****
Two patients without event are not included into the groups: Minimal tu-pcf (US) > 3.5**; Number of positive LN > 0**
* Log-rank test **cut off determined by ROC analysis, the criterion was the highest value of the sum of sensitivity and specificity

Group description: ***Group 1: Other combinations not included in Group 2,*** ***Group 2:*** **TFD ≤ 3.5**; Tumor type – adenosquamous**
One patient without event is not included into the groups: Minimal tu-pcf (US) > 3.5**; Tumor type – Adenosquamous
• Log-rank test **cut off determined by ROC analysis, the criterion was the highest value of the sum of sensitivity and specificity



Acknowledgements:
This work was supported by Charles University in Prague (UNCE 204065 and PROGRES Q28/LF1), by the project of Ministry of Health of the Czech Republic (MZ CR – RVO VFN64165) and by a grant from the Czech Research Council (No 16-31643A).