Archives of Gynecology and Obstetrics (2019) 299:203–209
https://doi.org/10.1007/s00404-018-4928-9

GYNECOLOGIC ONCOLOGY

Glucocorticoid receptor in cervical cancer: an immunhistochemical analysis

Bernd Peter Kost[1] · Susanne Beyer[1] · Lennard Schröder[1] · Junyan Zhou[1] · Doris Mayr[2] · Christina Kuhn[1] · Sandra Schulze[1] · Simone Hofmann[1] · Sven Mahner[1] · Udo Jeschke[1] · Helene Heidegger[1]

Received: 18 June 2018 / Accepted: 1 October 2018 / Published online: 10 October 2018

Abstract

Purpose Cervical cancer is one of the most frequent cancers in women worldwide. In most of all cases, a persistent HPV infection is the leading cause. HPV-specific sequences are able to bind glucocorticoid receptor (GR). Dexamethasone can increase the activity of early promoters in HPV16 and HPV18 interfering in transcription control of viral oncogenes. The aim of our study was to evaluate glucocorticoid receptor as transcriptional factor in its active form in the nucleus of in cervical cancer cells and to correlate the results with clinical patient specific parameters.

Methods A total of 250 paraffin-embedded cervical cancer samples obtained from patients having undergone surgery for cervical cancer were used for the study. The expression of GR was immunhistochemical examined and evaluated by a semi-quantitative scoring. SPSS software was used for the statistical evaluation of staining results and survival analysis of patients with cervical cancer.

Results GR is frequently expressed in cervical carcinoma tissue in favor of squamous cell carcinoma (SCC). An enhanced expression is correlated with rather small clinical stages. The expression of the GR is correlated with better overall survival and progression-free survival.

Conclusions The glucocorticoid receptor is frequently expressed in cervical carcinoma tissue in favor of squamous cell carcinoma. An enhanced expression is correlated with rather small clinical stages. The expression of the analyzed receptor is correlated with better overall survival. Further studies are needed to determine useful treatment targets for glucocorticoid receptor manipulation.

Keywords Cervical cancer · Glucocorticoid receptor · Survival

Introduction

Cervical cancer is one of the most frequent cancers in women worldwide. Regarding women's outcome, major prognostic factors are known as International Federation of Gynecology and Obstetrics (FIGO) stage, histological type or grade, tumor size, lymph node metastasis or rather lymphatics invasion. According to international guidelines, patients are treated with surgery or radiotherapy depending on staging and individual risk assessment [1–3].

In most of all cases, a persistent infection with high-risk human papillomavirus (HR-HPV) is the reason for cervical cancer [1, 4]. A total of 170 HPV types are known [5, 6]. In the genome of human papillomaviruses, there are approximately 8000 base pairs and six "early genes" (E6, E7, E1, E2, E4, E5), two "late genes" (L1, L2) and noncoding regions [7]. Integration of HPV is a vector for cervical carcinogenesis resulting in a loss of a suppressive function on E6 and E7. In consequence, disturbance of cell cycle, uncontrolled cell proliferation and possible carcinogenesis occur [8–10]. Although viral-specific pathogenesis of cervical cancer is well known, additional mechanisms as co-factors are assumed to induce HPV-related carcinogenesis. The role of steroid hormones in the pathogenesis of HPV-related cervical cancer is under investigation [8, 11–14].

✉ Udo Jeschke
udo.jeschke@med.uni-muenchen.de

[1] Department of Obstetrics and Gynecology, LMU Munich, University Hospital, Marchioninistrasse 15, 81377 Munich, Germany

[2] Klinikum Der Universität München, Pathologisches Institut, Munich, Germany

HPV-specific sequences (LCR, long control regions) are able to bind receptors like glucocorticoid receptor (GR) [8, 15]. Dexamethasone can result in an increased activity of early promoters in HPV16 and HPV18 interfering in transcription control of viral oncogenes E6 and E7 [8, 13, 16, 17].

Materials and methods

Specimens

We used 250 paraffin-embedded cervical cancer samples. They were obtained from patients with a median age of 47.0 years (range 20–83 years), and an overall median survival of 100.0 months. Patients had undergone surgery for cervical cancer in the Department of Obstetrics and Gynecology of the LMU Munich between 1993 and 2002. Clinic pathological variables are described in Table 1. Only patients with the most frequent histological subtype (adenocarcinoma or squamous cell carcinoma) of the cervix were included in our study; due to low number, other histological subtypes were excluded. For positive and negative controls, placenta tissue received from the Department of Obstetrics and Gynecology of the LMU Munich was used. Clinical and follow-up data for statistical analyses were provided by The Munich Cancer Registry and recruited from medical records. We used, therefore, the original data. This means that we used the FIGO classification which was available for 2002—as patients underwent surgery between 1993 and 2002. In this classification, patients were also staged in FIGO IIIC, which means that they were FIGO III with positive lymph nodes.

Table 1 Clinic pathological parameters of the patients included in this study

	No./Total no.	%
Age, years		
< 49	139/250	55.6
> 49	111/250	44.4
No. of positive nodes		
0	151/250	60.4
≥ 1	097/250	38.8
NA's	002/250	00.8
pT		
pT1	111/250	44.4
pT2	129/250	51.6
pT3/4	009/250	03.6
NA's	001/250	0.04
FIGO		
I	64/250	25.6
II	49/250	19.6
III	37/250	14.8
IV	07/250	02.8
NA's	93/250	37.2
Tumor grade, G		
I	021/250	08.4
II	143/250	57.2
III	078/250	31.2
NA's	008/250	03.2
Tumor subtype		
Squamous	202/250	80.8
Adenocarcinoma	048/250	19.2
Progression(over 235 months)		
None	210/250	84.0
At least one	29/250	11.6
NA's	011/250	04.4
Survival (over 235 months)		
Right censured	190/250	76.0
Died	049/250	19.6
NA's	011/250	04.4

Immunohistochemical staining

Specimens were formalin fixed and paraffin embedded, while stored at room temperature. Slides (3 µm) were dewaxed in xylol and afterwards washed in 100% alcohol. After blocking the endogenous peroxidase by 3% methanol/H_2O_2, rehydration of the tissue took place in a descending alcohol series. Sections were cooked at 100 °C in a sodium citrate buffer solution with pH = 6 to unmask the antigen and to prevent heat-associated protein agglomeration. After washing the slides (aqua dist./PBS buffer), the following antibody was added on the tissue and incubation at + 4 °C for 16 h was performed (Table 2): Anti-GR (mouse IgG2a; clone 4H2; Novocastra, Wetzlar, Germany). Post-block reagent and HRP polymer were added to increase the staining. Finally, the tissue was dehydrated in a rising series of alcohol and finally covered. The power of the staining was evaluated by an optical microscope with the immunoreactivity score (IRS), where intensity (0 = not stained; 1 = low intensity; 2 = moderate intensity; 3 = high intensity) and percentage of stained cells (0 = 0%; 1 = 1–10%; 2 = 11–50%; 3 = 51–80%; 4 ≥ 80%) were multiplied. The higher the result, the more powerful the expression (0 = no expression, 12 = very high expression). The slides were examined by two independent persons.

In our study, we examined the function of the glucocorticoid receptor as transcription factor, which is the case if it is present in the nucleus as active form. In the cytoplasm, the receptor is present but not active as a transcription factor; so, it was not detected.

Table 2 Antibody and chemicals used for the immunohistochemistry

Glucocorticoid receptor (GR)[a]
Blocking solution[b]: 5 min
Primary antibody[a]: 1:30 in PBS[d] incubation: 16 h, 4 °C
PostBlock[b]: 20 min
HRP Polymer[2]: 30 min
Chromogen: DAB[c] (1 min)

[a]Anti-GR, clone 4H2 (mouse IgG2a), company: Novocastra (Wetzlar, Germany), Order number: NCL-GCR

[b]ZytoChem Plus HRP Polymer Kit (Mouse/Rabbit) 3*100; company: Zytomed Systems (Germany) Nr. POLHRP-100

[c]Liquid DAB + Substrate Chromogen System 1 mg/ml, DAKO

[d]Dulbecco's phosphate-buffered saline

Ethics approval

The study was approved by the ethics committee of the Ludwig-Maximilians University Munich (reference number 259-16) and considered the Declaration of Helsinki. Patient data were anonymized. During experimental and statistical analyses, the authors were blinded for clinic pathological parameters and information regarding survival. All used cancer tissue was no longer needed for clinical tests as it had initially been collected for histopathological diagnostics after surgery.

Statistics

SPSS Statistics data version 23 (IBM, Armonk, USA) was taken to perform statistical analyses. Non-parametric tests (Mann–Whitney *U* test and Kruskal–Wallis test) were used to compare independent groups and bivariate correlations were showed by Spearman's rho correlation coefficient. Survival analyses were plotted in Kaplan–Meier curves and boxplots; for significant differences regarding survival, log-rank test was used, or additionally Mann–Whitney *U* test. Cox analysis was performed to find independent markers for survival. If p was < 0.05, we considered the result to be statistically significant.

Results

GR staining in cervical carcinoma

To control the GR staining, we used normal (non-pathological) placenta tissue, which showed strong nuclear expression in > 80% of epithelial cells (Fig. 1a) without any cytoplasmic reaction.

A total of 92.4% of all cervical cancer specimens showed an expression of GR receptor with a median IRS of 4, represented in 41.6% of all cases. In contrast, 7.6% did not show any expression at all. A low GR expression (IRS ≤ 3) was shown in 35.6% compared to an enhanced expression (IRS ≥ 4) in 64.4%.

GR staining in correlation with clinical parameters

Analyzing the histological subtype (Fig. 1b), squamous epithelial carcinomas showed a median IRS of 4 being represented in 45.0% of all cases (Fig. 1c), compared to a median IRS of 3 in 10.4% in adenocarcinoma tissue (Fig. 1d). The expression of the staining was significantly different between these two histological subtypes ($p = 0.000$; Table 3).

Correlating the GR findings with FIGO classification, the median IRS varied between 0 and 8 (Fig. 1e). FIGO I showed a median IRS of 4 (Fig. 1f), compared to a median IRS of 8 in FIGO IIA (Fig. 1g) and 0 in FIGO IIIC (Fig. 1h). GR staining was significantly correlated with FIGO stage ($p = 0.002$), whereas an enhanced staining was accompanied by a low FIGO stage (Rho = −0.174, $p = 0.030$; Table 3).

No significant difference between GR staining and grading, T- and N-status was found

GR staining and survival

Kaplan–Meier analysis showed a significant correlation between GR expression (IRS ≥ 4) and overall survival ($p = 0.045$): an advanced GR expression went along with significant better overall survival compared to low GR expression (IRS ≤ 3) in cervical cancer (Fig. 2a). Regarding release-free survival, an increased GR expression was also correlated with longer release-free survival ($p = 0.009$; Fig. 2b). This fitted to the correlation between GR and the FIGO status, where high GR expression was correlated with a low FIGO state.

Cox regression was performed to find independent prognosticators concerning survival. Regarding overall survival, clinical parameters like histological subtype ($p = 0.038$), N-status ($p = 0.002$), FIGO classification ($p = 0.003$) and age at surgery ($p < 0.001$) were independent prognosticators, as well as T-stage ($p = 0.003$) but not grading. Expression of GR turned out to be an independent marker for overall survival being correlated with better overall survival (Table 4).

Regarding relapse-free survival, neither analyzed clinic pathological markers (histological subtype, T-status, N-stage, FIGO stage, grading or age at surgery) nor GR expression turned out to be significant.

Discussion

Glucocorticoids are well-known substances in cancer treatment. They are used as co-medication to reduce side effects of cancer therapy or by effecting cell-cycle progression and

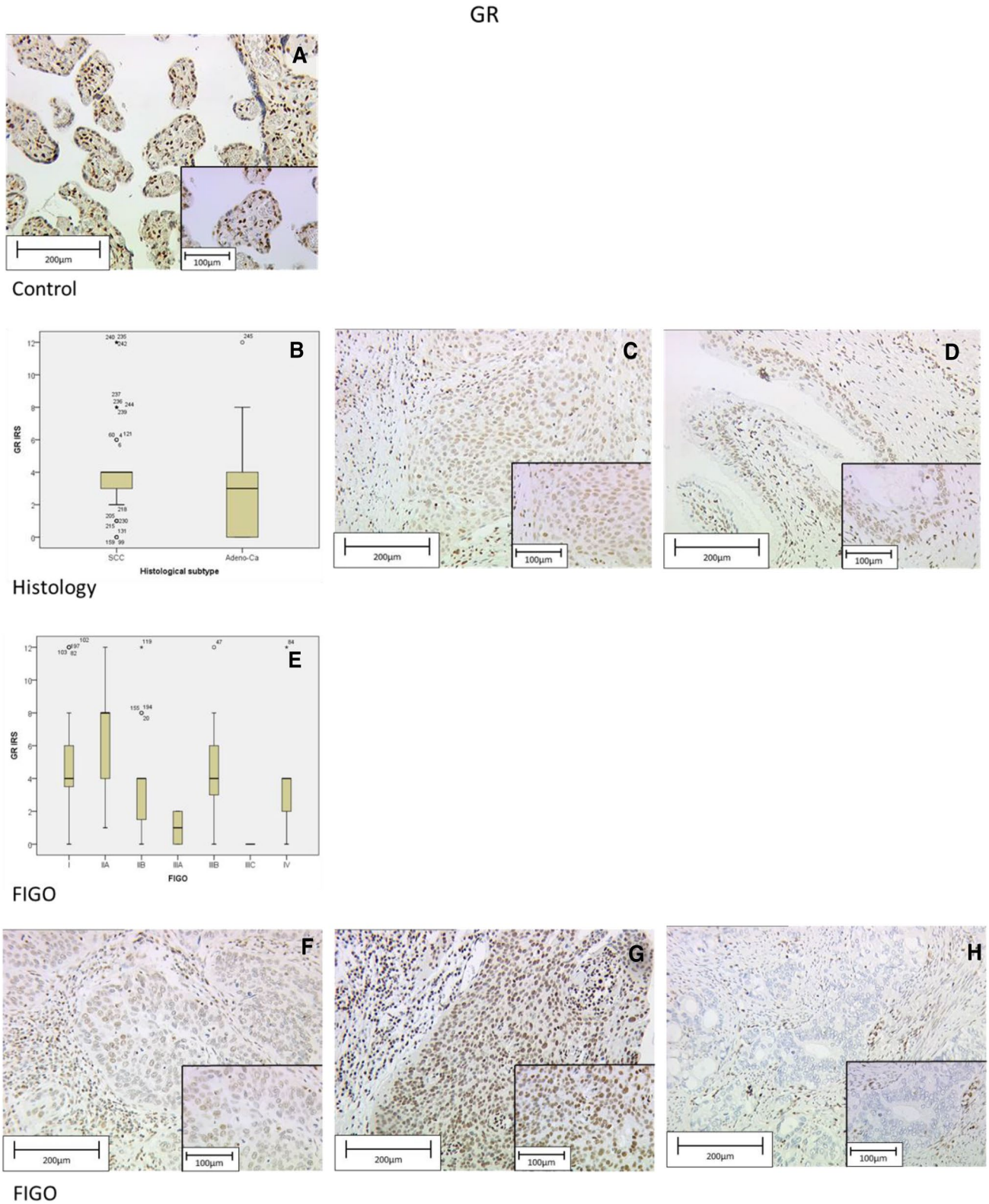

Fig. 1 Positive control of GR staining in placenta tissue with strong nuclear expression (**a**)**.** Correlation between GR expression and histological subtypes: (**b**). Median IRS of SCC was 4 (**c**), compared to the median IRS of Adeno-Ca of 3 (**d**). GR expression correlated with FIGO status, as summarized in the boxplot (**e**). FIGO I staged patient showed an IRS of 4 (**f**), FIGO II staged patient, a median IRS of 8 (**g**) and FIGO III staged patient, an IRS of 0 (**h**). Scale bar 200 µm, small pictures 100 µm

Table 3 Staining results and correlation analysis for GR expression

	GR			
	Median IRS (±SD)	%	*p* (NPAR)	*ρ*
Histology				
SCC	4 (±3.0)	45.0	0.000	–
Adeno-Ca	3 (±2.7)	10.4		
FIGO				
I	4 (±3.2)	48.4	0.002	−0.174 ($p=0.030$)
IIA	8 (±3.4)	50.0		
IIB	4 (±2.5)	45.0		
IIIA	1 (±1.4)	00.0		
IIIB	4 (±2.7)	33.3		
IIIC	0 (±0.0)	100		
IV	4 (±3.8)	42.9		
pT				
T1	4 (±3.1)	41.8	0.492	−0.068 ($p>0.05$)
T2	4 (±2.9)	41.4		
T3/4	4 (±3.0)	44.4		

SD standard deviation, % percentage of the subgroup with median IRS, *NPAR* non-parametric test, *p* p value, *ρ* correlation coefficient

apoptosis to treat malignancy itself [18]. The effect of glucocorticoids and their corresponding receptor or the interaction with other pathogens like HPV on cervical carcinoma is not clear yet.

Altogether, there are limited data about GR expression in cervical carcinoma. In a study by Block et al., glucocorticoid receptor expression in 20 solid tumor types was analyzed. 82% of the analyzed cervical cancer tissue in a small sample size was tested positive in their analysis [8]. Regarding our study, > 92% of the analyzed samples showed detectable GR expression in the nucleus with a high staining in > 64% of all cases. The study by Block et al. [19] indicated that GR expression varies by tumor subtype comparing different histological lung cancer types. Due to the low number of cervical carcinoma samples in their study, a sufficient analysis of histological subtypes was not done.

In favor of squamous epithelial carcinomas, a significant difference between squamous epithelial carcinoma and adenocarcinoma concerning GR expression was measured in our study. Differential expression of prognosis marker proteins in both carcinoma entities was described recently by our group. In cervical cancer, Histone H3 acetyl K9 staining was associated with low grading, low FIGO status, negative N-status and low T-status and showed a higher expression in adenocarcinoma compared to squamous cell carcinoma [23]. In addition, we found a positive correlation of the nuclear GR staining with p16 ($\rho=0.301$, $p<0.001$) and p53 ($\rho=0.237$, $p<0.001$), which were obtained from a former study [20]. The glucocorticoid receptor showed also a positive correlation with the G protein-coupled estrogen receptor (GPER, $\rho=0.233$, $p<0.001$), RIP140 ($\rho=0.171$, $p=0.008$) and Histone H3 Tri Methyl K4 ($\rho=0.143$, $p=0.023$) [21–23].

According to international guidelines, cervical cancer patients are treated with surgery or radiotherapy depending on individual staging and risk assessment. Risk assessment includes tumor size, stage, depths of tumor invasion, lymph node status, lympho-vascular space invasion and histological subtype. Regarding prognosis and risk assessment, there might be other biological markers in cervical cancer to assess individual therapy policy or prognosis [24–28].

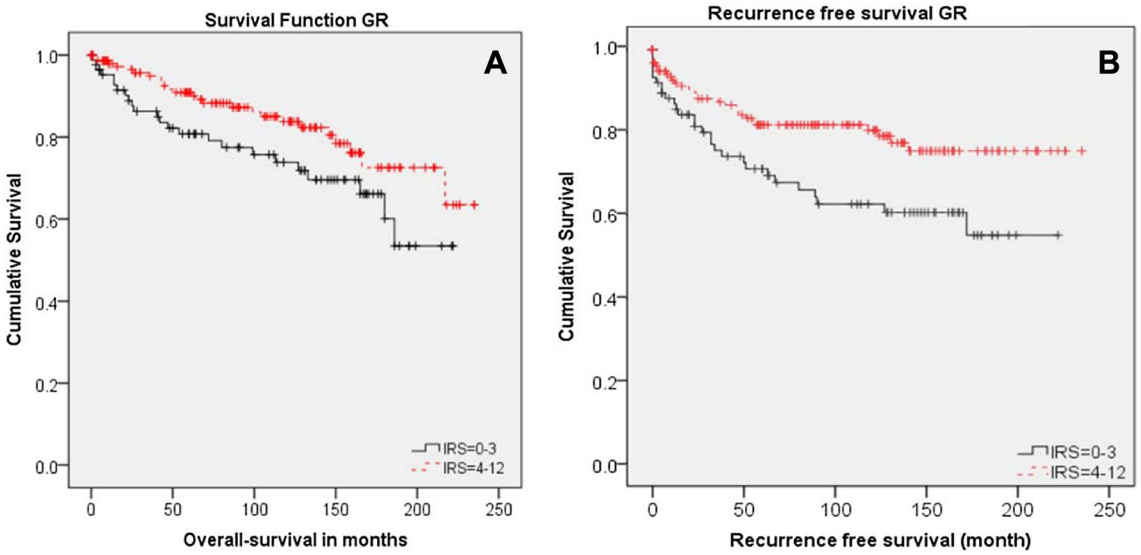

Fig. 2 Kaplan–Meier analysis regarding overall survival in cervical cancer: low GR expression (IRS ≤ 3) compared to high expression (IRS ≥ 4) regarding overall survival (**a**; $p=0.045$) and recurrence-free survival (**b**; $p=0.009$)

Table 4 Cox regression of clinic pathological variables regarding overall survival in cervical cancer

	Significance	Hazard ratio [Exp(B)]	Lower 95% CI of Exp(B)	Upper 95% CI of Exp(B)
Histology	**0.038**	**1.905**	**1.036**	**3.500**
pT	0.624	0.882	0.534	1.457
pN	**0.002**	**2.465**	**1.378**	**4.412**
FIGO	**0.003**	**1.258**	**1.080**	**1.465**
Grading	0.193	1.365	0.855	2.181
Age at surgery	**0.000**	**1.049**	**1.026**	**1.072**
GR	**0.054**	**0.575**	**0.328**	**1.009**

Significant results are shown in bold

In the present study, expression of GR was significantly correlated with survival: an advanced GR expression went along with significant better overall- and release-free survival compared to low GR expression in our analyzed cancer cells. In a study by Vanderbilt et al. [29], the effect of glucocorticoid growth arrest in lymphoid cell lines was proportional to GR content. Gehring et al. [30] showed a correlation between low-level GR expression with a poor treatment response or patient prognosis in ALL. Nevertheless, consistent with data in hematological malignancies, our data indicate a better prognosis of cervical cancer patients correlating with GR expression, fitting to the correlation between FIGO and GR expression. More data exist regarding mRNA expression of GR in cervical cancer. We think that it is not allowed to transfer these data one–one to our study design as we examined the active form of the glucocorticoid receptor with its expression in the nucleus. Interestingly, in a recent study, we could show that RIP140 as co-regulator of the glucocorticoid receptor is also an independent prognosticator for cervical cancer patients [22].

As therapeutic agents, glucocorticoids are effective in inducing apoptosis in many hematological malignancies. Besides positive effects of glucocorticoids in leukemia, different cancer cells seem to respond with increased resistance towards glucocorticoid induced apoptosis [31]. Limited data concerning the apoptotic effect of glucocorticoids in solid tumor cells exist from osteosarcoma or small-cell lung cancers. Their might be negative effects of glucocorticoids in solid tumors by causing faster growth or metastasis by providing a selection pressure [18].

Other studies identified the induction of glucocorticoid receptor as feature of drug resistance leading to worse survival rates, if GR is expressed [32]. These data seem to be in contrast to our results but they refer to special cases and mechanisms, for example, in prostate cancer. It is not clear if a one–one transfer to cervical cancer is possible.

Altogether, the wide range of mechanisms by which glucocorticoids are able to develop in different cell lines are not fully understood [31]. An ongoing clinical trial (NCT02762981) will provide initial data, if the glucocorticoid receptor can be targeted by the selective glucocorticoid receptor modulator CORT125134 in combination with nab-paclitaxel in different solid tumors [33, 34]. If the glucocorticoid effect on cervical carcinoma tissue is dependent on GR itself or other mechanisms has to be investigated.

Author contributions BPK: project development, data collection. SB: experiments, manuscript writing. LS: data collection, manuscript editing. JZ: data analyses. DM: supervision, data analyses. CK: experiments, methodology. SS: experiments, methodology. SH: experiments, methodology. SM: data analyses, supervision, funding. UJ: supervision. HH: manuscript edition, data analyses

Funding The study was supported by the "Heuer Stiftung" for Bernd P. Kost. The authors would like to thank Prof. Dr. med. Jutta Engel, M.P.H. and Max Wiedemann (The Munich Cancer Registry of the Tumorzentrum München [TZM—Munich Tumor Center]) for the follow-up data.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent The study was approved by the ethics committee of the Ludwig-Maximilians University Munich (reference number 259-16). Patient data were anonymized.

References

1. Munoz N, Bosch FX, Castellsague X, Diaz M, de Sanjose S, Hammouda D, Shah KV, Meijer CJ (2004) Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int J Cancer 111:278–285
2. Serrano-Olvera A, Cetina L, Coronel J, Duenas-Gonzalez A (2014) Follow-up consultations for cervical cancer patients in a mexican cancer center. Comparison with NCCN guidelines. Asian Pac J Cancer Prev 15:8749–8752
3. Horn LC, Beckmann MW, Follmann M, Koch MC, Mallmann P, Marnitz S, Schmidt D, German Cancer S (2015) s3 guidelines on diagnostics and treatment of cervical cancer: demands on pathology. Pathologe 36:585–593
4. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S (2007) Human papillomavirus and cervical cancer. Lancet 370:890–907
5. Wittekindt C, Wagner S, Mayer CS, Klussmann JP (2012) basics of tumor development and importance of human papilloma virus (HPV) for head and neck cancer. Laryngorhinootologie 91(Suppl 1):S1–S26

6. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ, Meijer CJ, International Agency for Research on Cancer Multicenter Cervical Cancer Study G (2003) Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 348:518–527
7. Liu J, Cheng Y, He M, Yao S (2014) Vascular endothelial growth factor c enhances cervical cancer cell invasiveness via upregulation of galectin-3 protein. Gynecol Endocrinol 30:461–465
8. Meng CF, Su B, Li W (2011) DNA demethylation is superior to histone acetylation for reactivating cancer-associated genes in ovarian cancer cells. Mol Med Rep 4:1273–1278
9. Gupta S, Takhar PP, Degenkolbe R, Koh CH, Zimmermann H, Yang CM, Guan Sim K, Hsu SI, Bernard HU (2003) The human papillomavirus type 11 and 16 e6 proteins modulate the cell-cycle regulator and transcription cofactor trip-br1. Virology 317:155–164
10. Scheffner M, Huibregtse JM, Vierstra RD, Howley PM (1993) The hpv-16 e6 and e6-ap complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. Cell 75:495–505
11. Pittayakhajonwut D, Angeletti PC (2010) Viral trans-factor independent replication of human papillomavirus genomes. Virol J 7:123
12. Bromberg-White JL, Meyers C (2002) The upstream regulatory region of human papillomavirus type 31 is insensitive to glucocorticoid induction. J Virol 76:9702–9715
13. Chan WK, Klock G, Bernard HU (1989) Progesterone and glucocorticoid response elements occur in the long control regions of several human papillomaviruses involved in anogenital neoplasia. J Virol 63:3261–3269
14. Webster K, Taylor A, Gaston K (2001) Oestrogen and progesterone increase the levels of apoptosis induced by the human papillomavirus type 16 e2 and e7 proteins. J Gen Virol 82:201–213
15. Kwasniewska A, Postawski K, Gozdzicka-Jozefiak A, Kwasniewski W, Grywalska E, Zdunek M, Korobowicz E (2011) Estrogen and progesterone receptor expression in HPV-positive and HPV-negative cervical carcinomas. Oncol Rep 26:153–160
16. Fonseca-Moutinho JA, Cruz E, Carvalho L, Prazeres HJ, de Lacerda MM, da Silva DP, Mota F, de Oliveira CF (2004) Estrogen receptor, progesterone receptor, and BCL-2 are markers with prognostic significance in cin iii. Int J Gynecol Cancer 14:911–920
17. Chen YH, Huang LH, Chen TM (1996) Differential effects of progestins and estrogens on long control regions of human papillomavirus types 16 and 18. Biochem Biophys Res Commun 224:651–659
18. Schlossmacher G, Stevens A, White A (2011) Glucocorticoid receptor-mediated apoptosis: mechanisms of resistance in cancer cells. J Endocrinol 211:17–25
19. Block TS, Murphy TI, Munster PN, Nguyen DP, Lynch FJ (2017) Glucocorticoid receptor expression in 20 solid tumor types using immunohistochemistry assay. Cancer Manag Res 9:65–72. https://doi.org/10.2147/CMAR.S124475
20. Stiasny A, Freier CP, Kuhn C, Schulze S, Mayr D, Alexiou C, Janko C, Wiest I, Dannecker C, Jeschke U et al (2017) The involvement of e6, p53, p16, mdm2 and gal-3 in the clinical outcome of patients with cervical cancer. Oncol Lett 14:4467–4476
21. Friese K, Kost B, Vattai A, Marme F, Kuhn C, Mahner S, Dannecker C, Jeschke U, Heublein S (2018) The g protein-coupled estrogen receptor (gper/gpr30) may serve as a prognostic marker in early-stage cervical cancer. J Cancer Res Clin Oncol 144:13–19
22. Vattai A, Cavailles V, Sixou S, Beyer S, Kuhn C, Peryanova M, Heidegger H, Hermelink K, Mayr D, Mahner S et al (2017) Investigation of rip140 and lcor as independent markers for poor prognosis in cervical cancer. Oncotarget 8:105356–105371
23. Beyer S, Zhu J, Mayr D, Kuhn C, Schulze S, Hofmann S, Dannecker C, Jeschke U, Kost BP (2017) Histone h3 acetyl k9 and histone h3 tri methyl k4 as prognostic markers for patients with cervical cancer. Int J Mol Sci. https://doi.org/10.3390/ijms18030477
24. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N, Committee E G (2017) Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 28:iv72–iv83
25. Reich O, Regauer S, Marth C, Schmidt D, Horn LC, Dannecker C, Menton M, Beckmann MW (2015) Precancerous lesions of the cervix, vulva and vagina according to the 2014 who classification of tumors of the female genital tract. Geburtshilfe Frauenheilkd 75:1018–1020
26. Freier CP, Stiasny A, Kuhn C, Mayr D, Alexiou C, Janko C, Wiest I, Jeschke U, Kost B (2016) Immunohistochemical evaluation of the role of p53 mutation in cervical cancer: Ser-20 p53-mutant correlates with better prognosis. Anticancer Res 36:3131–3137
27. Stiasny A, Kuhn C, Mayr D, Alexiou C, Janko C, Wiest I, Jeschke U, Kost B (2016) Immunohistochemical evaluation of e6/e7 hpv oncoproteins staining in cervical cancer. Anticancer Res 36:3195–3198
28. Kolben TM, Kraft F, Kolben T, Goess C, Semmlinger A, Dannecker C, Schmoeckel E, Mayr D, Sommer NN, Mahner S et al (2017) Expression of sialyl lewis a, sialyl lewis x, lewis y, gal-3, gal-7, stmn1 and p16 in cervical dysplasia. Future Oncol 13:145–157
29. Vanderbilt JN, Miesfeld R, Maler BA, Yamamoto KR (1987) Intracellular receptor concentration limits glucocorticoid-dependent enhancer activity. Mol Endocrinol 1:68–74
30. Gehring U, Mugele K, Ulrich J (1984) Cellular receptor levels and glucocorticoid responsiveness of lymphoma cells. Mol Cell Endocrinol 36:107–113
31. Herr I, Buchler MW, Mattern J (2009) Glucocorticoid-mediated apoptosis resistance of solid tumors. Results Probl Cell Differ 49:191–218
32. Arora Vivek K, Schenkein Emily, Murali Rajmohan et al (2013) Glucocorticoid receptor confers resistance to anti-androgens by bypassing androgen receptor blockade. Cell 155(6):1309–1322
33. Hunt H, Donaldson K, Strem M, Zann V, Leung P, Sweet S, Connor A, Combs D, Belanoff J (2017) Assessment of safety, tolerability, pharmacokinetics, and pharmacological effect of orally administered cort125134: An adaptive, double-blind, randomized, placebo-controlled phase 1 clinical study. Clin Pharmacol Drug Dev 7(4):408–421. https://doi.org/10.1002/cpdd.389
34. Hunt HJ, Belanoff JK, Walters I, Gourdet B, Thomas J, Barton N, Unitt J, Phillips T, Swift D, Eaton E (2017) Identification of the clinical candidate (r)-(1-(4-fluorophenyl)-6-((1-methyl-1 h-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexah ydro-1 h-pyrazolo[3,4-g] isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methano ne (cort125134): a selective glucocorticoid receptor (gr) antagonist. J Med Chem 60:3405–3421