UROLOGIC
ONCOLOGY

Original article

ERG expression can predict the outcome of docetaxel combined with androgen deprivation therapy in metastatic hormone-sensitive prostate cancer

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Abstract

Background: Our study aimed to analyze the potential association between clinical parameters and ERG expression and the outcome of docetaxel chemotherapy among patients with metastatic hormone-sensitive prostate cancer.

Patients and Methods: Fifty-five patients with metastatic hormone-sensitive prostate cancer were treated with docetaxel in addition to androgen deprivation therapy. Patient characteristics, clinical factors, and tumor expression of ERG by immunohistochemistry were analyzed with respect to therapeutic response and survival data.

Results: Relapse free survival (RFS) and overal survival (OS) were 10.5 and 40.4 months, respectively, and both correlated with PSA response (RFS: 16.8 with a ≥50% decrease in PSA vs. 5.9 months in the case of <50% decrease, $P < 0.001$; OS: 40.4 vs. 11.6 months, respectively, $P < 0.001$). There was an association between OS and early progression (OS: 40.4 months with progression after 12 months vs. 17.9 months with progression within 12 months, $P = 0.009$). ERG expression was detected in 21 (42%) samples. ERG positivity was associated with favorable RFS (ERG pos. vs. neg.: 26.0 vs. 11.4 months, $P = 0.003$).

Conclusion: ERG expression may have a potential predictive value with respect to the effectiveness and outcome of docetaxel chemotherapy combined with androgen deprivation therapy. © 2018 Elsevier Inc. All rights reserved.

Keywords: Metastatic prostate cancer; Docetaxel chemotherapy; ERG; Hormone-sensitive prostate cancer; Chemosensitivity

1. Introduction

The treatment of metastatic prostate cancer can be divided into hormone-sensitive and castration-resistant pathophysiological phases. Until recently, androgen

deprivation therapy (ADT) alone by surgical or medical castration was the standard-of-care for metastatic hormone-sensitive prostate cancer (mHSPC) [1], which, in most cases, results in the decrease of prostate-specific antigen (PSA) levels and the improvement of symptoms. Once the disease progresses to castration-resistant prostate cancer (CRPC), currently approved therapeutic options include sipuleucel-T, enzalutamide, abiraterone, docetaxel, cabazitaxel, and radium-223 [2,3].

Recently, there was a paradigm shift as a result of new data from clinical studies which opened up new perspectives and changed the standard-of-care in mHSPC. In the pivotal CHAARTEED [4] and STAMPEDE-Docetaxel [5] studies, the combination of docetaxel and ADT demonstrated a survival benefit over ADT alone among patients with mHSPC. The randomized, phase III CHAARTED study was the first pivotal study to convincingly demonstrate the efficacy of early docetaxel among patients with mHSPC, particularly in the case of high-volume disease. Subsequently, STAMPEDE-Docetaxel, an ongoing, multiarm trial investigating various therapeutic approaches in different stages of prostate cancer, confirmed the survival benefits of early docetaxel therapy seen in the CHAARTED study. As a result, early docetaxel is now recommended by all international guidelines as a part of standard therapy, and it is gradually being incorporated into Hungarian clinical practice, as well. Similarly, early abiraterone therapy was also integrated into the standard-of-care in combination with ADT among patients with newly-diagnosed, high-risk mHSPC due to the favorable results of the multinational, randomized, placebo-controlled phase III LATITUDE clinical trial [6], and the STAMPEDE-Abiraterone study [7].

Based on the available evidence, the decision-making process during the management of patients with mHSPC should involve the determination of disease volume as well as the assessment of individual risk, comorbidities, toxicity, and patient preference. In the case of high-volume disease, ADT *and* docetaxel *or* (if Gleason score ≥8) abiraterone, or ADT alone is recommended, while for patients with low-volume disease, ADT monotherapy *or*—in high-risk patients—ADT in combination with abiraterone should be administered [8]. Therefore, in many cases, clinicals are faced with the dilemma of choosing between docetaxel and abiraterone, especially among patients with a high burden of mHSPC. Furthermore, the therapeutic options and associated outcomes of patients progressing to castration-resistant disease after early docetaxel or abiraterone are currently not fully understood.

Although the histological classification of prostate cancer is well-established [9], tumors with the same histopathology may have different molecular subtypes and these molecular variants may respond differently to certain therapies. The identification of biomarkers which are potentially associated with response to therapy and clinical outcomes remains to be a major unmet need both in the hormone-sensitive and castration-resistant phases. During the previous years, a number of retrospective studies focused on the identification of factors with potential predictive value in prostate cancer with a view to help identify baseline resistance to docetaxel or abiraterone and optimize treatment decisions [10−12]. One of the genetic alterations which have been implicated in the development of taxane-resistance is the overexpression of ERG (erythroblast transformation-specific-related gene), a member of the ETS transcription factor family, which results from recurrent gene fusions with an androgen-regulated 5' gene partner, TMPRSS2 [13−15]. The *TMPRSS2:ERG* fusion gene is the most common ETS gene rearrangement in prostate cancer which can be detected in about 50% of patients [13]. Interestingly, Galletti et al. demonstrated that ERG overexpression was associated with decreased sensitivity to taxanes in in vitro and in vivo models of CRPC [16]. Therefore, the identification of ERG status may allow for a tailored approach and may help predict response to docetaxel chemotherapy (ChT) as well as clinical outcomes. While these studies provide valuable information, which may aid treatment decisions and patient selection for appropriate therapies, most of them focused on the predictive value of the examined factors in the castration-resistant phase. Consequently, it is not yet understood whether the biomarkers implicated in mCRPC might have a predictive value in the hormone-sensitive phase regarding response to early docetaxel therapy added to ADT.

Therefore, the aim of this retrospective study was to analyze the potential relationship between ERG expression and clinical outcomes among patients with mHSPC receiving docetaxel and ADT, and to investigate the efficacy and toxicity of docetaxel in this setting.

2. Materials and methods

Retrospective analysis of prospectively collected data at 2 Hungarian departments, the National Institute of Oncology, Budapest, and the Department of Oncotherapy, University of Szeged. The study was performed in accordance with Hungarian drug law and relevant guidelines and was approved by the ethics committee (21679-2/2016).

2.1. Study population

Potentially eligible cases were identified from a patient database with mHSPC receiving docetaxel ChT for mHSPC between August 1, 2014 and October 31, 2017 at one of the 2 centers. Patients were included in the study if they had paraffin tissue blocks from diagnostic samples or metastatic sites. All tumors were objectively confirmed by histological verification, and staging procedures as well as ADT were carried out according to the conventional protocol. For

each patient, treatment plan was designed by a multidisciplinary tumor board.

2.2. Systemic treatment

All patients received intravenous docetaxel ChT (docetaxel every 3 weeks at a dose of 75 mg/m^2 in 6 cycles depending on toxicity, without prednisone), starting within 120 days after the initiation of ADT. All patients signed a written informed consent prior to the initiation of chemotherapy. The use of prophylactic granulocyte colony stimulating factor was allowed. Dose reduction or delay was performed at the oncologist's discretion. Physical examination and laboratory tests were carried out every 3 weeks. The severity of AEs was evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [17]. Patients' general condition was assessed using the ECOG scale [18]. Data were collected prospectively starting in August 2014.

2.3. Response analysis

The assessment of outcomes was carried out before and 8 to 12 weeks after the completion of chemotherapy and involved clinical examinations, PSA measurements, bone scan, and diagnostic chest-abdomino-pelvic CT examinations. Response to therapy and follow-up were assessed according to the Prostate Cancer Working Group criteria system [19]. Good response was defined as a ≥50% decrease in baseline PSA levels. Relapse-free survival (RFS) and overall survival (OS) were defined as the period from the initiation of ChT to the detection of castration-resistant prostate cancer or death [20]. Early progression was defined as the development of CRPC within 12 months after the initiation of ChT.

2.4. ERG immunohistochemistry

Prostate cancer tissue samples were obtained from needle biopsies, transurethral resections of the prostate, prostatectomies (2 cases), or prostate cancer metastases (1 pulmonary and 1 lymph node metastasis). Before ChT, immunhistochemical (IHC) staining was performed to quantify ERG expression in the biopsy samples. Histological samples were obtained from different pathological departments where primary diagnoses were made. Prostate biopsy tissue samples were examined in a retrospective way with regards to ERG expression at the Department of Pathology, University of Szeged.

The following primary mouse monoclonal antibody was used for IHC: ERG (clone EP 111, Cell Marque # 434R-14) was diluted at 1:500. Deparaffinization and rehydration at room temperature were followed by antigen retrieval with the PT Link system (10 mM sodium citrate buffer, pH 6.0, for 30 minutes at 94°C; Dako, Glostrup, Denmark). After rinsing with Tris-buffered saline (EnVision FLEX Wash), the sections were placed in a Dako Autostainer Link 48 for endogenous peroxidase blockage and staining. Diaminobenzidine was used as chromogen. The sections were then counterstained with Mayer's hematoxylin, dehydrated, cleared in xylene and mounted. Negative controls were obtained by the omission of the primary antibody. The positive controls for ERG were endothelial cells. Only subjects with nuclear ERG immunoreactivity were classified as ERG positive [21] (Fig. 1). For the main analysis of ERG
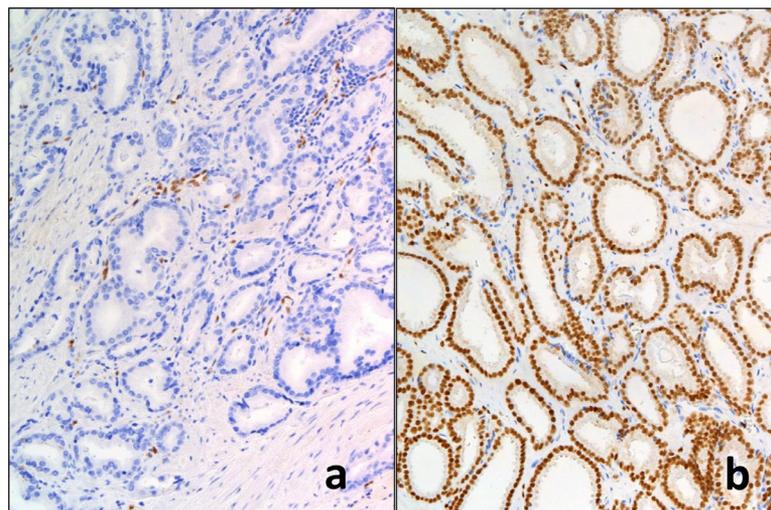

Figure 1. Immunohistochemistry: prostate cancer stained with ERG antibody. Brown tumor cell nuclei represent ERG positivity. (a) ERG negative prostate cancer. The endothelial cells serve as internal positive controls. (b) ERG positive prostate cancer. The glandular cells of adenocarcinoma are strongly ERG positive.

expression in relation to prostate cancer mortality, we used a dichotomous marker cut point (positive or negative for nuclear ERG immunoreactivity).

2.5. Statistical analysis

The association between patient characteristics and RFS or OS was analyzed by Kaplan-Meier analysis for categorical variables and by Cox regression for continuous variables. To detect the joint effect of the decrease in PSA level and ERG expression on RFS, multivariate Cox regression analysis (forward likelihood ratio method) was applied. All statistical analyses were performed using the IBM SPSS v22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

3. Results

3.1. Patient characteristics

Altogether 55 patients were included in the study, with a mean age of 65.6 ± 1.1 years (range: 43−79). Most patients (94.5%) had high-volume disease, defined as the presence of visceral metastases and/or ≥ 4 bone metastases with at least 1 outside the vertebral column and pelvis (CHAARTED study definition) [4]. Most of the patients also had a Gleason score of ≥ 8, with a mean value of 8.67 ± 0.14. Performance status was generally good (ECOG 0: 67.3%; ECOG 1: 27.3%), ECOG 2 status was detected in only 3 cases (5.5%). At the time of diagnosis, the mean PSA level of patients was 629.6 ± 161.7 ng/ml. The histological type of prostate cancer was adenocarcinoma in all cases; 2 patients had previously undergone radical prostatectomy. All patients were analyzed in 1 common cohort (Table 1).

3.2. Response and survival

The mean time between the initiation of ADT and docetaxel ChT was 73.9 ± 3.9 days. The mean number of docetaxel cycles received by patients was 5.69 ± 0.17.

Overall, RFS and OS were 10.5 ± 3.2 months and 40.4 ± 8.9 months, respectively. By the time of study completion, 17 patients had died (30.9%), 14 of which due to prostate cancer, 2 due to the development of pneumonia or ileus after ChT, and 1 due to subsequently detected advanced colorectal cancer. Disease progression was mostly detected with increasing PSA levels in 31 patients (56.4%), out of which 19 (34.5%) were bone, 8 (14.5%) were visceral, and 4 (7.3%) were distant lymph node metastases. Castration-resistant prostate cancer developed in 32 patients (58.2%), out of which 23 cases (41.8% of all patients) were detected within 12 months from the initiation of docetaxel ChT. The mean OS after the development of castration-resistant status was 17.2 ± 5.4 months.

PSA decrease was detected in 51 cases (92.7%), the mean rate of decrease was 84.7 ± 4.1 ng/ml. The nadir PSA level was 34.0 ± 19.8 ng/ml, a reduction of at least 50% was detected in 44 patients (80%) (Table 2).

Table 1

Patient characteristics. ECOG = Eastern Cooperative Oncology Group; n = number of patients included; N = number of patients analyzed; SE = standard error; PSA = prostate-specific antigen.

$N = 55$			Patients
Mean age, y $\pm$ SE			65.6 ± 1.1
Age range, y			43−79
Gleason score, mean $\pm$ SE			8.67 ± 0.14
Initial PSA, mean $\pm$ SE			629.6 ± 161.7
		n	%
ECOG performance status	0	37	67.3
	1	15	27.3
	2	3	5.5
Volume of disease	High	52	94.5
	Low	3	5.5
Location of metastases			
Bone		50	90.9
Distant lymph node		32	58.2
Visceral		13	23.6
Number of involved organs	One	21	38.2
	More	34	61.8

Table 2

Parameters of chemotherapy and clinical outcomes. ADT = androgen deprivation therapy; ChT = chemotherapy; CRPC = castration-resistant prostate cancer, N = number of patients analyzed; OS = overall survival; SE = standard error; PSA = prostate-specific antigen; pts = patients; RFS = relapse-free survival.

$N = 55$			
Mean time from ADT to ChT, d $\pm$ SE			73.9 ± 3.9
Number of ChT cycles, mean $\pm$ SE			5.69 ± 0.17
PSA response			
Nadir PSA level, mean ng/ml $\pm$ SE			34.0 ± 19.8
Number of pts with PSA decrease			51 (92.7%)
PSA decrease rate, mean % $\pm$ SE			84.7 ± 4.1
Number of pts with $\geq 50\%$ PSA decrease			44 (80%)
CRPC after ChT			
Number of pts with CRPC after ChT			32 (58.2%)
Median RFS to CRPC, mo			15.6 (95%CI 10.6−20.6)
Location of progression		n	%
PSA		31	56.4
Bone		19	34.5
Distant lymph node		4	7.3
Visceral		8	14.5
Site of progression	Only PSA	23	41.8
	One organ	5	9.1
	More organs	27	49.1
Subsequent therapies	Abiraterone	19	34.5
	Enzalutamide	4	7.3
	Alfaradine	4	7.3
	Cabazitaxel	3	5.5
	Docetaxel	1	1.8
OS from ChT, median, mo			40.4 (95% CI 22.9−57.9)
OS from date of CRPC, median, mo			17.2 (95% CI 6.7−27.8)

3.3. Clinical factors and outcomes

There was no significant association between RFS/OS and age, Gleason score, initial PSA level, the type of involved organs, or the number of docetaxel cycles.

Performance status was significantly associated with clinical outcomes: patients with an ECOG status of 0 had a mean RFS of 17.9 ± 4.6 and a mean OS of 40.43 ± 9.4; those with an ECOG status of 1 had a mean RFS of 8.9 ± 2.1 and a mean OS of 25.7 ± 3.7, while an ECOG status of 2 was associated with a mean RFS of 9.1 ± 6.6 and a mean OS of 10.2 ± 7.5.

There were significant differences in RFS and OS between patients with a good PSA response (defined as a $\geq 50\%$ decrease in PSA level) and those without (RFS: 16.8 ± 2.3 vs. 5.9 ± 0.1 months, $P < 0.001$; OS: 40.4 ± 12.2 vs. 11.6 ± 0.8 months, $P < 0.001$) [Figs. 2, 3]. Merely biochemical or oligoprogression were associated with better RFS and OS compared to progression to multiple organs (RFS: 40.2 ± 2.8 vs. 10.8 ± 0.9 months, $P < 0.001$; OS: 40.4 ± 8.9 vs. 23.6 ± 2.9 months, $P = 0.011$). Progression within 12 months from the initiation of docetaxel ChT was associated with poorer OS compared to progression after 12 months (17.97 ± 7.6 months vs. 40.4 ± 8.9 months, $P < 0.001$) (Table 3).

3.4. ERG status and outcomes

Prostate biopsy tissue samples of 50 patients were examined. Histological samples from the remaining 5 patients were used for primary diagnostic analysis and the remaining samples were too small for further IHC analysis to be performed.

RFS was 16.8 ± 3.6 months; ERG expression was detected in 21 patients (42%). ERG positivity was significantly associated with better RFS compared to ERG negativity (median RFS: 26.0 vs. 11.4 months, $P = 0.030$) (Figure 4).

ERG positivity was also significantly associated with a lower frequency of early progression: progression within 12 months was detected in 5 ERG positive patients vs. in 16 ERG negative patients (23.8% vs. 55.2%, $P = 0.026$). Late progression was detected in 16 cases in the ERG positive, and in 13 cases in the ERG negative groups (76.2% vs. 44.8%). There was no statistically significant association between ERG status and OS ($P = 0.107$).

3.5. Toxicity

Adverse events were detected in 28 patients (50.9%), mostly after the first cycle of docetaxel ChT (23 cases,
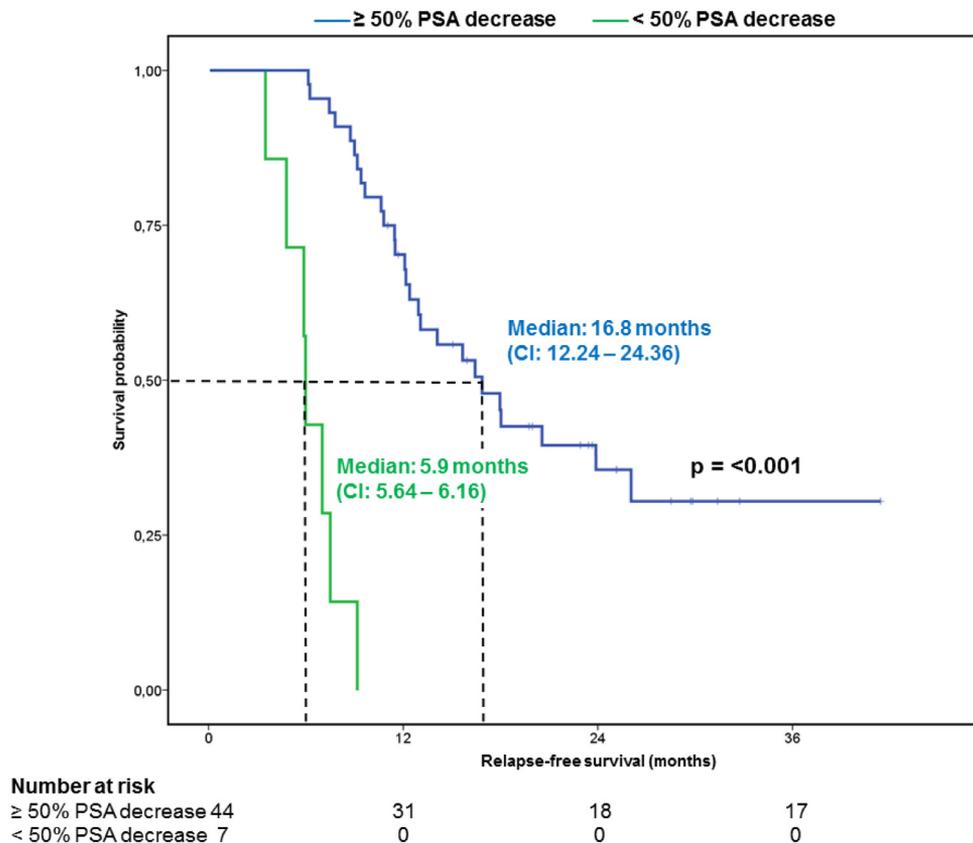

Figure 2. RFS as a function of PSA decrease. CI = confidence interval; PSA = prostate-specific antigen.
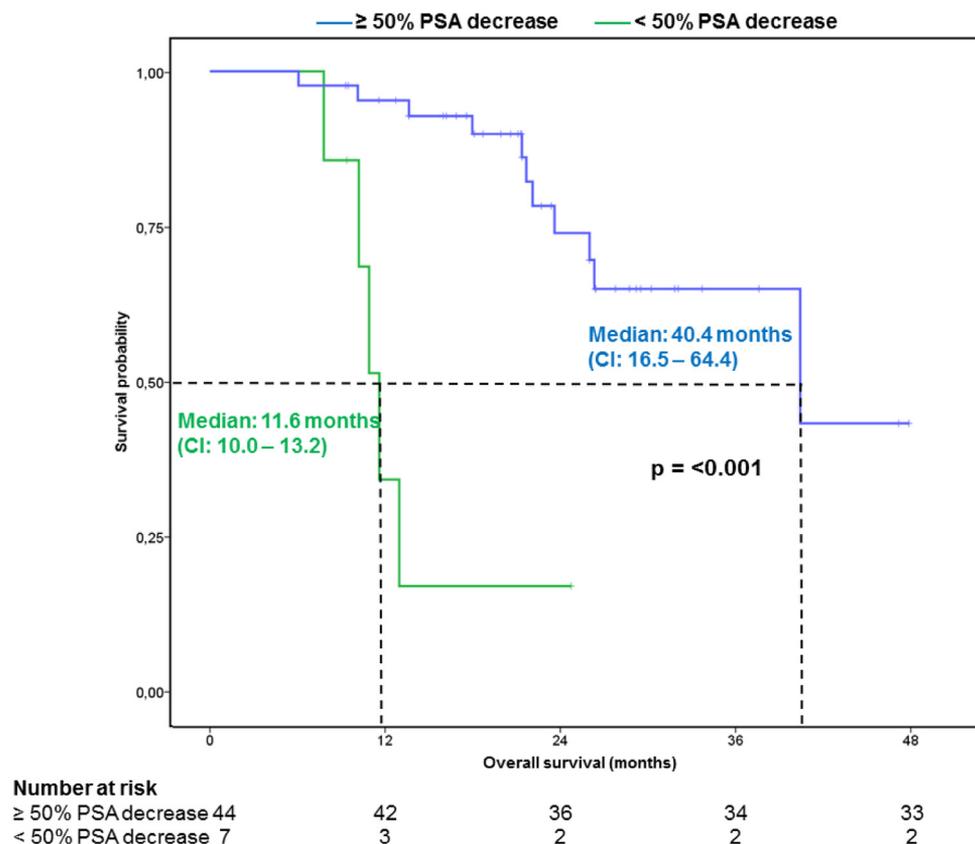
Figure 3. OS as a function of PSA decrease. CI = confidence interval; PSA = prostate-specific antigen.

Table 3
Clinical factors influencing the outcome of docetaxel ChT in addition to ADT; bold *P* values are significant (*P* < 0.05). ADT = androgen deprivation therapy; ChT = chemotherapy; CI = confidence interval; HR = hazard ratio; MSKCC = Memorial Sloan Kettering Cancer Center; mOS = median overall survival; mRFS = median relapse-free survival; NA = not applicable; OS = overall survival; PSA = prostate specific antigen; RFS = relapse-free survival; SE = standard error.

| Specifications of analyzed patients *N* = 55		RFS-HR (95% CI)	*P*	OS-HR (95% CI)	*P*
Age		0.988 (0.947−1.031)	0.592	1.018 (0.960−1.079)	0.553
Gleason score		1.405 (0.908−2.174)	0.127	1.425 (0.773−2.627)	0.256
Initial PSA level (ng/ml)		1.000 (0.999−1.000)	0.264	0.999 (0.997−1.000)	0.093
Level of PSA nadir (ng/ml)		1.010 (0.999−1.021)	0.085	0.999 (0.995−1.004)	0.728
Rate of PSA decrease (%)		0.964 (0.950−0.978)	**<0.001**	0.979 (0.966−0.992)	**0.001**
Number of ChT cycles		1.231 (0.809−1.873)	0.332	0.910 (0.646−1.281)	0.589
		mRFS ± SE (mo)	*P*	mOS ± SE (mo)	*P*
Pts with ≥50% PSA decrease	No/Yes	5.9 ± 0.13/16.8 ± 2.3	**<0.001**	11.6 ± 0.8/40.4 ± 12.2	**<0.001**
ECOG status	0/1/2	17.9 ± 4.6/8.9 ± 2.1/9.1 ± 6.6	**0.002**	40.4 ± 9.4/25.7 ± 3.7/10.2 ± 7.5	**0.002**
Extension of volume	High/Low	12.8 ± 1.2/16.8 ± 2.4	0.944	30.5 ± 8.7/40.8 ± 8.9	0.475
Location of metas-tases	Bone No/Yes	18.9 ± 2.3/25.6 ± 2.4	0.711	22.5 ± 6.3/33.5 ± 2.7	0.368
	Lymph node No/Yes	26.7 ± 3.1/23.9 ± 2.9	0.354	38.5 ± 3.7/29.2 ± 2.5	0.307
	Visceral No/Yes	27.3 ± 2.7/17.2 ± 2.5	0.188	32.6 ± 2.8/34.3 ± 5.3	0.932
Number of involved organs	1/More	28.5 ± 3.2/22.8 ± 2.7	0.111	42.1 ± 3.0/29.0 ± 2.9	0.066
Location of prog-ression	PSA No/Yes	45.3 ± 1.7/11.4 ± 0.8	**<0.001**	30.5 ± 3.2/40.4 ± 11.6	0.323
	Bone No/Yes	33.2 ± 3.1/11.2 ± 1.2	**<0.001**	37.4 ± 3.2/26.6 ± 3.1	**0.043**
	Lymph node No/Yes	17.9 ± 2.8/5.9 ± 2.8	**0.002**	40.4 ± 7.5/10.9 ± 3.2	0.158
	Visceral No/Yes	20.5 ± 4.8/7.4 ± 0.4	**<0.001**	40.4 ± 8.9/11.6 ± 1.8	**<0.001**
Number of organs in progression	1/More	40.2 ± 2.8/10.8 ± 0.9	**<0.001**	40.4 ± 8.9/23.6 ± 2.9	**0.011**
Progression	≤12 m/>12 m	NA	NA	17.97 ± 7.59/40.43 ± 8.9	**<0.001**
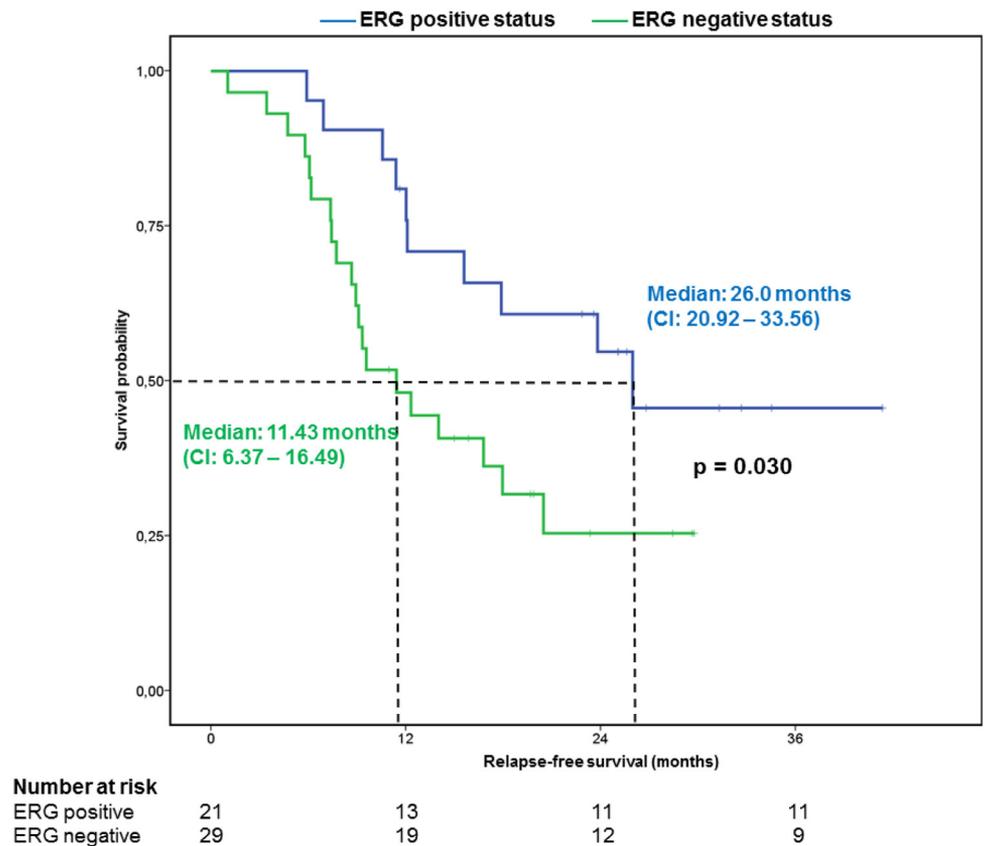
Figure 4. RFS as a function of ERG status. CI = confidence interval; RSF = relapse-free survival.

41.8%). The most common adverse events were alopecia, anemia, and diarrhea. The majority of adverse events was grade 0−1 and could be managed conservatively. None of the observed adverse events led to the discontinuation of docetaxel ChT (Table 4).

Table 4
Side effects of docetaxel ChT.

	Grade	n	%
All	0	28	50.9
	1	23	41.8
	2	2	3.6
	3	2	3.6
Anemia	0	48	87.3
	1	5	9.1
	2	2	3.6
Diarrhea	0	46	83.6
	1	9	16.4
Leukopenia	0	36	65.5
	1	5	9.1
	2	0	0
	3	5	9.1
	4	9	16.4

4. Discussion

In our cohort of mHSPC patients treated with early docetaxel and ADT, we examined the potential relationship between clinical factors as well as ERG expression and response to docetaxel therapy. ERG positivity and good PSA response were strongly associated with better relapse-free survival, and ERG expression was also associated with a lower frequency of early progression. The combined docetaxel + ADT regimen was well-tolerated; no new adverse events were recorded during a mean cycle number of 5.69.

Recently, there was a paradigm shift in the management of mHSPC. Until 2014, the only available therapy for these patients was ADT, and the majority of research focused on patients with castration-resistant disease. The introduction of early docetaxel or abiraterone in addition to ADT in the hormone-sensitive phase opened up new perspectives in the management of mHSPC by providing similar benefits in terms of OS compared to ADT alone. However, there are certain aspects that need to be taken into consideration when choosing between docetaxel and abiraterone in eligible patients, such as the expected duration of therapy, and treatment costs. Although early

docetaxel chemotherapy may be associated with well-known side-effects, it is cost-effective compared to abiraterone, and the fix number of 6 cycles allow for the planning of therapy. However, biomarkers predicting response to docetaxel are needed to identify patients who would benefit from early docetaxel.

The role of the *TMPRSS2:ERG* fusion gene as a potential biomarker of response to docetaxel chemotherapy among patients with mHSPC receiving ADT has been suggested by several authors [16,22,23]. Rajpar et al. analyzed data from the phase III GETUG-12 and GETUG-15 studies, which assessed the role of docetaxel chemotherapy in combination with ADT in the setting of high-risk localized or metastatic HSPC, respectively. In both datasets, docetaxel-based chemotherapy was associated with improved RFS in ERG positive patients, but not in ERG negative patients, suggesting a potential role for ERG as an important biomarker of the effectiveness of docetaxel chemotherapy [24]. In the present study, ERG positivity was also significantly associated with better RFS and a lower frequency of early progression, than ERG negative status among mHSPC patients treated with early docetaxel and ADT. Furthermore, the finding that good PSA response was associated with better RFS is in line with previous observations suggesting a predictive value for PSA progression in terms of survival in metastatic prostate cancer [25] and complements the existing knowledge base with new data from mHSPC patients receiving the early docetaxel + ADT regimen. Limitations of our study include the small sample size and the retrospective nature of our research.

In conclusion, the results of the present study suggest that ERG expression may help predict the effectiveness of docetaxel chemotherapy when administered in addition to standard androgen deprivation therapy among patients with mHSPC. Our study was the first to demonstrate an association between ERG positivity and response to early docetaxel therapy in terms of relapse-free survival in a real-world patient population. Large multicentric, prospective studies are required to further investigate the role of ERG and other biomarkers in identifying mHSPC patients who would benefit from the addition of early docetaxel to ADT.

Conflicts of interest

Zsófia Küronya, Lajos Géczi and Anikó Maráz have received honoraria from Janssen-Cilag Ltd and have served on advisory board for Janssen-Cilag Ltd.

Krisztina Bíró and Fruzsina Gyergyay have received honoraria from Janssen-Cilag Ltd.

Farkas Sükösd, Linda Varga, Krisztián Nagyiványi, Kliton Jorgo, Tibor Szarvas, Ágnes Kovács, Ibolya Laczó, Zoltán Varga, Boglárka Pósfai and Judit Pepó have no actual or potential conflicts of interest to report.

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