Received: 2 December 2019 | Revised: 3 January 2020 | Accepted: 11 March 2020

DOI: 10.1002/cac2.12021

CANCER COMMUNICATIONS Open Access

LETTER TO THE EDITOR

Psychological and physiological impacts of a fast-track diagnostic workup for men with suspected prostate cancer: Preliminary report from a randomized clinical trial

Dear Editor,

The increasing number of men who undergo workup for suspected prostate cancer are subject to severe emotional stress [1]. Stress levels seem to be elevated as soon as a suspicion of cancer is raised and the waiting time before a final diagnosis may be equally stressful as the post-diagnostic period [1, 2]. We recently demonstrated a marked increase in risk for different psychiatric disorders during the six months before prostate cancer diagnosis, highlighting the potential impact of emotional stress experienced while waiting for the diagnosis [3].

While a delayed diagnosis may confer to a reduced survival due to deferred treatment among patients with rapidly growing tumors, it may also increase the psychological stress experienced by patients undergoing a slow process of diagnostic workup. There is currently no organized screening for prostate cancer in Sweden, and the median waiting time from referral to surgery for men with suspected prostate cancer is around five months with considerable geographic variation [4]. No randomized trial has, to our knowledge, assessed the influence of waiting time on stress-related symptoms in this group of men before. Here, we performed a randomized clinical trial to evaluate the psychological and physiological influence of different waiting times during diagnostic workup for prostate cancer. We present the preliminary report from this clinical trial, focusing on the time leading up to the first urologist visit.

In this randomized, hospital-based, parallel-grouped study, we randomized 204 eligible men out of the 206 men who visited the Urology Department at the Örebro University Hospital (Sweden) with suspected prostate cancer between April 14, 2015, and May 21, 2018 (Figure 1). All men were randomized to either a fast-track diagnostic workup process or usual care workup. The fast-track intervention entails a diagnostic workup process where the shortest possible waiting-time is targeted. Men in both arms were first assessed at the urology clinic directly after randomization at their first hospital contact with a research nurse and again during their first urologist visit when a diagnostic biopsy was usually taken. The participants were monitored during the process of diagnosis and treatment decisions. This preliminary analysis focused on patients who returned questionnaires both at randomization and first urologist visit, comprising of 88 patients from the usual care group and 97 patients from the intervention group. Self-reported symptoms of stress were the primary outcomes of the study, and stress biomarkers, including heart rate variability and diurnal cortisol levels, were considered secondary outcomes. The methods of the present study are detailed in Supplementary file 1. This randomized clinical trial was approved by the ethics committee of Örebro University Hospital. Written informed consent was obtained from all participants. The study was registered at the ISRCTN registry (www.isrctn.com, No. ISRCTN45953686).

Men in the fast-track group had a shorter mean waiting time than men in the usual care group (11 days vs. 51 days, $P < 0.01$). Patients in both groups had similar baseline characteristics, including age, prostate-specific antigen (PSA) level, International Prostate Symptom Score (IPSS) score, Charlson comorbidity index, educational level, living area, civil status, smoking status, social support level, and use of anxiolytics/antidepressants during the month prior to randomization (Supplementary Table 1).

For self-reported stress symptoms, we assessed the levels of depression and anxiety with the Hospital Anxiety and Depression Scale (HADS), self-evaluated distress with the National Comprehensive Cancer Network (NCCN) distress thermometer, and sleep quality and disturbances with the Åkerstedts Karolinska Sleep Questionnaire. A self-rated sleep quality score (1-5) was also included. For all

Abbreviations: AUC_G, area under the curve with respect to ground; AUC_I, area under the curve with respect to increase; HADS, Hospital Anxiety and Depression Scale; IPSS, International Prostate Symptom Score; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RR, inter-beat interval; SDRR, standard deviation of R-R intervals.

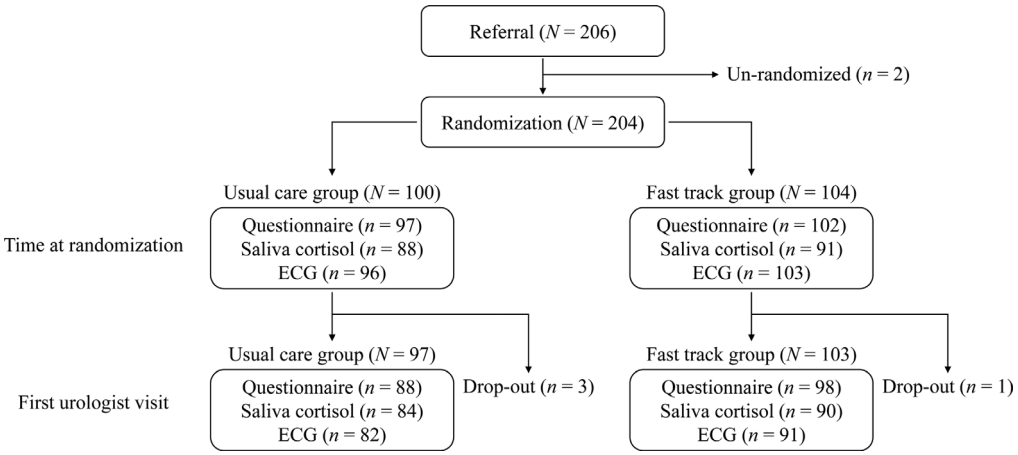

FIGURE 1 Flow diagram depicting the enrollment of study participants into the fast track and usual care groups

TABLE 1 Between group comparisons of changes in self-reported indicators of stress, heart rate and heart rate variability, and diurnal saliva cortisol from randomization to first urologist visit among the 88 patients from the usual care group and 97 patients from the fast-track group

Outcome	Usual care group	Fast-track group	*P* (unadjusted)[†]	*P* (adjusted)[†,‡]
Self-reported indicators of stress	Within Group Percent Change [Mean (SD)]			
Distress (NCCN)[§]	10.37 (31.13)	7.21 (25.24)	0.47	0.10
Anxiety (HADS)[§]	−2.98 (20.21)	−2.05 (20.56)	0.76	0.39
Depression (HADS)[§]	1.41 (22.34)	−4.71 (21.57)	0.06	<0.05
Sleep quality index[§]	−0.36 (12.32)	0.90 (8.66)	0.50	0.90
Sleep apnea index[§]	−3.37 (15.20)	−4.05 (11.77)	0.77	0.72
Self-rated sleep quality	19.23 (43.32)	4.31 (34.27)	<0.05	<0.05
Heart rate and heart rate variability	Within Group Percent Change [Mean (SD)]			
Heart rate	1.71 (12.28)	4.70 (11.99)	0.10	<0.05
Variation in the RR intervals[¶]	6.17 (40.01)	10.14 (40.45)	0.51	0.48
SDRR	2.28 (26.52)	2.91 (21.19)	0.86	0.93
Assessment of diurnal saliva cortisol	Within Group Percent Change [Median (Interquartile range)]			
Slope[¤]	14.85 (−47.35–79.04)	1.24 (−51.27–46.67)	0.69	0.67
AUC_G[*]	−1.44 (−27.19–29.55)	1.00 (−14.83–21.95)	0.89	0.83
AUC_I[ξ]	0.68 (−1.75–3.22)	0.40 (−2.26–3.06)	0.78	0.75

Abbreviations: SD, standard deviation; NCCN, National Comprehensive Cancer Network; HADS: Hospital Anxiety and Depression Scale; RR, inter-beat interval; SDRR, standard deviation of R-R intervals; AUC_G, Area under the curve with respect to ground; AUC_I, Area under the curve with respect to increase.

[†] *P* values for comparison between the fast-track group and the usual care group using generalized linear model.

[‡] Model adjusted for age, PSA levels (logarithmically-transformed), Charlson co-morbidity score, university education, co-habitation, living in urban areas, cigarette smoking, snuff use, previous treatment for psychiatric problems, social support from partner, and social support from others.

[§] Percent change of square root [$\sqrt{(x+1)}$] transformed value.

[¶] Defined as the degree of variation in the inter-beat intervals series (Standard deviation of QRS to QRS intervals series)/(Mean of QRS to QRS intervals series) × 100%). Percent change of natural log (x+1) transformed value was calculated.

[¤] Linear regression was performed on the three measures of cortisol levels within the day for each individual. The slope presented is the median of parameter coefficient (and interquartile range) of the variable indicating time point (i.e., morning, noon, and night).

[*] Percent change of ln (x) transformed value.

[ξ] Percent change of −ln (−x+20) transformed value.

assessment scales, a higher value indicated a worse outcome. From randomization to first urologist visit, the depression score (HADS) was found to increase slightly in the usual care group while it decreased in the fast-track group (Table 1). Indicating an increase in stress over time, the self-rated sleep quality score increased in both groups between randomization and first urologist visit, but more markedly in the usual care group (Table 1). An increase in NCCN distress was noticed from randomization to first urologist visit in both groups, with no significant difference (Table 1).

For measurement of stress biomarkers, we included the heart rate variability and diurnal saliva cortisol level. Compared with the levels at the time of randomization, both groups showed an increase in resting heart rate at the first

urologist visit, but the increase was higher in the intervention group (Table 1). Heart rate variability (variation in the inter-beat interval and standard deviation of inter-beat intervals [SDRR]) increased slightly between visits in both groups but without any statistically significant difference observed between them. The diurnal cortisol slope became slightly flatter in both groups, especially in the usual care group, indicating increasing stress levels over time; however, no significant difference was observed in change from randomization to first urologist visit between the groups (Table 1). No clear difference was further noted for changes between visits in the area under the curve with respect to ground (AUC_G, representing the total amount of cortisol secreted in the day) or with respect to increase (AUC_I, representing the total amount of cortisol increased in the day) between the two groups (Table 1).

This randomized clinical trial systematically evaluated the dynamic changes of psychological stress in men undergoing a fast-track or usual diagnostic workup process for prostate cancer. Earlier observational studies have suggested a peak increase in psychological stress during the waiting time before diagnosis, which may be equal to or even greater than the stress after cancer diagnosis [1, 5, 6]. However, no studies have previously compared the psychological and physiological stress experience of different waiting times during a prostate cancer diagnostic workup.

This preliminary report, focusing on the waiting time between first hospital contact with a research nurse and first urologist visit did not indicate a coherent pattern with regard to differences in indicators of anxiety, distress, and sleep quality index. However, significant changes in depression symptoms and self-rated sleep quality suggested a benefit of the fast-track workup intervention. Studies based on self-evaluated questionnaires have shown limited sensitivity of those questionnaires in detecting changes in emotional stress [7, 8], and it is possible that physiological measurements would better reflect the severe or chronic burden of emotional stress [9, 10]. Compared with men in the usual care group, men in the fast-track workup group had a higher increase in heart rate variability, suggesting a decreased autonomous nervous system response. However, the difference was not significant. There is a possible indication that the diurnal cortisol slope became flatter in the usual care group between visits, suggesting a stronger physiological stress response among men with longer waiting time, but the change was also not significantly different between the groups.

The strengths of our study include its randomized design, comparisons between different waiting times during diagnostic workup of prostate cancer, and systematic assessments of dynamic changes in different aspects of stress response, including well-validated questionnaires and physiological biomarkers. Neurobiological evidence suggests that heart rate variability is influenced by stress, and a growing body of literature supports its use as an objective assessment of psychological health and stress [10]. However, variation in the measurement method exists. For instance, varying duration of assessment and the use of time- and frequency-domain analysis can potentially influence its sensitivity [10]. Based on short-duration measures, we used the simplest time-domain analysis variables, the inter-beat (RR) intervals and SDRR, which may have limited our ability to detect differences in heart rate variability between the groups. Another potential weakness pertains to missing data, although questionnaires from 204 participants were initially collected, some of them were not completely filled. This could be attributable to the fairly large number of items required to be filled out by the respondents. Only questionnaires with complete data from both randomization and first urologist visit were therefore included in the analysis. Based on the preliminary analyses of this ongoing study, strategies to improve data collection to reduce missing data will be employed. While the main focus of this preliminary report is to show the feasibility and potential effect of the fast-track workup intervention on psychological stress before urologist visit, many of the performed analyses are still underpowered to detect meaningful associations. As we still await the final results of this clinical trial, conclusions regarding changes in stress experienced across the workup process and the impact of waiting time on such changes cannot be made yet.

In conclusion, this study suggests that a fast-track diagnostic workup intervention among men with suspected prostate cancer may help to reduce psychological distress. The final results of this clinical trial are required to clarify its potential for improvement in longer-term outcomes, including disease characteristics and quality of life.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This randomized clinical trial was approved by the ethics committee at Örebro University Hospital and was registered at the ISRCTN registry www.isrctn.com (No. ISRCTN45953686). Written informed consent was obtained from all individual participants included in the study.

CONSENT FOR PUBLICATION

All authors accept the publication of this work and all patients provided signed inform consent to use their data.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are not publicly available to protect participant confidentiality but can be partly provided from authors on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interest.

FUNDING

This study was funded by The Swedish Cancer Society (CF2016/795 and 2018/765) and Nyckelfonden, Örebro, Sweden (2015). The funders had no role in the design and conduct of the study, collection, analysis, and interpretation of the data, and writing and approval of the manuscript.

AUTHORS' CONTRIBUTIONS

JZ, RC, OA, SOA, UV, FF, and KF conceived of and designed the study; JZ, SD, JC, AME, JF, OA, and SOA contributed to collection of the data; JZ and RC analyzed the data; JZ drafted the manuscript; JZ, RC, SD, JC, AME, JF, OA, SOA, UV, FF, and KF revised the manuscript critically for important intellectual content; All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors thank all the subjects who have participated in this clinical trial.

Jianwei Zhu[1]
Ruoqing Chen[2,3]
Sabina Davidsson[4]
Jessica Carlsson[4]
Anna Messing-Eriksson[4]
Jonna Fridfeldt[4]
Ove Andrén[4]
Sven-Olof Andersson[4]
Unnur Valdimarsdóttir[1,2,5]
Fang Fang[6]
Katja Fall[3,6]

[1]*Department of Orthopedic Surgery, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan 610000, P. R. China*
[2]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 171 77, Sweden*
[3]*Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro 701 85, Sweden*
[4]*Department of Urology, Faculty of Medicine and Health, Örebro University, Örebro 701 85, Sweden*
[5]*Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts 02115, SA*
[6]*Institute of Environmental Medicine, Karolinska Institutet, Stockholm 171 77, Sweden*

Correspondence
Ruoqing Chen, Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, 701 85 Örebro, Sweden.
Email: ruoqing.chen@ki.se

ORCID

Ruoqing Chen https://orcid.org/0000-0003-4911-3543

REFERENCES

1. Awsare NS, Green JS, Aldwinckle B, Hanbury DC, Boustead GB, McNicholas TA. The measurement of psychological distress in men being investigated for the presence of prostate cancer. Prostate Cancer Prostatic Dis. 2008;11(4):384-9. https://doi.org/10.1038/pcan.2008.21.
2. Lofters A, Juffs HG, Pond GR, Tannock IF. "PSA-itis": knowledge of serum prostate specific antigen and other causes of anxiety in men with metaststic prostate cancer. J Urol. 2002;168(6):2516-20. https://doi.org/10.1097/01.ju.0000032824.52830.55.
3. Lu D, Andersson TM, Fall K, Hultman CM, Czene K, Valdimarsdottir U et al. Clinical Diagnosis of Mental Disorders Immediately Before and After Cancer Diagnosis: A Nationwide Matched Cohort Study in Sweden. JAMA Oncol. 2016;2(9):1188-96. https://doi.org/10.1001/jamaoncol.2016.0483.
4. Regionala Cancercentrum. Nationella prostatacancerregistret (NPCR). http://npcr.se/wp-content/uploads/2018/09/20180913_npcr_nationell_rapport_2017.pdf. 2017. Accessed May 29 2019.
5. Wade J, Rosario DJ, Macefield RC, Avery KN, Salter CE, Goodwin ML et al. Psychological impact of prostate biopsy: physical symptoms, anxiety, and depression. J Clin Oncol. 2013;31(33):4235-41. https://doi.org/10.1200/JCO.2012.45.4801.
6. Kobayashi M, Nukui A, Kamai T. Psychological impact of serial prostate-specific antigen tests in Japanese men waiting for prostate biopsy. Int J Clin Oncol. 2017;22(1):174-80. https://doi.org/10.1007/s10147-016-1038-1.
7. Kohler N, Friedrich M, Gansera L, Holze S, Thiel R, Roth S et al. Psychological distress and adjustment to disease in patients before and after radical prostatectomy. Results of a prospective multi-centre study. Eur J Cancer Care (Engl). 2014;23(6):795-802. https://doi.org/10.1111/ecc.12186.
8. Seklehner S, Hladschik-Kermer B, Lusuardi L, Schabauer C, Riedl C, Engelhardt PF. Psychological stress assessment of patients suffering from prostate cancer. Scand J Urol. 2013;47(2):101-7. https://doi.org/10.3109/00365599.2012.700946.
9. Looser RR, Metzenthin P, Helfricht S, Kudielka BM, Loerbroks A, Thayer JF et al. Cortisol is significantly correlated with cardiovascular responses during high levels of stress in critical care personnel. Psychosom Med. 2010;72(3):281-9. https://doi.org/10.1097/PSY.0b013e3181d35065.
10. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. Psychiatry Investig. 2018;15(3):235-45. https://doi.org/10.30773/pi.2017.08.17.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.