Sponsor/Sponsor-Investigator: PD Dr. med. Volker Arndt

Study Title: PROSTATE CANCER SURVIVORSHIP IN SWITZERLAND: A MULTICENTER POPULATION BASED RETROSPECTIVE COHORT STUDY

Short Title/Study ID: PROCAS – Prostate Cancer Survivorship in Switzerland


Trial Registration: Nicht anwendbar

Study Category with Rationale: HFV Project - Category A, observational study linked with minimal risk. This research projects only involves a questionnaire based investigation of health related data and subsequent use of non-genetic personal health data, which is related only with minimal risks and stress for participants.

Clinical Phase, see Basisformular: Nicht anwendbar

Background and Rationale: Prostate cancer (PC) is the most frequent diagnosed cancer in men in developed countries with age-adjusted incidence rates (ASRs) up to 184 per 100,000 in North-America (2013, world-standard). However, not only incidence rates of prostate cancer are high. PC survivors account for the largest group of male cancer survivors on the world. In Switzerland, the age-adjusted incidence rate (ASR=159 per 100,000 persons per year; European-standard) is among the highest in Europe (European mean: ASR=106 per 100,000 persons per year; European-standard) and it is projected that already 60,200 men (41% of all cancer cases in men) have a history of prostate cancer. This number increased since the year 2000 by more than 30,000 cases. The number of projected long-term prostate cancer survivors (i.e. more than five years after diagnosis) even tripped since 2000 (2015: 32,818). This rise is a result of a combined effect of demographic aging, improvements in therapy, and increased incidence due to wide-spread of PSA testing (in 2012 31% men in Switzerland – age 50 to 74 - reported that they did a PSA test in last 12 months). Improvements in therapy and diagnostics have led to 5-years relative survival rates of prostate cancers of almost 90 % in Switzerland.

In summary there are many men diagnosed with prostate cancer in Switzerland and their number will increase due to demographic aging. Although most men with PC nowadays survive the disease, they may experience disease- and/or treatment-related long-term effects on their physical, psychological, or social health.

Health-Related Quality of Life

Cancer is now considered as a chronic disease, which affects patients life over years and many survivors continue to experience negative effects of cancer and/or treatment on their daily lives well beyond the completion of therapy. The life-altering burden of cancer has frame-shifted from a narrow focus on the direct effects of anti-cancer therapy and overall survival to a spectrum of medical and non-medical issues termed cancer survivorship. An individual is considered to be a cancer survivor from the time of diagnosis and cancer survivorship is defined as process of living with, through, and beyond cancer. Moreover, cancer survivorship encompasses quality of life aspects such as physical, psychosocial, and...
economic sequelae of cancer diagnosis and its treatment but it also includes issues related to health care delivery, access, and follow up care. Quality of life (QoL) has been defined as the difference, or the gap, between the hopes and expectations of the person and one’s present life experience.\textsuperscript{14} It is generally considered that QoL is best defined and measured from the individuals’ perspective. QoL or even more specific and appropriate health-related quality of life (HRQoL) as a multidimensional concept, defines all aspects of survivors’ well-being, as physical, psychological, social and spiritual well-being.\textsuperscript{10,15–20}

According to the literature, overall QoL of long-term survivors of prostate cancer is comparable to age-matched controls.\textsuperscript{21,22} However, issues of urinary, sexual, and bowel dysfunction remain problematic for prostate cancer survivors over the long term. Survivors report worse problems with urinary (e.g. leakage or incontinence) and sexual functioning (e.g., obtaining and maintaining erection) than controls. Although type of treatment appears to have no influence on overall HRQoL of life the severity of these specific problems varies according to primary treatment.\textsuperscript{16,20,23}

This study wants to fill the gap in existing knowledge about health-related quality of life as well as disease and treatment related late effects of long-term survivors of prostate cancer in Switzerland. So far, the entire research regarding HRQoL and further survivorship issues in long-term survivors of cancer is relying on data mostly from the US and to a small proportion from Scandinavian countries, Netherlands, and the UK. Differences in health care administration including follow-up of cancer survivors and cancer rehabilitation may limit the generalizability of the current knowledge regarding quality of life in cancer survivors. Therefore, one of the primary objectives is to describe HRQoL in long-term prostate cancer survivors in Switzerland depending on personal and medical factors. Additionally, it will be tried to identify determinants and mechanisms for negative (as well as positive) effects on HRQoL in long-term prostate cancer survivors. This will help us to identify potentially modifiable factors amenable to intervention aiming to improve HRQoL in long-term prostate cancer survivors.

### Objective(s):

#### Primary Project Objectives

To describe long-term health-related quality of life of prostate cancer survivors in Switzerland depending on personal and medical factors:

- What is the health-related quality of life among long-term prostate cancer survivors?
- Does health-related quality of life of survivors differ between certain groups? (e.g. age; tumour stage; rural/urban; language group; socioeconomic status; comorbidities etc.)
- What is the impact of the primary treatment (prostatectomy, radiotherapy, hormone therapy, watchful waiting and active surveillance, etc.) on health-related quality of life of prostate cancer survivors?

#### Secondary Project Objectives

2a. To identify determinants and mechanisms for negative (as well as positive) effects, such as pain, fatigue, mental health, comorbidities, resources, on health-related quality of life in long-term prostate cancer survivors.

2b. To compare long-lasting physical effects (such as incontinence, memory problems, pain syndromes, osteoporosis, or fatigue) of prostate cancer survivors with respect to age, tumour stage, and treatment factors.

### Outcome (if applicable, see Basisformular):

#### Primary Outcome

- General and prostate cancer specific health related quality of life (EORTC QLG-C30, QLQ-PR25, EPIC-26)
<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome</td>
<td>Fatigue: EORTC QLQ-FA13[12] (Remark: The new version of the EORTC QLQ-FA13 will be used, EORTC QLQ-FA12 expected to be published by spring/summer 2016)</td>
</tr>
<tr>
<td></td>
<td>Mental Health (MHI-5)</td>
</tr>
<tr>
<td></td>
<td>Spirituality: FACIT sp</td>
</tr>
<tr>
<td></td>
<td>Data about comorbidities</td>
</tr>
</tbody>
</table>

| Study Design, see Basisformular: | This is a Swiss multicentre population based retrospective cohort study with additional collection of current information about HRQoL, personal and medical data of long-term prostate cancer survivors using questionnaires and data of cancer registries. |

<table>
<thead>
<tr>
<th>Inclusion/Exclusion Criteria, see Basisformular:</th>
<th>Inclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Participants will receive once a questionnaire which includes the following international validated instruments:</td>
<td></td>
</tr>
<tr>
<td>General and prostate cancer specific health related quality of life (EORTC QLQ-C30, QLQ-PR25, EPIC-26)</td>
<td></td>
</tr>
<tr>
<td>Fatigue: EORTC QLQ-FA13 (Remark: new version EORTC QLQ-FA12 will be used, EORTC QLQ-FA12 expected to be published by end of 2015)</td>
<td></td>
</tr>
<tr>
<td>Mental Health (MHI-5)</td>
<td></td>
</tr>
<tr>
<td>Spirituality: FACIT sp</td>
<td></td>
</tr>
<tr>
<td>Additionally, referring physicians are asked to answer eight questions about the patients' prostate cancer stage, secondary cancer, treatment details and recurrence of prostate cancer.</td>
<td></td>
</tr>
</tbody>
</table>

| Measurements and Procedures: | Study Duration: 20 months |
| Study Schedule: | Enrolment of participants between 11/2016 – 06/2017 |

| Study Product/Intervention according to KlinV, if applicable: | Not applicable |

| Comparator(s) (if applicable): | Not applicable |

| Number of Participants with Rationale (if no Power Analysis conducted): | A total of 1400 patients will be approached in order to be enrolled in the project. Assuming a drop-out rate of 50%, based on previous pertinent studies of the PI, and the impracticality to send reminders we expect to recruit 700-800 participants. |
Person involved in the research project:

Salome Adam, MSc
Coordinating Investigator
Epidemiology, Biostatistics and Prevention Institute
University of Zurich
Hirschengraben 84
CH-8001 Zürich
Email: salome.adam@uzh.ch
Phone: +41 44 634 53 79
Fax: +41 44 634 54 44

Dr. Matthias Lorez
Senior Biostatistician
National Institute for Cancer Epidemiology and Registration
Seilergraben 49
CH-8001 Zürich,
Email: ml@nicer.org
Phone: +41 44 634 46 45
Fax: +41 44 634 54 4

Dipl.-Psych Anita Feller, MSc
Epidemiologist
NICER
c/o Universität Zürich
Seilergraben 49
CH-8001 Zurich
Email: anita.feller@nicer.org
Phone: +41 44 634 59 35

Nina Pupikofer
Administration
NICER
c/o Universität Zürich
Seilergraben 49
CH-8001 Zurich
Email: nina.pupikofer@nicer.org
Phone: +41 44 634 53 74

Regina Nanieva
Medical Information Specialist
c/o Universität Zürich
Seilergraben 49
CH-8001 Zurich
Email: regina.nanieva@nicer.org
Phone: +41 44 634 53 74

Student assistants and cancer registries assistants to be hired

Study Centre(s):

Krebsregister beider Basel
Dr. med. S. Mohsen Mousavi
Gesundheitsdepartment des Kantons Basel-Stadt, Medizinische Dienste
Bewilligungen und Support
Gerbergasse 13
CH-4001 Basel
Email: mohsen.mousavi@bs.ch
Phone: +41 61 267 49 23
Fax: +41 61 267 49 21
Registre fribourgeois des tumeurs
Dr. med. Bertrand Camey
St-Nicolas-de-Flüe 2, CP 96
CH-1705 Fribourg
Email: camey@liguessante-fr.ch
Phone: +41 26 425 54 05
Fax: +41 26 424 54 01

Krebsregister St. Gallen–Appenzell
MPH, Dr. med. Harald Frick
Krebsliga St. Gallen-Appenzell
Flurhofstr. 7
CH-9000 St. Gallen
Email: Harald.Frick@kssg.ch
Phone: +41 71 494 21 17
Fax: +41 71 494 61 76

Krebsregister Graubünden und Glarus
Dr. med. Harald Frick
Kantonsspital Graubünden
Institut für Pathologie und Rechtsmedizin
Loestrasse 170
CH-7000 Chur
Email: silvia.ess@kssg.ch,
Harald.Frick@kssg.ch
Phone: +41 81 256 65 56
Fax: +41 81 256 65 44

Registre Valaisan des Tumeurs
Dr. med. Isabelle Konzelmann
Observatoire valaisan de la santé
Avenue Grand-Champsec 86
CH-1950 Sion
Email: isabelle.konzelmann@ovs.ch
Phone: +41 27 603 48 55
Fax: +41 27 603 49 74

Krebsregister Zürich und Zug
PD Dr. oec. troph. Sabine Rohrmann, MPH
Universitätsspital Zürich
Vogelsangstr. 10
CH-8091 Zürich
Email: sabine.rohrmann@usz.ch
Phone: +41 44 255 56 36
Fax: +41 44 255 56 36

Statistical Analysis incl. Power Analysis
Descriptive, univariate and multivariate statistics.
Comparison of mean values, correlations and regression analysis.
E.g. The association between primary treatment(s) received and mean (a)
global HRQoL, (b) functional and (c) symptom scores will be assessed by
multivariate linear regression while controlling for potential confounding
factors.

GCP Statement:
This study will be conducted in compliance with the protocol, the current
version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as
far as applicable) as well as all national legal and regulatory requirements.

Explanation for the Inclusion of vulnerable Subjects (if applicable):
No vulnerable subjects are included in the study.
Recruitment Procedure (if applicable: Advice/Flyer have to be submitted; if applicable, please indicate the Localisation/Medium (which Newspaper))

The study is based on a pooled analysis of retrospectively constructed cohorts of long-term prostate cancer survivors (men, diagnosis between January 2006 and December 2010, age between 25 and 75 years at diagnosis). A postal data collection is supposed to assess HRQoL 5-10 years after their prostate cancer diagnosis.

Potential participants will be identified via the cancer registries BS/BL, FR, GR/GL, SG/AR/Al, VS & ZH.

In principle, potential participants will be identified by participating cancer registries, whereas information of survivors and obtaining informed consent will be accomplished by the referring urologist. Participants will receive once a questionnaire. In case of missing information participants will be once recontacted.
<table>
<thead>
<tr>
<th>Study Procedure/Flowchart with Timelines: Study specific Examinations have to be clearly identified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Construction of cohort including vital status review</strong></td>
</tr>
<tr>
<td><strong>Data Collection</strong></td>
</tr>
<tr>
<td><strong>Getting confirmation of urologists in the study region that they want to participate in the study</strong></td>
</tr>
<tr>
<td><strong>First recruitment phase</strong></td>
</tr>
<tr>
<td><strong>Informing patients’ referring physicians</strong></td>
</tr>
<tr>
<td><strong>Mailing Questionnaires to patients</strong></td>
</tr>
<tr>
<td><strong>Monitoring of feedback (including checking completeness of questionnaires and informed consent)</strong></td>
</tr>
<tr>
<td><strong>Informing patients’ referring physicians that his patients participated and asking for patients’ medical information</strong></td>
</tr>
<tr>
<td><strong>Potential second recruitment phase</strong></td>
</tr>
<tr>
<td><strong>Informing patients’ referring Physicians</strong></td>
</tr>
<tr>
<td><strong>Mailing Questionnaires to patients</strong></td>
</tr>
<tr>
<td><strong>Informing patients’ referring Physicians that his patients’ participated and asking for patients’ medical information</strong></td>
</tr>
<tr>
<td><strong>Monitoring of feedback</strong></td>
</tr>
<tr>
<td><strong>Data Entry and Validation</strong></td>
</tr>
<tr>
<td><strong>Data Analysis &amp; Preparation of Publications</strong></td>
</tr>
</tbody>
</table>

|  | 2016 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 07 | 08 | 09 | 10 | 11 | 12 | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 |
| **Construction of cohort including vital status review** | | | | | | | | | | | | | | | | | | | | | | |
| **Data Collection** | | | | | | | | | | | | | | | | | | | | | | |
| **Getting confirmation of urologists in the study region that they want to participate in the study** | | | | | | | | | | | | | | | | | | | | | |
| **First recruitment phase** | | | | | | | | | | | | | | | | | | | | | |
| **Informing patients’ referring physicians** | | | | | | | | | | | | | | | | | | | | | |
| **Mailing Questionnaires to patients** | | | | | | | | | | | | | | | | | | | | | |
| **Monitoring of feedback (including checking completeness of questionnaires and informed consent)** | | | | | | | | | | | | | | | | | | | | | |
| **Informing patients’ referring physicians that his patients participated and asking for patients’ medical information** | | | | | | | | | | | | | | | | | | | | | |
| **Potential second recruitment phase** | | | | | | | | | | | | | | | | | | | | | |
| **Informing patients’ referring Physicians** | | | | | | | | | | | | | | | | | | | | | |
| **Mailing Questionnaires to patients** | | | | | | | | | | | | | | | | | | | | | |
| **Informing patients’ referring Physicians that his patients’ participated and asking for patients’ medical information** | | | | | | | | | | | | | | | | | | | | | |
| **Monitoring of feedback** | | | | | | | | | | | | | | | | | | | | | |
| **Data Entry and Validation** | | | | | | | | | | | | | | | | | | | | | |
| **Data Analysis & Preparation of Publications** | | | | | | | | | | | | | | | | | | | | | |

FP, LV, LV, LP
Risks/ Inconveniences, which are Study specific:

Through the questionnaire it is possible that participants and their relatives/friends can have bad memories about their diagnosis/therapy or a flashback. Moreover, they maybe start to question their health status again what can cause stress.

Coverage of Damages: Insurance: no

Category A project, no insurance needed

Ethical Considerations:

1. Please describe the potential gain of new knowledge obtained with this study, and its meaning for patients/society.

The results of the envisioned project will help (a) to create a better knowledge regarding adverse diagnosis and treatment-related outcomes after prostate cancer such as late effects of treatment and poor quality of life; (b) to develop strategies to prevent and to control these adverse cancer diagnosis and treatment-related outcomes; and (c) to optimize health after prostate cancer treatment including better follow-up care and surveillance of cancer in the long run.

2. Please give an assessment of the benefit/risk relationship for the patient.

Participation in the study is only linked with very small psychological risks (e.g. flashback of bad memories). Moreover, participants will not have a direct benefit from participating in the study. However, it might be that participants and/or their referring physicians become attentive on potential impacts of the prostate cancer diagnosis and the following therapies. These impacts can be addressed later-on. So this study can increase the sensitivity on health problems related with prostate cancer diagnosis and prostate cancer treatments.

3. Please explain, why the methodology is also ethically appropriate to gain new generalizable knowledge (for ex. double-blind, placebo, sham, vulnerable subjects, emergency cases, partial information only etc.)

The population based approach of this project allows gathering new generalizability knowledge. So far, no data about HRQoL of long-term prostate cancer survivors is available in Switzerland. Moreover, patients are the most important data source for HRQoL assessment.
The most relevant References: